Upper gastrointestinal cancer: Do our clinical services work towards the 'two week rule' and how?

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UPPER GASTROINTESTINAL CANCER: DO OUR CLINICAL SERVICES WORK TOWARDS THE "TWO WEEK RULE" AND HOW?

by

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THESIS SUBMITTED TO THE UNIVERSITY OF WALES IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN MEDICAL AND HEALTH CARE STUDIES

in the Department

of

School of Medicine

UNIVERSITY OF WALES SWANSEA - December 2006

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Approval

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Degree:	Doctor in Philosophy
Title of thesis:	Upper Gastrointestinal Cancer: Do our clinical services work towards the "two week rule" and how?

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Summary

The present research work investigates the results observed in the management of those patients diagnosed with Upper Gastro-Intestinal Cancers subsequent to the use of algorithms of referral and clinical services such as Open Access Endoscopy and Rapid Opinion Clinic. This is a retrospective analysis based on the auditing methodology which looks to the experience gained in two NHS Trust hospitals in South Wales over a period of six calendar years.

An uncensored cohort of 440 patients diagnosed with various forms of Upper Gastro-Intestinal cancers are examined and their referral pathway, positive diagnosis, investigation and staging, as well as treatment and 5-year follow up is analyzed. The traditional methods of referring patients from the Primary Care sector are compared with the new open-access type of clinical services such as Open Access Endoscopy and Rapid Opinion Clinic in the context of the "two week rule" for cancer referral. It has been found that using the open access services the median delay for appointments is reduced to 11 days which is below the required threshold imposed by The NHS Cancer Plan. The mean GP delay interval remains slightly higher at 17.09 days mainly due to cases with atypical clinical picture; the same applies to the mean treatment delay which at 44.43 days is related with the staging investigations.

The results of these referral methods are also discussed from the perspective of patients' outcome as a measure of the benefits gained through the introduction of these clinical services. It has been noted that the rate of newly diagnosed early stage cancers has not increased and there was no gained benefit in diagnosing patients with more favourable stage of the disease. There was a hint that patients diagnosed through Open Access Endoscopy may have a less advanced disease with a higher rate of operability and a smaller benefit in survival probability.

This study concludes that new open-access style clinical services backed up by clear referral algorithms may increase the speed of patients' appointments and diagnosis in the Secondary Care sector but there is only little clinical and statistical evidence of benefits such as early cancer detection, operability and survival probability.

Areas of improvement in referral algorithm such as the combination of "alarm symptoms", exclusion of uncomplicated dyspepsia as a referral criterion in young adults, pooling all patients at risk with gastroenterological symptoms under the open access style of referral and streamlining of the staging and treatment pathway are amongst recommendations made at the end of this study.

Keywords: **Upper Gastro-Intestinal Cancer, malignancy, clinical services, Open Access Endoscopy, Rapid Opinion Clinic, referral, two week rule, speed of referral, speed of diagnosis, delay in referral, positive diagnosis, operability, TNM, stage, survival**

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

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STATEMENT 1

This thesis is the result of my own investigations, except where otherwise stated. Where correction services have been used, the extent and nature of the correction is clearly marked in a footnote(s).

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Dedication

To my late father who guided my first steps in Medicine and taught me that medicine is an art practised to the benefit of my fellow man.

Table of Contents

List of Tables & Illustrations

Acknowledgments

I would like to express my deepest gratitude to those people who have assisted me in completing this study. First of all my warmest thanks go to Professor John G. Williams at the University of Wales Swansea who assisted me all along with advice, professional guidance and encouragement. His expertise as a gastroenterologist and strong promoter of open access clinical services in South Wales was invaluable for this work which was carried out at the interface between gastroenterology and surgery. A warm thank you is addressed to his Academic Secretary Gaynor Demery who assisted at all times with logistical, communication and editing issues. I am also extremely grateful to our Medical School statistician Dr. Wai-Yee Cheung for her input with statistical calculations and her vision in shaping the statistical correlations in this study.

As this was an unfunded research study, I am expressing my gratitude to those members of staff who assisted me with the retrieval of so many medical records – Mrs. Jennifer George and Mrs. Marilyn Smart from the Clinical Records Departments of Neath General Hospital and Morriston University Hospital Swansea respectively – as well as with the identification of all gastroenterological patients – Mrs. Teryl Stoneman from the Gastro Office Neath -. A token of gratitude to Mr. John Elias – my mentor and colleague for years – as well as my NHS secretary Mrs. Melissa Powell and my friend Dave Clare for their invaluable support and encouragement throughout this work.

Finally but not least, my deepest gratitude to my family – my wife and my children – who created for me a warm working environment and have accepted with understanding those long hours at night when this research was carried out.

Serban Gheorghiu

PART I - *Literature Review*

Chapter I

INTRODUCTION

Oesophageal, Gastric and Duodenal cancers, but excluding pancreatic and biliary localizations, are commonly grouped and known as Upper Gastro-Intestinal Cancers; they represent a distinctive entity with common epidemiological, diagnostic, therapeutic and prognostic features. The clinical common ground between these topographic entities remains the late presentation and late diagnosis, translated in advanced TNM staging, as well as poor long term therapeutic results after uni- or multifactorial treatment[35;43;45;67;96;102]. These cancers appear to be diseases associated with highly developed countries, in both the eastern and western hemispheres, with evidence that within various regions the lower socio-economic groups are more frequently affected by the disease[25;35;71;113].

The socio-economic and populational importance of these cancers reside in their progressively increased absolute numbers over the last four decades or so[45;67;81;113] with heavy burden onto the health providers, changes in the topographic distribution within the upper

gastrointestinal tract, with adenocarcinoma of the lower oesophagus gaining ground against the more traditional prevalence of squamous carcinoma[42;79;81] and some improvement of life expectancy after radical treatment, but with significant overall mortality and high postoperative mortality rates[34;43;90;128;144].

Despite widespread efforts for quicker diagnosis and treatment, as well as improved surgical and anaesthetic equipment, technique and facilities, the most disappointing revelation by far remains that of the advanced stage of the disease at the time of positive diagnosis. Here, the reality contrasts painfully between Japan and the rest of the world. Whilst the Japanese experience shows "early carcinoma" detection rate in excess of 40%[43], in the US and Europe these figures are well below 30%; for example, over 56% of patients with oesophageal carcinomas are diagnosed in the United States in stages III and IV, which makes curative treatment impossible[35;43]. Bearing in mind this difference between Japan and the rest of the western world, both health providers and medical professionals alike tried not only to replicate the services and methods used by the Japanese counterparts, but also to understand the reasons behind their successes in diagnosing so many cancers in curative stages.

The clinical and pathological importance of the gastro-oesophageal cancers has been discussed in a multitude of studies, all of which invariably show that in Western European countries the diagnosis and management, and as a consequence, the outcome of the

patients with such conditions is far poorer than in Japan[35;43;45]. Over the last four decades or so Japan has leapt forward in the diagnosis and treatment of Upper Gastro-Intestinal Cancers, mainly because of its greater efforts directed at combating these conditions through widespread use of mass screening using double-contrast barium meal and, more recently, using endoscopy. These methods have shown to be very effective in the Japanese setting for diagnosing Upper Gastro-Intestinal Cancers in early stages and, combined with aggressive standardized surgical and adjuvant treatment, offered extremely good 5-year survival rates in excess of 60%[15;45]. Whilst Japan employed during this process both mass and targeted screening procedures, western countries were more reluctant to introduce such measures, mainly because of the consideration given to issues such as incidence, cost and patients' compliance[39;118;127].

As such, the early diagnosis of Upper Gastro-Intestinal Cancers in Europe and North America remains a far reaching dream; it is accepted that the main contributor to this failure is the late stage of the tumour when patients initially present with symptoms[34;35;141;144]. To improve both the staging at diagnosis time, as well as the long term outcome after treatment, most authors agree that two categories of actions should be considered:

a) one category of actions targets the period before the presentation of patients to their doctor, - the so called "incubation" period -; this period of the natural history of the disease (*see Appendix*

A01: Natural History & Defined Intervals) includes both the time when the disease is asymptomatic and the interval when the patients, already symptomatic, fail either voluntarily or involuntarily to make their way to the family doctor. Essentially, most authors agree that Upper Gastro-Intestinal Cancers diagnosis as "early cancer" can be achieved only during this period; here, the Japanese experience made significant inroads by mass screening or, at least, targeted screening of high risk groups. These methods of early diagnosis seem to be the only ones currently available, that can feasibly to be applied on a community-wide scale, at least until other means of early diagnosis become available, such as genetic testing and mapping[93;148];

b) the second category of actions which may improve the diagnosis of Upper Gastro-Intestinal Cancers in early stages, at least on a logical basis, is targeting the segment of the natural history of the disease after the patients seek first consultation; this segment is closely linked with the provision of health care in the primary and secondary care sector[50;79;135] and is mostly targeted by health care providers; the aim is to speed up the patients "journey" through investigations, positive diagnosis, staging and treatment, with the declared goal of speeding up the clinical management as well as improving patients' satisfaction both in the health care system and in the outcome of the treatment of their disease[7;105].

Whilst the diagnosis of early gastro-intestinal cancers during their asymptomatic phase represents the ideal answer to treating this

condition[75;109], with many efforts understandably being channelled in this direction, the second segment of the natural history of this pathology has attracted a lot of interest from clinicians and politicians alike in an attempt to limit the delay between presentation and treatment[4;40;65;67;80]. The efforts made in this respect may vary from country to country due to the structure of their health care system and the perceived popular and political impression of failure in "speeding the patients through the system"[65]. Japan fares best by far, where the mass screening and targeted risk-group screening programs have been in place for decades; with their "walk-in centres" for one-stop consultation and radiological / endoscopic assessment[90], the Japanese medical system is able to limit to a minimum the delays between presentation and positive diagnosis as well as reducing the pre-surgical interval as a whole[90].

In Western Europe the situation is more complicated, with delays occurring in different countries at various levels of the diagnostic and treatment pathway; for example Siewert[90] acknowledged that Germany is delaying their patients at family doctor level with often unnecessary treatment for symptoms like dyspepsia or anaemia instead of referring the patients for investigation; once the patient has been referred, Siewert and Stein[90;144] found that German patients are going through the process of diagnosis and treatment quicker then other European counterparts. In the UK it was found that delays occur both at family practice level as well as at the

hospital level[50;90;96;119;122;137;159]; these findings confirmed the general perception of the population, politicians and medical professionals alike that the British system is slower in diagnosing and submitting patients to curative treatment[4;50;65;90;96;122;139]. It is therefore easily explained why most of the reports related to delays in diagnosis and treatment of Upper Gastro-Intestinal Cancers during the last decade emanate from Britain[66;90;96;137]. However, there is no clear cut consensus amongst British authors as to whether these delays would influence the outcome of these patients and, even if they do, how to improve the situation[90;118;127;135;145;159].

In the absence of nationally funded - Japanese style - programs for mass screening or at least targeted screening, gastroenterologists and surgeons in Britain have tried to find ways to speed up the processes of diagnosis, staging and treatment of these patients. In the last decade many UK hospitals started to use the benefits of Open Access Endoscopy and One-Stop or Rapid Opinion clinics to speed up the process of diagnosis of patients with upper gastro-intestinal malignancies[20;39;60]. Whilst these new methods were introduced initially in the 1980's with the specific aim of eliminating patients' waiting time for an outpatient appointment, soon it appeared reasonable for physicians to use the same setting for reducing the inherent delay in seeing patients with worrying symptoms as well as improving the pick-up rate of gastro-intestinal cancers.

Given the background of worse survival rates in England and Wales comparative with the rest of the European countries for various forms of cancer in general and gastro-oesophageal in particular[33], and given the public discontent in the UK with the continuous perceived deterioration of health care facilities, the UK government has "pledged" to address the issue of waiting times for cancer diagnosis and treatment[80]. To achieve that, the same assumption applied, which is that reduced waiting times will inevitably lead to more rapid diagnosis, earlier instigation of treatment and care, reduced morbidity and increased life expectancy in these patients[40;65;139]. In the UK, with its particular structure of health care delivery, this issue remains controversial amongst medical staff; most clinicians are not sure whether the scarce resources will be wisely used in this way without clear evidence that reducing waiting times from the previous level of 24 days for oesophagus and 27 days for stomach respectively[139] to the target of the "two-week rule" interval would actually improve the early diagnosis in these cancers, and more importantly, would induce an increase in the survival rate as an ultimate goal for such actions[135;149].

The majority of hospitals in the UK are running, in one form or another, services such as Open Access Endoscopy, One-Stop Clinic, Rapid Opinion Clinic, etc.; these services are widely used by the Primary Care sector for referral of patients with digestive symptoms and most of the gastroenterologists consider them a good method to speed up the process of positive diagnosis for cancers; if the health

care professionals have to comply with the government's "two week rule" for cancer appointment, it is important to see if such methods can actually make a difference in the early diagnosis and in the outcome of these patients. It is unclear yet if such methods of referral and diagnosis, besides reducing the waiting time, could actually pick-up cancers in earlier phases and ultimately improve the outcome of such patients.

There is very little information in the medical literature with reference to the effect of these new methods of referral and diagnostic services upon the improvement of early management and outcome of patients with Upper Gastro-Intestinal Cancers alone. Whilst it is at least logical that for these patients the impact of the new services and referral methods on waiting times is beneficial, albeit ignoring their associated costs, it is still unclear whether the evidence supports the "two week rule" with regard to early stage diagnosis and better prognosis of these cancers; it is also unclear whether these services can actually contribute positively to improved outcome for those patients with Upper Gastro-Intestinal Cancers, be this outcome measured in survival ratios, quality of life indicators or indeed patients' satisfaction with regard to their speedy clinical management. Also, in view of the limited financial and infrastructural capacity of the health care providers, concerns have been raised in respect of the "boomerang" effect upon waiting times as a whole due to clogging up the system by increased referral ratios. It is therefore worthwhile to

look to the experience gained in two of such units where these services were in place for a period of time long enough to enable valid evidence-based conclusions.

The aim of this work was to assess the impact of such new services on the speed of diagnosis, treatment and outcome of the patients with upper gastro-intestinal cancers alone. Whilst both the costs associated with the implementation of these services and patients' satisfaction indexes are more complex issues to assess[40] and remain outside the clinical remit of this study, several other parameters and variables might be more feasible to be interpreted, such as the speed of patients' throughput, staging and treatment measures and, not least, outcome after treatment and survival rates. Although there is sufficient quantitative and qualitative data to suggest that the implementation of these services is followed by increased patients' satisfaction in terms of waiting times [80;82;110;121;140], it is important to ascertain whether all these efforts are followed or not by encouraging results in stage levels, operability and ultimately, better survival for these patients diagnosed with Upper Gastro-Intestinal Cancers.

Chapter II

EARLY DIAGNOSIS vs. DIAGNOSE EARLY

Summary: *Based on the medical literature, this chapter makes an attempt to summarize the efforts sustained in diagnosing the Upper Gastro Intestinal Cancers early. After a brief overview of the current situation in gastrointestinal cancer diagnosis, in both the eastern and western hemisphere, the two realities in diagnostic capabilities are examined. This way the dichotomy between "Early Diagnosis" and the "Diagnose Early" aspiration is established. The comparison between Japan and the Western World provide much of the basis for the superiority of the realities and successes of the Japanese setting. The screening procedures so popular in Japan are discussed together with the reasons why these procedures have not taken off in the Western World. Until the advent of genetic mapping and testing through screening programs, other possible strategies were employed in the early diagnosis and these are discussed here; these strategies are based on the expertise gained in clinical settings which were established for general non-specific Gastro-Intestinal pathology. New clinical services such as Open Access Endoscopy is seen as a solution to both decrease in the waiting time and increase the potential benefit in picking up early cancers and improving outcomes.*

Subheadings in this Chapter:

The Upper Gastro-Intestinal Cancers are neoplasms that appear either as primary tumours or as secondary involvement of the oesophagus, stomach and first two segments of the duodenum. In the majority of cases - more than 95% [69;100;108;152] - these cancers are

adenocarcinomas and arise from the epithelial lining of the upper gastro-intestinal tract; they will reflect therefore, subject to certain degree of differentiation, the epithelial tissue they are arising from. Only in a minority of cases are these cancers arising from other structures of the oesophago-gastro-duodenal wall and thus the histological type would mirror more or less these wall structures: sarcomas, lymphomas, Gastro-Intestinal Stromal Tumours, malignant angiomas, schwanomas, etc. With extreme rarity[69;98] and mostly suspected as secondary involvement, other forms of cancers have also been reported in the literature as cancers of the Upper Gastro-Intestinal Tract: melanomas, small cell carcinomas, desmoid and carcinoid tumours, etc.[108;137;152;157]. Due to this incidence, the majority of the studies and series reports incorrectly incorporate all Upper Gastro-Intestinal Cancers under a common name of gastro-intestinal carcinomas or oesophago-gastric carcinomas. Due to their prevalence and despite clear differences between all these cancers, the impact of non-carcinomas upon the statistical results of any study involving large case-mix series is quite minimal. As such, very few studies examining large gastro-oesophageal case-mix will make specific reference to the different forms of Upper Gastro-Intestinal Cancers, perhaps with the notable exception of oesophageal squamous carcinomas and gastric lymphomas[37;98].

The socio-economic and epidemiological importance of these cancers reside in their progressively increased occurrence in absolute

figures over the last four decades or so[45;67;81;113], changes in the topographic distribution within the upper Gastro-Intestinal Tract, with adenocarcinoma of the lower oesophagus gaining ground against the more traditional prevalence of squamous carcinoma[34;42;72;79;81;134] and some improvement of life expectancy after radical treatment, with significant mortality and postoperative mortality rates[34;43;48;90;128;144].

A. Overview

To understand the huge medical and social importance and implications of these cancer localizations it is sufficient to briefly quote the reported incidence and prevalence figures. When cancer mortality is examined on a world scale, gastric cancer ranks second, just below lung cancer, with considerable geographic variation; oesophageal cancer ranks fifth as a cause of cancer mortality; most of these cases occur in the developing countries, with pockets of high incidence in some areas of China, South Africa and Iran.

In Japan the incidence and prevalence of gastro-oesophageal cancer is the highest in the world; it is noted that the prevalence in Japan can exceed 25%[79] making it the number one priority for the national health policy.

In the United States in 1995 alone Daly M. et al.[35] reported through the National Cancer Data Base NCDB an incidence of 12100 new cases of oesophageal cancer and an estimated death toll from this localization of more than 10000 cases. Looking to The American

Cancer Registry, Lambert[79] found an age-specific incidence of gastric cancer in the US of 7.5/100000 cases. This incidence appears much closer to the published European figure than to the Japanese Osaka Cancer Registry data.

In contrast with Japan and the United States, the incidence and prevalence of the Upper Gastrointestinal Cancers in Europe is situated somewhere in the middle. The most authoritative source of data for the European region remains the EUROCARE II Study[23] based upon the EUCAN[1] Database[22;45]. For the period 1978 to 1990 this registry published information on more than 86500 gastro-oesophageal cancers for the population of 17 European member states, underlining the importance of these cancer localizations in comparison with other cancers. However, it is likely though that the number of patients with malignant tumours of the upper digestive tract is much higher, as the database contains only primary tumours and excludes cancers in-situ and lymphomas also. In addition, some country-specific registry reports did not cover the whole population, as is the case of the United Kingdom's registry reports, covering only 50% of its population[45]. Based on this register, Lambert[79] found in Europe for the interval 1983-1990 a crude rate of incidence of 5.7/100000 for oesophageal and 21.5/100000 for stomach localization.

[1] EUCAN Database:1996 estimates, version 3.1(Created 29-09-2000)

In Britain gastro-oesophageal cancer remains a significant health care problem; it causes in excess of 10000 deaths per annum in England and Wales alone, placing it as the fourth and fifth respectively amongst the most common causes of cancer death[1;23]. The Scottish Cancer Intelligence Unit in Edinburgh[24] reported more than 8000 cases diagnosed in a five year period. For the whole of the United Kingdom the EUROCARE II Study[22;23] shows during the period 1990-1996 a crude incidence rate of 11.80/100000 for oesophagus and 16.32/100000 for stomach respectively; the prevalence rates for the UK are for the oesophagus 8.0/100000 and for the stomach 25.7/100000 respectively[79].

A simple look to these rates in comparison with the other European countries shows Britain as having one of the highest crude incidence and prevalence rates throughout the European Union for the oesophageal cancers, with only Portugal, Austria and France trailing it for the stomach localization. It is also easy to spot the trend over a decade, as seen in the EUCAN databases I and II[23], with the decrease in incidence of gastric localization in favour of the oesophageal localization - gastric incidence rates from 21.5 to 16.32 per 100000 compared with the oesophageal incidence from 10.4 to 11.80 per 100000 respectively. The crude mortality rates present similar data, situating Britain towards the bottom of the league in the EUROCARE II Study[23] with mortality rates of 11.48/100000 for the oesophagus and 13.11/100000 for the stomach.

In Wales carcinoma of the oesophagus, cardia and stomach is the fourth most common cause of malignancy[1;114]. For a country with a population of nearly 3 million people, it is sufficient to mention the number of patients registered during the year 1992 at 15816 in order to understand the implications for the health care providers in struggling with the management of these patients[114]. The crude incidence rate of 31.4 per 100000 population ranks Wales worse off than the UK average and well below the European average. Monitoring the incidence rates for a period of 10 years to 1992, Pye et al.[114] found that Wales followed the pattern seen in the rest of the Western World with a slight decrease of the incidence of gastric cancer - 29.8 to 24.9 per 100000 population - and a modest increase in the incidence of oesophageal carcinomas - 9.8 to 13.8 per 100000 population.

Before completing this overview on the current epidemiological data, a word is necessary about the most recent population trends in the world noted during the last two decades in relation with the incidence of the Upper Gastro-Intestinal Cancers. These epidemiological trends are not only mentioned by many reviewers, but also appear to play a more and more important role in the process of diagnosing the patients with Upper Gastro-Intestinal Cancers; also, these trends are currently taken into consideration and have direct implications in the design of various methods of referral or screening, as well as offering variable prognostic significance in assessing an individual's suitability for one or another method of treatment.

One of the most visible trends since the early 1980's was noted as being related to a perceived ever increasing incidence of the oesophageal carcinoma. Many authors[24;25;35;45;51;79;81;111;113;117;134] noted that the incidence of oesophageal carcinoma started to rise in the Western World progressively and sometimes at alarming speed. For instance Daly et al. concluded that the rate of increase of the oesophageal carcinoma in the US may be as high as 10% per annum or from 33% incidence to 43% over a period of 5 years. Similar trends were seen in Europe too[111;117;129;133;142;153].

One statistical observation in respect of this topographic trend is the progressive reduction in distal gastric forms of cancer. Not only in Britain[113;114], but also in Europe,[77;111;130], there are significant reports suggesting a drop in the incidence of distal gastric cancers. Beside the statistical relevance, this trend may suggest that the balance in clinical management and post-treatment morbidity and mortality may have to change in the future.

Although not certain yet, many authors[43;79;154] suggest that this rise may have sociological and behavioural causes such as gastro-oesophageal reflux, smoking and obesity[25;28;154], whilst many others consider that the rise is only relative and due to a progressive decline in the prevalence of distal stomach localizations[45;67;81;113]. However, Okabayashi et al.[109], in contrast to the reports from the Western World mentioned above, found in a large study that the incidence of early cardia carcinoma in Japan was very low and obesity, smoking,

drinking, Barrett's oesophagus or GORD were not related to its occurrence. Similarly, Kitamura[72] found that the chronological changes in gastric cancer patients over the past 27 years have included an increase in the incidence of earlier-staged gastric cancers, which has had a significant impact not only on the ratio of oesophageal / gastric localizations, but also on the improved post-operative survival rate.

Extensive studies[39;54;55;131;154] also raised suspicions in relation to Barrett's metaplasia in the lower oesophagus as being a precursor for carcinomatous changes. The estimated incidence of adenocarcinoma in Barrett's oesophagus ranges from 1 in 52 to 1 in 441 patients years, representing an increased risk of 30 to 125- fold[49]. Although being accepted that Barrett's oesophagus carries a 30-fold to 40-fold increased risk of carcinoma, Van der Burgh[154] found that these patients might not have benefited from surveillance. This is a very significant study showing that most of Barrett's patients he looked at had multiple unwarranted endoscopies and despite these, all but one died of unrelated deaths. Other authors [54;49;158] found the incidence of carcinoma transformation in Barrett's oesophagus much higher, and from here advocated the idea of endoscopic surveillance.

In relation with this increase in incidence of the oesophageal adenocarcinoma, it is important to mention the changing perspective to the cardia as an anatomical region. Here the work of Siewert et al.[77;130;132] and Stein et al.[141-144] is essential in redefining and

reclassifying this segment of the upper gastro-intestinal tract. Whilst many authors consider cardia a separate segment and others include cancers of the cardia with the stomach localization, Siewert introduced the concept of type I, II and III tumour of the cardia; he based his classification on topographical localization of the centre of the tumour in the clinico-radiological studies of the relevant patient; as such, Type III of cardia carcinoma may have much more in common with the fundus of the stomach than with the oesophagus. This classification tends to eliminate the confusion related to the topography of the cardia and paves the way to structured algorithmic approach to the management of these patients based on evidence-based data[129;142].

The different way to classify cancers in this segment under the ICD-9 and ICD-10[1] classification may introduce variations in the case-mix and may be responsible for the change in the oesophageal carcinoma prevalence we have seen in the Western world[111;143;144] over the last few years. However, there are many authors who have expressed reservations in respect of the possibility of establishing accurate topographic diagnosis; the reason used to defend this position was the size of the tumour and the advanced TNM staging of the disease, which may require more extensive anatomical dissection and more extensive oncological security margin.

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[1] International Classification of the Diseases, ver.9 and ver.10

Another important trend to highlight is the slowly progressive age-standardized incidence[52;154]. Although this trend is not as spectacular as the previous one, it may have important implications not only in the diagnostic methodology employed by the health care providers, but also significant consequences in treatment and survival. A few papers[154;156] are already published suggesting that an increased number of patients followed-up in various trials died of unrelated deaths. Although various environmental factors may not be ruled out, most authors agree that this trend may be related with a progressive ageing population. In fact, simply looking at the patients' mean and median age figures reported in various papers, it transpires that the Upper Gastro-Intestinal Cancers affect mostly people in the third generation, whilst being seen quite rarely below the age of 45.

When taking into consideration crude figures, it appears that in most Western countries the mean age at diagnosis is somewhere around 68 to 69 years. One of the highest figure was reported by Barchielli[18] in a large study from Italy where the mean age at diagnosis was quoted as being 70.5 years. Looking at the data obtained from 41 EUROCARE cancer registries in 17 European countries and 9 U.S. SEER registries, Gatta et al.[52] have found that survival declines with the increasing age at diagnosis for most cancers in both the U.S. and Europe, but was more marked in Europe. What is interesting though is that the studies taking into consideration early Upper Gastro-Intestinal Cancers alone[39;43;62;104] are offering much

reduced figures for mean age at diagnosis; as such, in his Japanese series from Fukuoka, Ikeda[62] reported a mean age of 59.9 years and Everett[43], looking at the European papers, found similar figure for early cancers; Everett[43] concluded in his study that patients with early gastric cancer are a number of years younger than those with advanced cancer; this appeared not too surprising as, for those patients deemed unable to sustain any surgical approach, the estimated median duration of early cancers was only 37 months before becoming advanced ones.

These facts raised at least two major questions for clinicians: one is related to the age of the patients submitted to treatment, where their co-morbidities may play a significant role both in designing their treatment methodology and in the postoperative morbidity, mortality and prognosis rates[45;52]; the second question refers to the hypothesis that early cancers are only an initial phase in the natural history of Upper Gastro-Intestinal Cancers [15;43;79;95]; incidental diagnosis of early gastro-intestinal cancers, as well as non-treated cases due to clinical co-morbidities seem to suggest that the asymptomatic period in these cancers' natural history may be in excess of 5 years [43;73-75]; based on the median age difference between early and advanced cancers, as well as on the fact that the results in the treatment of the cancers in early stages are far better, several authors[90;128] suggested that one way to improve the prognosis of these patients would be to move the emphasis from late diagnosis to early diagnosis.

B. Early or Late Diagnosis?

A longstanding aim of the clinician dealing with cancers of the Upper Gastro-Intestinal Tract is that of diagnosing these patients at as early a stage as possible during the natural history of the disease. In keeping with this aim, the concept of early and late diagnosis has been introduced as a potential ticket to curable treatment. However, the problem appeared to be not as simple due to the devious character of cancer as a disease and due to the current diagnostic means applicable on a populational scale. A clear example is the number of asymptomatic patients who are incidentally diagnosed in the advanced stages of the disease, or indeed, the large proportion of patients still diagnosed in stage II and beyond just after the onset of the symptoms. Whilst the term late diagnosis becomes day by day more clearer and unambiguous from diagnostic and prognostic points of view, signifying either a diagnosis established late or in the late stage of the disease - i.e. advanced cancer -, the same does not apply to the term of "early diagnosis". As such, the term Early Diagnosis is occasionally used to mean either the diagnosis was established as soon as possible after the onset of the symptoms - i.e. diagnose the condition early -, or indeed as that of early cancer - i.e. diagnose the condition in early stage -.

Ideally, it would be of great benefit to bring the two situations as close together as possible, whereby an early diagnosis would ensure

the diagnosis of an early cancer. Unfortunately, as real life and statistical data show, this is not always the case. Based on the assumption that, by "diagnosing early", these patients would be at a lower stage of the disease at treatment time, it was a matter of judgement to find ways to obviate the "bottlenecks" in their referral and treatment pathway and try to improve them.

Therefore, before adopting any new strategy to diagnose these cancers as early as possible, both clinicians and healthcare providers need to justly assess in clinical, infrastructural, financial and medico-legal terms the implications and the potential benefits of such strategies in order to achieve the early diagnosis at a stage as early as possible. Bearing this aim in mind, it appears interesting to dissect the connotation of the two entities in Upper Gastro-Intestinal Cancers - Early Diagnosis and Early Gastro-Intestinal Cancer - and highlight the areas of action where the two entities can be forced to come close to each other; in other words, to find a common course of action where the methods employed to diagnose early can actually improve the ratio of early cancers diagnosed. To have a wider comprehension of the importance of issues such as early cancer and early diagnosis and before having an overview of their prevalence in the Western World, it is worthwhile to briefly revisit the topic of late diagnosis as an unfortunate reality of present times.

a) Late diagnosis means advanced cancer

Undoubtedly one of the major disappointments in our daily practice is the moment when we realise that a patient recently diagnosed with Upper Gastro-Intestinal Cancers may have an advanced form of disease which cannot sustain curative treatment. This disappointment however, may turn into despair, depression, sorrow or even denial for the patient himself or his family, although some patients may present a positive approach to the news and actively fight the disease, albeit with little hope of survival. The advanced form of cancer of the gastro-intestinal tract painfully translates the reality of late diagnosis, irrespective of the incriminated cause of delay. Most of the time late diagnosis and advanced cancer go hand in hand. This is due to the length of time elapsed between the moment of the first carcinogenetic changes that escape immunologic suppressive control and the moment when the diagnosis is established, when the Muscularis Propria is penetrated by the tumour and/or dissemination occurred.

Due to the devious character of this condition, much of the beginning of the growth process takes place "behind the scenes", quite insidiously and with or without minimal symptoms[96;122]. It is this period of the natural history of the disease which is the most suitable for curative treatment. Once this opportunity is lost, the tumour growth penetrates and invades structures of the gut wall and/or

disseminates through blood or lymph channels, becoming advanced cancer.

Several studies attempted to establish what length of time is needed for a cancer to become advanced. This was a difficult task, but essential in establishing the "plâge" of interaction between disease and the measures or actions to be taken to establish an early diagnosis. The "in vitro" laboratory results are not always confirmed by "in vivo" clinical observations. Based on laboratory results, many authors agreed with what appears to be the "doubling time" of a tumour; although variations can occur from tissue to tissue and indeed, from individual to individual, it appears that it will take approx. 12 weeks for a tumour to double its size[56;74;75;94]. However, it is still not clear yet what happens in this interval with the other feature of cancerous cells, which is that of dissemination through blood / lymph channels.

The situation is less clear on clinical grounds. The difficulty resides in the ethical approach to such studies by the impossibility to create randomised trials. However, several studies[43] have been released where some patients diagnosed with early cancers were not submitted on clinical grounds to the surgical therapeutic algorithm. Based on these types of observations, it has been postulated that it may take approx. 37 months for a tumour to grow from the stage of early cancer to the stage of advanced cancer. Other studies[56;74;75] have postulated that the rate of doubling is variable; whilst early gastro-intestinal cancers appear to have a doubling time between 1.5 and 10

years, the advanced gastro-intestinal cancers might have a much shorter period of doubling, between 2 months and one year. In fact, these clinical observations go hand in hand with the paradoxical observation whereby the longer the symptomatic history is, the more likelihood there is of diagnosing a less advanced form of gastro-intestinal cancer[90;118;127].

Although the interval early - advanced cancer sequence is only observational, there may be a multitude of variables which may influence the growth process from case to case: age, gender, hormonal status, environmental factors, nutrition, immune defence, etc. Beside the importance of such studies showing the length of time before which a tumour's chance to be treated curatively diminishes considerably, these studies also highlight the interval of time where positive diagnosis is delayed for one reason or another.

Both physicians and healthcare systems are adopting a self-confessed criticism when assessing the crude reality of advanced cancer. Whilst Japanese reports sound much more optimistic, with continuous decreases of cases in advanced stages, the Western experience is plagued by far poorer results. In Japan the *ratio early vs. advanced cancer*, - i.e. T_0+T_1 vs. $T_2+T_3+T_4$[1] cases, where T represents the Tumour and the indexes represent the degrees of penetration of

[1] Stages of the Tumour as defined in ***TNM Classification of Malignant Tumours (UICC)*** (Paperback), Union Internationale Contre Cancer, Geneve, Switzerland, 1990

the tumour within the wall of the viscuses concerned -, is continually increasing, based on increasing numbers of early cancers diagnosed.

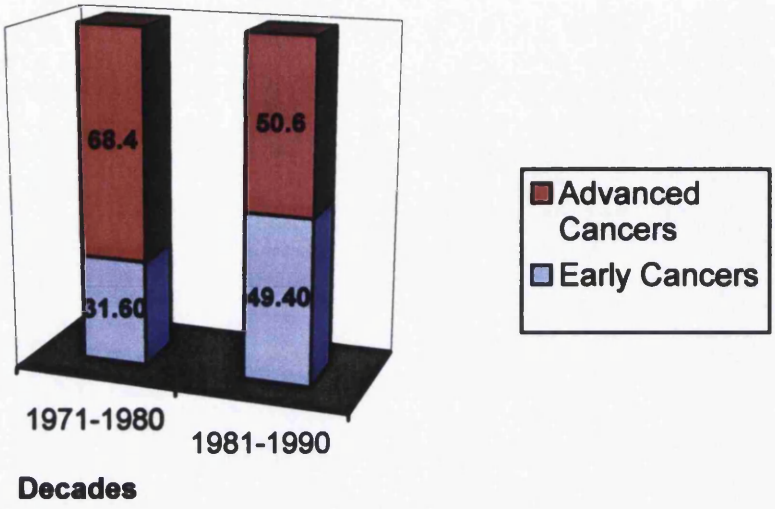

Fig. 2.01 - The Incidence of Early and Advanced Cancers in Japan[1]

There may be many reasons behind this situation and they include not only the provision of healthcare services as a response to a clearly populational health problem, but also individual factors such as public awareness, genetics issues or indeed the genetics of the tumours in the Japanese population. Many papers highlight this diagnostic trend[10;62;72;90;151] and the work of Ikeda et al.[62] clearly shows this reality (Fig. 2.01).

In the Western World late diagnosis and implicitly advanced cancer diagnosis is unfortunately the norm. In the United States around 56% of all cases of Upper Gastrointestinal Cancers diagnosed are in stages III and IV according to the TNM Classification, whilst

[1] Courtesy of Ikeda et al., Br. J. Cancer62

stages 0 and I (i.e. T_0+T_1 and N_0) are found in less than 40%[35;138]. In Europe the situation is not much better with early cancers diagnosed in between 15% to 26% of all cases, but these figures refer to surveillance protocols[118]. There is no perceived evidence that symptoms or localization play a role in late diagnosis, however if cumulative conditions are considered such as staging, medical co-morbidity, nutritional status, etc, then it appears oesophageal cancers as being less favourable in their presentation and subsequent offered therapeutic possibilities [96;122].

At first glance, in Britain the situation appears much worse due to very poor figures offered by the EUROCARE II study[22;23] in respect of outcome and survival rates. Until recently both oesophageal and stomach cancer were regarded as fatal conditions due to the stage in which the diagnostic and treatment was instituted. Martin et al.[90] appreciated that, when finally the diagnosis of cancer of the Upper Gastro-Intestinal Tract is established, this is late and surgery is less extensive than in Japan. He postulated this purely on evidence grounds, although the authors acknowledged that the situation is largely due the more advanced age of the patients in Britain as well as the more advanced staging of their disease[90]. He also noted that, even with his hospital being a tertiary centre for referrals, the unit was still diagnosing more than 80% of Upper Gastro-Intestinal Cancers in stages II, III and IV where curative treatment is not achievable. Similarly, Renehan and Tweedle[118] found that up to 74% of cases in

their experience are diagnosed as advanced. More depressing still, Mikulin et al.[96] found that in their experience only 13% of patients were diagnosed as early cancers.

In Wales there were several reports showing the high rate of cancers presenting beyond surgical possibilities. Pye et al.[114] found that only a third of cases in his Welsh review were suitable for resection and the CRC database[23] for England and Wales showed a high rate of advanced cancers putting the Welsh figures well below the European average[1].

It is therefore possible to say that, particularly in the case of advanced cancer of the gastro-intestinal tract, late diagnosis may be regarded as a failure of the system, which is inefficient in its approach to the diagnosis and treatment of the malignant process; be it from an educational point of view or indeed due to the absence of implemented pathways and methodology to pick-up cancers at an earlier stage, it is the healthcare system which is blamed for the poor results.

Due to this unacceptable incidence and outcome, no wonder that a strong alarm signal has been raised recently for Britain to improve the current situation. The topic was embraced both by patients' groups and politicians alike and recently came more to the centre stage of the politico-social debate. Whilst many accept that in Britain the number of cases diagnosed as advanced is higher and the survival somehow poorer than in the rest of Europe[22;23;65;135] due to several factors such as patients' late presentation, reduced public

awareness of non-specific symptomatology and absence of alarm symptoms in the early stages of the disease, the causes of this situation and the answers to this problem are not so clear. Some authors[65;135] consider that the principal cause is the under-investment in the healthcare infrastructure and the services for health provisioning, including targeted screening and adequate public awareness campaign, whilst others[90;96;127;145] raise questions regarding the delay in diagnosis as the main cause for discrepancies between the healthcare systems[7;140].

Nevertheless, many clinicians were ready to accept both explanations and, whilst the financial side of the argument was left to the politicians and health managers to deal with, the clinicians started to introduce clinical services and innovative methods of referral, as well as algorithms for diagnosis of Upper Gastro-Intestinal Cancers in an attempt to establish the this diagnosis earlier.

b) Early cancer is the ideal stage for diagnosis

Early Gastro-Oesophageal Cancer was defined as a diagnostic entity by the Japanese Society of Gastroenterological Endoscopy in 1962 as the adenocarcinoma confined to the mucosa and submucosa, irrespective of lymph-node involvement. The starting point for this definition was based on the observation that these cancers have a more favourable prognosis. The detection of early cancer in gastro-intestinal localization is currently common in the majority of the

Japanese hospitals and the rate of the early cancer detection exceeds the 50% mark. This process has apparently contributed the most to the improved postoperative survival rate and this observation has been unequivocally acknowledged by physicians worldwide[72].

However, this definition may be contradicted by the current observations whereby one paramount criterion for prognosis remains lymph-node involvement. Indeed, many authors[8;57;61;72] have reported that lymph-node involvement, and particularly the topography of the lymph-stations affected, represent the most important factor in assessing the postoperative prognosis[57]. It follows that, at least in a few cases reported as early cancers according to the Japanese definition but with lymph-node dissemination in stations 6 to 13, the prognosis may be translated more closely to an advanced cancer rather then an early one. In fact, the classification issued by the UICC[1] considers the involvement of these lymph-node stations as loco-regional dissemination and assigns, based on prognostic factors, advanced stages II or indeed III as staging of the disease. Based on these observations, particularly linked with the outcome issues, the question arises as to whether we should use the term "early cancer" for cases diagnosed as invasive to the submucosa only and overlook the lymph-node involvement or, indeed classify the extent of cancer involvement clinically and based on prognostic criteria[61]?

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[1] Union Internationale Contre Cancer, Geneve, Switzerland, 1990

In contrast with Japan, the Western World does use the TNM classification issued by UICC which takes account of both T size and N category of lymph-node dissemination. According to the TNM Classification of Cancers, stage 0 and I are made up solely of T_0 and T_1 categories, but only as associated with N_0 dissemination. As such, this observation may be only one of the explanations as to why the rate of detected Early Gastro-Intestinal Cancers is higher in Japan than the rest of the Western World.

Another factor which may play a very important role rests on histo-pathological grounds: whilst Western pathologists disregard mild and moderately dysplastic lesions as cancers, Japanese counterparts include these lesions as well[15;57;126;151], with the obvious consequence of an improved index in respect of nearly all of the parameters considered; for instance, once recorded as cancers and operated upon, these cases may actually improve significantly the statistical overall figures for morbidity, mortality, survival and quality of life issues. Schlemper et al.[126] concluded in their histo-pathological study that the difference in diagnostic practice may contribute to the relatively high incidence rate and good prognosis of superficial carcinoma in Japan. However, Kitamura et al.[72] is reporting as a " like for like " example that stage I gastric cancers are diagnosed in Japan in excess of 54%, whilst the Western experience does not go beyond the 20% figure[17;43]; Kitamura also demonstrated that gastric cancers are being diagnosed earlier in Japan, even within the same stage of classification. It

appeared that in the Japanese settings the incidence of lymph-node metastasis has decreased in Stage II patients and the depth of invasion has become more superficial in Stage II patients. On epidemiological grounds it is difficult to interpret this trend otherwise than accepting that these cancers are diagnosed at an increasingly early stage when lymph dissemination still does not yet occur.

Having said all that, one fact is widely acknowledged: it appears that the Japanese patients are diagnosed at an earlier stage in the Gastro-Intestinal cancers' natural history compared with the Western patients and their overall outcome such as mortality and 5-year and 10-year survival ratios are better[13;17;43;63]. The importance of diagnosing an early cancer is paramount. It relies upon several factors with proven track record in the medical literature. Firstly is the fact that due to the natural history of these cancers, the patients tend to be younger and fitter and thus suited to multi-modal treatment, including D3 type of surgery[43;72]. Secondly, the depth of invasion is much reduced[72;104] and lymph-node metastasis is likely not to have occurred yet[72]. Thirdly, the postoperative morbidity and mortality tend to be much reduced[151] and, more importantly, the 5 and 10 years survival rate is in excess of 54%[15;43;72;104].

Many authors have described the just balance in the infra-structural provisions of the healthcare system in Japan, based on the existence of mass screening programmes for the high risk population, particularly employed people, and backed up by "walk-in centres" with

on-the-spot Barium Meal or Endoscopy facilities for patients presenting any gastroenterological symptoms[90]; on top of this, particularities such as the Japanese speediness of the results-reporting process, direct referral to the tertiary centre - including the by-pass of the General Practitioner link - and the wide availability of space in the specialized centres have contributed to the implementation of a very short delay between the presentation and treatment. Beside the human and financial cost put in place to create such a network, the improvement in the general awareness of the population for gastro-intestinal malignancy induced by educational programs has also contributed towards an improved compliance with the rigour of the gastroenterological diagnosis algorithm and consequently better results translated by a better pick-up rate.

No wonder that due to such of an extensive network and continuous learning curve over the last three decades, in Japan the balance has tilted in favour of diagnosing the cancers of the Gastro-Intestinal Tract in early stages, reaching a ratio of nearly four to one for early stage cancers. As a consequence of this approach, many Japanese papers[72] currently report rates in excess of 60% of early cancers diagnosed during the last decade, although some tertiary centres may report figures aiming for 90%[151]. The consequence of such exercises is automatically translated in several results which may be the envy of the whole world: the age of patients reported by Japanese authors appear to be lower than the Western patients, somewhere

between 59 and 64[43]; also, the postoperative morbidity and mortality is amongst the lowest in the world with figures for mortality around 0.6% to 2%[39;72], although Japanese surgeons are renowned for their surgical aggressiveness in lymph-node clearance during their D2 and D3 types of gastrectomies; and most of all, the survival rate at 5 and 10 years is the highest in the world[9;86;103]. To this results may contribute not only the more favourable staging at diagnosis time, but also possible different structure of patient group such as different age bracket, co-morbidities, reduced obesity ratios, etc.

Having said that, the statistical figures from the Japanese National Records show that the incidence of early Gastro-Intestinal Cancers rose year on year from 40% in 1985 to more than 60% at present[43;72]. This trend was also mirrored by improved figures for 5 and 10 years survival. Not only the Japanese trend in diagnosing more and more early Gastro-Intestinal Cancers was responsible for better post-therapeutic survival rate, but also, as Kitamura et al.[72] suggested, the perceived trend of gastric cancers to be diagnosed in more superficial and small-sized form, as well as less frequent lymph-node dissemination contributed to the result. Many authors however, accept nowadays that the improved survival rate in Japan is largely due to the process of diagnosing early cancer, although constant use of more aggressive treatment protocols might be responsible for this effect as well[43;72;104]. It may well be that, based on the natural history

of these cancers, an early cancer does not have the time to produce distant lymph-node metastasis.

However, the Japanese approach to the issue of diagnosing early cancers appeared highly impractical to both physicians and healthcare providers in the Western World[42]. There were many reasons which counterweighted the balance. Firstly, it has been accepted that, based upon the incidence rate of gastroenterological cancer and in contrast with other cancers such as breast, lung or colorectal cancer, the Gastro-Intestinal Cancer pathology cannot be considered more important than other conditions which might gain greater benefit from the energy and financial resources spent by the system. Another viewpoint refers to the number of patients with Upper Gastro-Intestinal Cancer who will actually be submitted to radical treatment compared to the number of newly diagnosed cases; however, it is suggested that the increase in the ratio of early cancers diagnosed may be subsequently followed by a higher operativity ratio which, as a consequence, may backup the spiralling costs of treatment infrastructure. Secondly, the spectrum, prevalence and dynamics of Gastro-Intestinal Cancer pathology makes the increase in infrastructure provisions impractical and also raises some questions in respect of the balance between results obtained and staffing requirements[32;39;123].

It is no wonder then why none of the Western countries have implemented the Japanese model and introduced services compatible

with mass screening, limited screening for working population, walk-in centres and fast-track treatment in tertiary centres[90]. With its infrastructure in place and appropriate dissemination of guidelines and pathways of care, Japan is prepared, better then anyone else, to absorb the burden of an expected 25% crude incidence rate of gastro-intestinal malignancies[79].

One entity, particularly pertinent to gastric localization, was recently much debated and needs to be mentioned. It was named by the Japanese researchers as "mp cancer" or Muscularis Propria carcinoma[104]. It is agreed that this form of carcinoma is an intermediate form between early cancer and advanced cancer. Nakamura et al.[104] looked at this entity from a pathological point of view and found that the overall parameters like resectability, mortality, and survival rates are very similar to the results obtained in early cancer treatment; this was a surprise since, if strict definitions criteria are being applied, the "mp" cancer as a pathological entity may belong to the advanced cancer rather than early cancer due to the penetration of the Muscularis Propria layer.

Leaving aside the hypothesis, not proven yet, that patients diagnosed with early cancers may have a totally different type of cancer[43] and to achieve results similar with the Japanese figures, one would need to look to other options such as: methodology and speed of diagnosis, aggressiveness of treatment and quality of "after care" settings. These options bring us to the current reality which is the

attempt to pick-up early cancers by trying to diagnose them early after the onset of the symptoms.

c) "Diagnose Early" is what we aim to do

The issue of methodology and speed of diagnosis introduces the second face of the early diagnosis issue, which is the "diagnose early" option. Due to the higher costs, patients' compliance and required infra-structure necessary to be implemented to achieve the "early cancer" diagnosis in the pre-symptomatic phase of cancer development, the "diagnose early" approach was considered, by many at least, an interim way of aiming towards diagnosing cancers in early stage - i.e. as early cancers[15] -. This approach was based on the logic that throughout their natural history these cancers would evolve from a small, containable lesion, to a much larger and certainly disseminated disease. Several reports[15;43] back up this hypothesis by observing the time lag between diagnosis and death in cases with early cancers which for one reason or another were not submitted to radical treatment.

An important role in advancing the hypothesis that the "diagnose early" approach may shorten the natural history of the disease is also offered by the laboratory results; after researching the doubling time of tumour cells, which is translated on clinical grounds by the calculation of the time taken by the tumour to double its size, it was postulated according to some research that a "diagnose early"

approach in these cases would obviously submit patients to the multi-modal treatment in earlier stages where the results may be more acceptable.

The conclusion which transpires after all these studies is the one that every day lost in establishing the positive diagnosis of Gastro-Intestinal Cancer takes its toll on the stage of the disease with which these patients are found at treatment time and with important consequences upon survival chances. It is this conclusion which triggered the interest given to the issue of delay in diagnosis and treatment and perhaps the reason why certain innovative modalities of referral and services were introduced to tackle this matter. It must be added though that the patients themselves contributed also to this imperative by voicing their expectation to be treated quicker. In an attempt to diagnose these cancers early, medical professionals and healthcare providers tried to find ways to speed up the "journey" these patients face through the referral, diagnosis and treatment pathway. Various organizations contributed to the debate and several areas were identified where the speed of patients' management could be optimised. Pressure has been put on the health care providers and medical staff to improve the delivery of improved waiting times to diagnosis and treatment for those patients suspected of developing malignancies.

Based on the assumption that through "diagnosing early" these patients during the natural history of their disease, one can lower the

cancer stage at diagnostic time, it was a matter of judgement to scrutinize the delays in diagnosis and treatment and their causes. Although some authors voiced their concerns[65;135;149] that this approach is not entirely researched and bringing the diagnosis forward by weeks rather than months is not necessarily increasing the numbers of early cancers diagnosed, health providers in Britain increased locally the funding for the provision of the diagnosis sequence in an attempt to please both sides of the argument. However, in the absence of hard core evidence that certain measures, services or educational programmes may actually increase the absolute figures of early cancers diagnosed, the increase in funding was unstructured and without a major redesign of the upper gastro-intestinal service. It involved new but fringe measures such as contractual allocation of programmed activities for multi-disciplinary assessment of cancer patients or indeed moderate infra-structural expansion of services implicated in the diagnostic algorithm.

The issue of delays in the diagnosis and treatment of cancer in general [29;47;139] and gastro-oesophageal in particular[114] is monitored closely by every medical community, although it seems it has become more recently a prominent political and social awareness entity in Britain, where it goes hand in hand with the debate of adequacy of the financial and infrastructure provisions.

C. Strategies to diagnose early

Most of authors nowadays believe that one of the potential keys to improve the outcome of those patients with Upper Gastro-Intestinal Cancers is to practise "early diagnosis", i.e. to diagnose as early as possible either any lesion which may progress to full blown cancer or, even better, to pick-up those lesions which are at risk of developing such a dreadful disease before any carcinomatous change takes place. It is also aired that a very important step supporting the latter action would be genetic mapping and testing[83;94]. Until this method of diagnosing early gastro-intestinal cancers becomes clinically and epidemiologically feasible and widely available, clinicians have put to use other methods which tried to pick up cancers in early stages. These are mass screening, targeted screening of certain groups of individuals and other methods attempting to speed up the patients' diagnosis and treatment.

a) Genetic testing strategy

The hypothesis that the Gastro-Intestinal Cancer has a conditional genetic occurrence was long debated. Advocates of this hypothesis showed in many studies that Eastern immigrants, such as patients of Asian origin in the United States, maintain their statistically increased risk of gastric cancer even after a long period of time spent in the Western World[28;148]. In addition to this, many studies have shown that, for the same stage of the disease, Japanese patients

seem to live longer than their Western counterparts, with a significantly higher percentage of 5-year and 10-year survival ratios[15], even if this result may be influenced by other factors, such as more aggressive surgical approach and better designed aggressive adjuvant therapies in Japan[90] comparative with the rest of the Western World. Also, it has been observed that the prevalence of early-stage cancers diagnosed in Japanese setting appears to be higher than in the Western World, although a few authors tried to find a reasonable infrastructural explanation for this conclusion, such as the effect of mass and/or targeted mass screening policy and differences in pathology reporting pattern, with Japanese pathologists considering severe dysplastic lesions as early cancers[15;109].

Based on the above observations, many authors suggested that Japanese patients may have a different gastro-oesophageal cancer altogether[83;94]. From here to the genetic hypothesis of carcinogenesis was only a small step to be considered. McCulloch et al.[92] looking to the genetic expression of cancer cells in Japanese and British patients concluded that there are certain similarities; for instance, they found similar molecular genetics, including p53 expression[94;132]. However, a significantly greater proportion of tumours in Japanese patients expressed the "anti-metastasis factor" mm23, whilst the mean proliferating cell nuclear antigen index was quite reduced[83;94]. Although further studies are needed to compare tumours between Eastern and Western patients and to define genetic differences[94], one

thing becomes clearer: the diagnostic pathway for oesophago-gastric cancer, with special emphasis on early diagnosis, has to move from the clinical setting to the preclinical and genetic means.

Once the genetic features of these cancers are known and in particular if the genetic risk of developing these cancers in an individual can be assessed, the diagnosis of upper gastro-intestinal cancers can be brought forward from the current clinical phase. Under these circumstances it is believed that the screening process for such conditions will be much improved, perhaps narrowed through targeting towards high risk groups, with the expected end result of diagnosing these cancers in early, subclinical stages. The aim is not unreachable as very good results have already been obtained in Britain in various other forms of cancers where the "genetic stamp" was deciphered to a certain extent, such as in certain forms of colon cancer in FAP patients or certain forms of breast cancer.

Until such time, it was necessary to design other methods and strategies which may help clinicians to diagnose these cancers early, preferably at a stage as close as possible to the early cancer.

b) Mass-screening & targeted-screening programmes

These are almost exclusively the feature of the Japanese medical system. With its high incidence and prevalence of the disease, Japan spared little cost in the early 1960's to set up a national network of centres which were dealing exclusively with the upper

gastro-intestinal localization of cancers. These were not only therapeutic secondary and tertiary centres, but also units dedicated to the early diagnosis of these clinical entities. In parallel, Japanese health authorities funded national programs for active screening to help identify those patients carrying the disease in an as early stage as possible[18;62;90].

Like any new programme that rolls out on a national basis, the aim was initially to include certain groups or sections of the population. The term "targeted screening" was born based on the initial impossibility to start screening the whole population and relied on several epidemiological features such as age standardized groups[12;147], profession related cohorts such as it was the case of fishermen, second generation of Hawaiians emigrants, etc. Following the assessment of the initial results, targeted mass screening was extended to the rest of working population. The rational behind this approach was observational and relied on the age corrected incidence of the disease amongst Japanese patients[99;108]. The modalities of screening at the beginning included Double Contrast Barium Meal techniques and Japanese radiologists became masters at identifying the various types I,II and III of gastro-intestinal cancers[79]. With the advances in endoscopy from technical and skills points of view, the accent has moved from the early 1980's to this method of investigation which allows for direct visualization and tissue diagnosis

as well. It must be said however, that targeted screening was only one face of the coin.

As targeted screening cannot cover the whole of the population, a different approach was introduced for patients who became symptomatic. This way the "walk-in centres" or the "one-stop units" have been born where symptomatic patients could benefit "on the spot" from a radiological, or more recently, an endoscopic examination. To shorten the time taken to definitive treatment, these centres had the facility of by-passing the patients' general practitioner and offering direct referral to secondary or tertiary units specialized in upper gastro-intestinal pathology. As a consequence of these facilities and supporting infrastructure, the number of cases in early stage had progressively increased in Japan and the outcome and survival figures have subsequently improved considerably.

Several authors have questioned the possibility to import such an approach to the Western World[16;26;93]. Whilst the Japanese model was not questioned as to its reliability and potential to guarantee better outcome figures, there were several stumbling blocks that prevented western health providers embarking on the same road[79]. The first reason was related to the compliance of the population at large with such of an invasive examination which was supposed to be done on a regular basis at certain intervals. A second reason was purely economical and related to the financial burden associated with creating the necessary infrastructure and staff requirements. Another

option taken into consideration was that of a targeted screening of certain age groups where the disease is more prevalent or where there are risk factors associated with a benign condition such as GORD or Barrett's[31;116;131;150;155]. After examining a cohort of 92 patients for epidemiological, pathological and clinical features Koea[73] recommended that, based on the high frequency of a positive family history in young patients, an opportunity exists to identify a high-risk population for screening. This strategy was found to have limited value by MacDonald who suggested that it might be appropriate to restrict surveillance to patients with additional risk factors[76;79;85]. Rana et al.[116] reached at the same conclusion in his Scottish study; he found that endoscopic surveillance is unlikely to alter overall mortality even in certain high risk group of patients such as those with Barrett's oesophagus[154].

c) Improving healthcare provision - algorithms & services

The Japanese experience with walk-in centres highlighted the need to identify services, resources and algorithms which may help western clinicians to replicate this model to a certain extent and, what is more important, achieve better results in the early diagnosis of Gastro-Intestinal Cancer. Since mass screening is not yet feasible as an option because of the reasons cited earlier, western health care providers and clinicians alike have given consideration to alternative methods by which they can achieve similar results, but within the

existent infrastructural and financial constraints; their attention was focused on the introduction of mechanisms suitable to speed up the management of these patients from the moment they became symptomatic to the definitive treatment. One of the first methods to be used was the Open Access Endoscopy which initially was employed to lower the waiting time in gastroenterological patients at large.

Open Access Endoscopy systems - those in which endoscopy is performed without prior gastroenterology consultation - have become more common in the cost-conscious healthcare environment, sparing doctor-hours of activity and increasing throughput of symptomatic patients. It must be mentioned that the open access service had both its advocates and opponents. Health care providers, pressurised to achieve higher throughput and shorter waiting times, embraced the idea as a solution to public discontent in waiting times. The signals coming from the opposition side were technical and related not only to the financial costs[123] - sometimes difficult to assess accurately - and time consumed associated with inevitable high ratios of inappropriate referrals[30;81;87;125], but also related with the diagnostic yield of upper gastrointestinal endoscopy[53;58;70].

Irrespective of the benefits or the difficulties in introducing Open Access Endoscopy systems in the clinical practice for patients at large, one benefit seen by many clinicians was that one of speeding up the sub-group of patients with symptoms suggestive of malignancy. It has been agreed by many gastroenterologists[14;146] that Open Access

Endoscopy is a useful tool in accelerating the diagnosis of gastro-intestinal cancer by several weeks or even months. Several authors reported various results with their experience in delivering Open Access Endoscopy services to the Primary Care sector and, besides discussing the issue of appropriateness in referral, emphasized the benefits in diagnostic yield. However, most of the authors agree with the view that Open Access Endoscopy has a self-limiting yield in cancer diagnosis. It has been noted that the pickup rate of cancers in centres serving a certain catchment's area has not changed with the use of these services and remained roughly similar with the pre-Open Access Endoscopy era[32;53;146].

One question persisted and this was related with the stage of the cancers diagnosed within those settings. The Axon group in Leeds[15;43] reported a favourable change in the proportion of patients with early lesions and the authors attributed this to the more frequent use of endoscopy, particularly as a result of Open Access Endoscopy. There were other authors[32;146] who looked to their own practice and found no increase in the number of stage 0 and I picked up at Open Access Endoscopy. They acknowledged however that certain advantages of Open Access service appear to be compromised by delayed referral to hospital by the responsible General Practitioner and, in some instances, the failure of the endoscopists to recognize some lesions with early kariochinetic transformation.

There are two questions that may arise in relation to the facts mentioned above: one refers to the capability of the Open Access Endoscopy service to speed up the referral process, the positive diagnosis and the treatment of patients with Upper Gastro-Intestinal Cancer; the second question relates to the benefits induced by the increased speed with which cancer patients are seen and examined in the Open Access service compared with the traditional referral method.

Many papers[65;79;139;149] dealt with the answer to the first issue. The overall agreement was that the Open Access Endoscopy and related clinical services can bring a significant improvement in the speed with which patients are being examined, but this is subject to certain limitations, such as appropriate referrals, selection of urgency criteria based on "alarm symptoms", infrastructure capability, etc. In a retrospective study Spurgeon[139] found in England significant differences between the waiting time for urgent and non-urgent referrals. Although the median time to the first appointment seems to be acceptable - 10 days for urgent referrals and 27 days for non-urgent requests -, the time needed to see 90% of all patients is much longer - 70 days for the stomach localization and 57 days for oesophageal topography of tumours -. These figures may need to be discussed in the context of the definition for urgent and non-urgent referrals; it is believed that urgent referrals are related to those cases that bear the hallmarks of definitive malignancy such as findings at

clinical examination, association of sinister symptoms or indeed epidemiological criteria; as to the non-urgent ones, these cases may represent actually the group of patients who may have benefited mostly from the offerings of Open Access Services. As to the time taken by patients to receive definitive treatment, this is much longer, rising to a median figure of 75 days and 65 days respectively.

One issue which attracted much attention was that one of the referral criteria. It has been noted that approximately 30% of referrals to the Open Access Endoscopy service refers to dyspepsia and, since dyspepsia is seen as a symptom in many cases of Upper Gastro-Intestinal Cancer, it was this symptom which was chosen for modulation of the referral threshold[32;79]. Some authors added age group as a limiting factor to dyspepsia as a symptom, in an attempt to modulate the imbalance between referral volume and diagnostic yield; this was based on the observation that less than 3% of gastro-intestinal cancers are diagnosed below the age of 45. Christie et al.[32] concluded that the age limit for screening patients with uncomplicated dyspepsia can be raised even to 55 since only 7.8% of dyspeptic patients aged under 55 in their cohort have been diagnosed with cancer.

When issues such as referral volume, cost effectiveness of endoscopy and diagnostic yield are put together, the need to have guidelines for referral of patients to an Open Access Endoscopy service becomes stringent[36;125;136]. Most of the UK secondary care centres have

in a more or less structured form guidelines which assist the primary care sector in the task of filtering patients through the correct channels. These guidelines are elaborated in conjunction with the existence of the so-called "alarm symptoms" - these are symptoms recognized by clinicians as being highly associated with Gastro-Intestinal cancer, such as anorexia, weight loss, newly diagnosed dyspepsia or anaemia -. Although there is some degree of variation between centres, in general there is a common framework within which these guidelines operate. The British Society of Gastroenterology has already issued guidelines in an attempt to improve the functionality of the Open Access Endoscopy service and to respond to the variations in service provision seen in many units[87;136;145]. It is only fair to briefly mention that there are some authors who dispute the effectiveness of channelling patients based on guidelines to open access services and consider these guidelines a "waste of energy"[135].

If the answer to the first question related to the benefits seen in the waiting times to diagnosis by using the Direct Referral services seems to be more apparent, the answer to the second question as to whether Open Access Endoscopy can bring real benefits in the diagnosis and management of Upper Gastro-Intestinal Cancers as a consequence of speeding up the process of examination, diagnosis and treatment of these patients is more controversial and is dealt with in the next section.

Chapter III

DELAYS

Summary: *This chapter describes the areas where delays can occur in the management of the patients diagnosed with Upper Gastro-Intestinal Cancer. By looking at the medical literature, the first part defines issues such as onset delay, delay in referral, or delay in treatment. In the second part reference is made to a few papers that seem to quantify various intervals of delays. From here it is established that the delay the patient face from the onset of his symptoms to treatment is in the range of 6 weeks to 17 weeks. It has been established that for part of the length of delay the patient himself is responsible, whilst the health care provider for around 70%; other authors place more emphasis on patient's related delay. The end of the chapter shows that, whilst the reduction in waiting times started to be documented in the literature, there is very little indication as to the benefits of reducing waiting times on patients' outcome; it is explained that the role of this study is to fill up the gap in bringing to light any evidence which relates the innovative clinical services and waiting times reduction to the effect on outcome and survival of these patients.*

Subheadings in this Chapter:

A. Delays @ the onset of disease
B. Healthcare sector induced delays

I have looked earlier to the potential measures taken by the medical community at large to diagnose the gastrointestinal cancer earlier as the only key to better prognosis for these patients. This approach to "diagnose early" issue brings us to the concept of delays in diagnosis. These delays are important because cancers grow continuously, albeit at a variable rate. Decreasing the interval between onset of symptoms and treatment should logically result in tumours diagnosed at earlier stage and with better potential for cure. It is

therefore important to pinpoint the time segments where the delay in diagnosis and clinical management can occur and examine the possibilities and actions available to facilitate early diagnosis of these cancers.

A. Delays @ the onset of disease

There is a general consensus throughout the scientific community that, at least at the present time, one way to improve the poor prognosis of those patients with Upper Gastro-Intestinal Cancers is to diagnose these cancers as early as possible. This represents the so-called "Japanese Gold Standard" and is an approach much sought after both by medical professionals and health providers alike. But how to achieve this? How to earmark those future individuals at risk of developing cancers with this localization? How to diagnose early carcinogenetic changes in the mucosa of upper gastro-intestinal tract during the asymptomatic phase in these individuals? What are the implications for the health care systems and patients alike the process of using various methods of cancer detection currently available? Given the natural progression of an Upper Gastro-Intestinal Cancer and since the majority of well known symptoms appear usually late or after the disease became quite advanced, many authors are accepting nowadays that a certain degree of diagnostic delay[122] might be unavoidable. However, what actually would be an "acceptable" time interval between onset and treatment is much more difficult to

answer. Various studies[90;96;122;159] tried over the last decade to look to the issue of delay in diagnosis and treatment through various clinical hypothesis such as: onset symptoms, referral patterns, socio-economic and environmental issues, staging, treatment modalities and outcome.

To answer these questions it is imperative to obviate which are the segments where delay may interfere with a speedy diagnosis and treatment. Many authors[96;122;159] agree that based on primary cause, delays in diagnosis occur firstly due to late presentation of the patient and secondly indeed due to the health care setting. Although the literature names these delays or intervals with various terms, a common key transpires and is not far from a general consensus that the length of the following intervals can induce delays in the patients' management:

1. **Onset Delay** = ***Delay induced by the patients because of late presentation with their complaints/symptoms;***
2. **GP Delay** = ***Delay occurring at the level of patients' local surgery, defined by the interval between patients' presentation and actual referral made by the General Practitioner to the specialist gastroenterologist;***
3. **Hospital Delay** = ***Delay induced by the secondary centre or specialist service, defined by the interval between General Practitioners' referral and actual clinical examination in the specialist setting;***
4. **Diagnostic Delay** = ***Delay occurred at the level of the specialist service, defined by the interval between specialist examination and positive diagnosis of the disease;***
5. **Treatment Delay** = ***Delay induced at the specialist secondary or tertiary centre, defined by the interval between positive diagnosis and the commencement of the actual definitive treatment.***

Some papers use a cumulative name of *NHS Delay* or *Medical Delay* for cumulated segments 3 to 5. Although not all the papers at hand use the same terminology, the essence is much the same.

The first segment where delay can appear is invariably labelled as Onset Delay and essentially refers to the time interval taken by the patient to seek advice for his/her symptoms. The only situation where this segment is completely eliminated is when an asymptomatic Upper Gastro-Intestinal Cancer is diagnosed by chance during the investigation of other medical conditions, and of course the desired situation of active screening. Otherwise, the delay after the clinical onset due to the patients' negligence can be variably long, typically measured in months rather than weeks; Martin[90] found that 29% of the time interval Onset of symptoms to Treatment was due to delay prior to the first presentation, which represented cca. 5 weeks of the median delay figure of 17.1 weeks. Mikulin et al.[96] looking to the same onset interval found a median delay of four weeks, whilst Rothwell[122] found in his cases a slightly longer median value for onset delay of up to 6 weeks. In contrast, Wayman et al. consider that up to four fifths of delay can be attributable to the patients and only one fifth to the system[159].

It is important to emphasize that the papers referred to above quantify the delay retrospectively and use the whole interval between onset of symptoms and the commencement of treatment. This general approach leaves however little room in pointing to various segments

where the delays can actually occur with a view to find scope for their elimination.

At least one question might arise in relation with the delay and this is related with the identification of those factors which may contribute to the late presentation of patients. During the previous pages we have seen that the largest part of the natural history of the Upper Gastro-Intestinal Cancer evolves silently. However, even after the clinical onset, a large number of patients delay to seek medical advice and the question arises whether the symptoms and/or signs of the underlying condition can be stigmatised as indicators. Looking at the causes of the onset delay, Mikulin and Hardcastle[96] found that these can be attributable to patients' misinterpretation of overt symptoms, dismissal of their importance, self-medication or even oncophobia (16%); the authors also found that 81% of the patients were aware of their symptoms and discussed them with their close family but negligently omitted to seek medical advice. This is a very important finding showing the level of public awareness, in contrast with Japanese situation[96] where patients are using actively the so-called "walk-in centres" for gastroenterological diagnosis. Rothwell[122], Martin[90] and Wayman[159] found that a significant number of patients, sometimes up to 50%, delay their presentation due to symptomatic self-medication, namely acid suppressants or indeed, H_2 blockers.

Different studies tried to seek an explanation for this onset delay by looking at the symptoms presented by the patient. Most of

the studies[60;90;96;159] found that the majority of symptoms were regarded by the patients as non-specific or ulcer-like symptoms and triggered in more than 50% of cases by self-administered treatment with H_2 Blockers, proton-pump inhibitors or antacids[96;159]. A notable observation was made by Rothwell[122] in respect of dysphagia in patients with oesophageal carcinoma; he found that dysphagia was not triggering a shorter interval of onset and was only the third symptom of relevance in patients' symptomatic phase.

In relation to this issue, more recently and with the advent of the open access services, a number of authors[14;16;78;79] raised questions about the role of dyspepsia as a symptom in the selection of patients for urgent investigation. Without entering the heated debate between gastroenterologists, the effectiveness of dyspepsia as an "alarm symptom" is not completely clear[38]. Recent reports suggest that in open access systems, dyspepsia may account for at least 30% of referral volume and generates only 3% of Upper Gastro-Intestinal Cancer diagnosis. Recent observations[32] show that patients with dyspepsia under the threshold of 45 years may elicit only 1.7% to 3% of the cancers diagnosed. Although the British Society of Gastroenterology, NICE[1] and DOH[2][40;105] have issued recently updated guidelines with the declared scope of assisting the selection of

[1] The National Institute of Clinical Excellence

[2] The United Kingdom Department of Health

referrals, the role of dyspepsia as a triggering factor of suspicion seems to be slightly hyper valued.

Another important question to answer in relation to this onset delay is whether at this median delay of between four and six weeks are there any consequences upon the staging of the tumour or indeed upon survival. Given the cancer's doubling rate as seen above, it would be logically expected the answer to be yes. However, the opinions are quite split amongst researchers. Martin[90] failed apparently to prove a direct link other than the logical hypothesis and Gillison[127] showed that his small study can make no link between delay and stage at presentation.

It is difficult to suggest a line of action in order to improve the patients' onset delay; perhaps the only hope resides in repeated actions to increase the public awareness of the non-specificity of the symptoms and create the appropriate infrastructure in the community to allow easy, unrestricted, free and convenient access of the potential patient to the medical consultation. Although there is no convincing link between the delay at onset and the advanced stage of the disease, rapid presentation to the doctor can only diagnose quicker any condition at best and variably increase the activity of medical practitioners at worst.

B. Healthcare sector induced delays

Bearing in mind the Japanese experience and results achieved throughout the last three or four decades in the diagnosis and management of patients with Upper Gastro-Intestinal Cancers, many clinicians tried to design various settings in their clinical practice with the specific aim to increase as much as possible the ratio of early gastro-oesophageal carcinomas diagnosed and consequently to submit these patients to the adequate treatment in a stage which may permit an improved prognosis.

The previous subheadings dealt with issues such as late diagnosis and early cancers; the "diagnose early" approach was particularly scrutinized as an attempt to define those actions taken by clinicians in order to bring as close as possible the positive diagnosis from the advanced stage to the stage of an early cancer. The principles of such actions rely upon two major presumptions: one refers to the necessity, but not the possibility yet, to diagnose these cancers in the asymptomatic phase using methods based on the screening principle; the second refers to the presumption that the earlier the diagnosis is being established, the greater the chances would be to find a patient in an earlier stage and with better chances for long term results[90].

It is interesting to start the debate on various causes of delay in diagnosis and treatment with two interesting remarks: the medical literature as a whole reflects this issue mostly in relation to the delay

induced by late presentation of the patients themselves after the onset of symptoms, whilst the British and Irish authors[90;93;96;122;127] raise also questions related with the delay imposed by the health care infrastructure. Explicitly, Siewert and Fink[90] looking at the results published by I.G.Martin[90] accept that, in general terms, the German hospital setting acts more quicker than in Britain where more than a third of the delay in establishing the diagnosis belongs to the NHS establishment.

Interestingly, when studying the same paper, Sano et al. noted that much of the segments of delay mentioned in Continental Europe are completely eliminated in the Japanese system due to different approach in healthcare structure and pathways of referral. He suggests that the Japanese system is much quicker in delivering the gastro-intestinal cancer patient to elective treatment due to both increased level of awareness and by eliminating the link of family practitioners in the referral process. However, it is omitted from their assessment several key factors such as: patients' compliance is different, general awareness is increased due to the perceived severity of the disease within the patients' mentality and different methodology in picking up cancers, although credit is being given to the many generous health policies established in Japan in recent decades without much consideration to the cost involved.

Based on these observations, as well as on the difference in outcome between Europe and Japan on one hand and between Britain

and Continental Europe on the other hand, many papers emerging from British authors tried very hard to answer the questions as to whether the delay imposed on patients in general, once they are referred, does actually have any importance in the overall outcome and how the delay can be modulated, if not abolished altogether. For this purpose they looked at various innovative methods of referral and services introduced recently, though not particularly with this declared goal in mind, and compared the results obtained with the European standard.

There are two angles that the current debate on delays is looked at in the medical literature. The most important and well researched seems to be that of the quantification of the delay in itself. Conscious of the importance of reducing to as much as possible the interval to treatment, various researchers[36;47;65;68;122;139;149;158] have already looked to the extent to which the delay intervals are extending and to the ways to improve them. It is interesting to mention a few facts related to this issue: firstly, the prevalence of the reports coming from the British Isles and the second, the scarcity of the reports dealing with the Upper Gastro-Intestinal Cancers. The fact that the reports are coming mostly from Britain is perhaps related to the way the health care infrastructure is organized in this country.

Without going into details, the current debate on waiting lists and waiting times is an indicator of the importance placed on the issue. Whilst the various reports are quantifying the delays variably

and between different landmarks, everyone agrees that waiting for appointments through the traditional pathway of referral to Outpatients Department is not an option when dealing with potential malignant pathology. Notably, Saunders[125] still believes that for selected patients this pathway may still be an option. Various papers[21;41;68;124] started more recently to quantify the length of the delays and compare them with the requirements of the "two week rule" in cancer services. Notoriously, the majority of papers are looking at sub-specialities where the delays were in the "public eyes" or where national programmes were in place. For instance, the breast cancer and colonic cancer pathologies[21;46;47;64;68;91;120] seem to fare better in this respect; detailed assessment is already available on the extent of the delay for either referring patients or examining them by the specialist in the hospital.

However, it seems that, with a few exceptions[36;89;90;139], the gastrointestinal pathology is less well researched. Available data[139] suggest the median delay for patients referred urgently for gastric cancer is 10 days (cohort of 241 cases) and for oesophagus 11 days (cohort of 249 cases). Martin[90] found that the delay from onset to positive diagnosis is in the range of 17 weeks for gastric cancer; he calculated that for cca. 71% of the total interval the health care provider may be responsible. However, the only correlation he could make was related to the oesophageal cancer where he could find a link between shorter waiting times and stages II and III of cancer.

These segmental delays, faced by the patients and generated by various factors, also present us with a different and more important aspect for which unfortunately very few references are available. It relates to the effect of reducing waiting times on the patients' outcome. Although, as shown above, there are only a few papers referring tangentially to this particular aspect - that of the quantification of the segmental delays in Upper Gastro-Intestinal cancers -, neither of them are looking into the impact that various services employed in reducing these delays may have on the outcome of those patients. Essentially, data is not available yet in respect of a thorough analysis of the outcome improvement in those patients in which the various mechanisms and clinical services have reduced the waiting time. Again, for other pathologies such as breast[21;68;132] or colon[47;91;158], evidence started to emerge as to the effectiveness of reducing these delays on outcome. For instance, Sainsbury[124] found that delays in hospital appointments and diagnosis of 3 months or more do not seem to be associated with decreased survival in patients presenting with breast cancer. On the same note, Walsh[158] found for colorectal cancer that the "fourteen-day rule" with respect to colorectal cancer has reduced waiting times for a first appointment to see a specialist, but he acknowledged that further improvements will require additional resources to reduce the delay for investigations whilst the effect on long-term survival still remains to be seen.

Beside monitoring the actual delay in the case of the Upper Gastro-Intestinal Cancer patients, if the efforts to reduce the waiting time to appointments, positive diagnosis and treatment are to be paid off, we need to find out if the outcome of these patients has changed and how. Unfortunately, the medical literature seems to be looking so far only to the actual improvement of the delay intervals, but conspicuously missing references to the outcome studies. It is the role of the following pages to see not only how innovative services acted towards reducing the delays in patients with Upper Gastro-Intestinal Cancers, but more importantly, if they had any impact on the patients' outcome.

PART II - *Original Research*

Chapter IV

AIMS AND OBJECTIVES

Summary: *This chapter introduces the reader to the null hypothesis of this research, which questions whether the new clinical services and new algorithms of referral can significantly reduce the waiting times of our patients diagnosed with Upper Gastro-Intestinal Cancer and if, consequently, can improve their outcome. The aims of this retrospective study are briefly emphasized together with their reasoning. Entities such as waiting times, sinister symptoms, pre-existent gastroenterological disorders, staging of the disease, operability and survival assessment are considered valid criteria to be used in assessing the efficiency of the new innovative services and therefore their critical interpretation is considered amongst the declared objectives of this study.*

In the previous chapters I have highlighted the interest shown by many authors in issues such as waiting times, early diagnosis, delays in diagnosis and treatment, as well as methodologies used for speeding up the referral process and treatment for gastroenterological patients in general. It became obvious to many clinicians and healthcare managers involved in the Primary, Secondary and Tertiary sector that improvement in the waiting times to examination and treatment might represent not only a way to change the public's perception of the effectiveness of the healthcare sector in general and of the gastroenterological services in particular, but also a tool in achieving a more effective management of many gastroenterological conditions, with improved outcome and fewer relapses. With the above

aim in mind, clinicians have devised innovative means of speeding up patients' access, consultation, diagnostic and treatment. Thus clinical services such as Open Access Endoscopy, One Stop Clinic and Rapid Opinion Clinics have been introduced since the late 1980's with the specific aim to reduce the waiting time the gastroenterological patients in general face between their presentation and definitive treatment.

The clinical need to submit the cancer patients to radical therapy during the early stages of their disease in order to maximize their treatment possibilities and survival rate is well endorsed at present time by many clinicians. Bearing this in mind, it is hypothesized that reducing the waiting time intervals patients face from their first presentation at the General Practitioner's surgery to the definitive treatment may improve the stage of their disease at diagnosis and/or treatment time and, ultimately, their survival rate. This hypothesis may apply though mostly to those patients in which the symptoms appear in the early stages of the disease. However, in those patients in whom the onset of the symptomatology is correlated with advanced stage of the disease, a quicker diagnosis and definitive treatment might improve only certain parameters, such as operability, symptomatic relief and quality of life issues without necessarily influencing the stage of the disease.

Prior to the commencement of the study, the aims and objectives were set and the null hypothesis of the research was established. This was set to prove that:

1. **The new modalities of referral and the new clinical services - Open Access Endoscopy and Rapid Opinion Clinic - have no impact on the waiting time to treatment of gastroenterological patients who are subsequently diagnosed with Upper Gastro-Intestinal Cancers within these settings;**
2. **Compared with the conventional methods of referral and without taking into consideration other improvements in patients' management such as surgery techniques, palliation, nutrition, etc., these new modalities of referral and innovative clinical services - designed initially for gastroenterological patients in general and based upon the their ability to speed up the patients' throughput - can improve the management, stage at diagnosis and outcome of those patients subsequently diagnosed with cancer.**

Since it has already been shown that adopting various algorithms of referral and new clinical services might possibly improve the overall waiting times to medical care for the patients in general, in this study I will research using a retrospective analysis the implications of introducing all the above methods and services to the particular group of patients with Upper Gastro-Intestinal Cancer. I will also try to ascertain whether these services, besides reducing the overall waiting times, can confirm the assumptions for this particular group of patients alone that the introduction of "novel" clinical services is followed by better stage at treatment time and improved treatment outcome. In other words, I will try to establish if these new services will significantly reduce cancer patients' waiting intervals between presentation to the General Practitioner and treatment and whether this is followed by a significant improvement in their outcome

parameters compared to the general outcome seen by patients coming through the more conventional channels of referral such as outpatient referral or indeed acute admission.

The results will inevitably have to be discussed in the context of the requirement for the "two week rule" in cancer services and may or may not backup the assumption that this rather arbitrarily chosen target for dealing with cancer patients can actually deliver improvement in their outcome. The NHS Cancer Plan and consequently the NICE Guidelines on referral of patients with possible underlying cancer pathology[80;105] have emphasized already the clinical need for the "two week rule" to be achieved before the year 2005 as a measure of public reassurance in the quality of care offered by the healthcare providers. As the British medical literature is scattered with reports suggesting various degrees of compliance with this target for different oncological sub-specialties but with rare indications of the benefits achieved in terms of the outcome parameters and survival figures, the present study will aim to complement the debate and underline on a specific case mix, the outcomes benefits, if any, of channelling resources for various new clinical services.

One of the most obvious objectives to look at in relation to these new algorithms and innovative services is that of the waiting time these patients face between presentation and definitive treatment. Since this delay was allegedly linked with late diagnosis and poor

prognosis, it is important to see what will be the benefit of introducing new referral algorithms and clinical services upon waiting times in general and if one can identify certain intervals where these new clinical settings might have a beneficial impact. The issue of patients' satisfaction in respect of the speed of their referral and treatment was widely looked at both from medical and socio-political standpoints and clearly influenced the introduction of the so-called "two week rule" in cancer referrals[40;92;121;149]. This being only one single side of the argument for speeding patients' throughput - already widely researched - and because the present study was set as a retrospective analysis based on medical records, I have deliberately not included patients' satisfaction issues in the current set of analysis criteria for patients with Upper Gastro-Intestinal Cancer.

A simple analysis of the waiting times in patients diagnosed with Upper Gastro-Intestinal Cancer may not reveal the complete picture related to the efficiency of the new services and referral algorithms. Beside the inevitable comparison of the waiting times and outcomes of these patients diagnosed in either conventional settings or through the new referral methods, there are several factors that need taking into account as well. For instance the dynamics of the pathology in itself, such as variation in overall incidence, or indeed, the modification of the prevalence of the anatomical segment involved, with certain changes in symptomatology. Since all these factors may

have a certain influence in the referral patterns, it is sensible to have a critical look at their influence upon the waiting times when patients are being referred for specialised services.

Referring patients from primary to secondary care must take account of the severity of the symptoms these patients present. Whilst NICE and The British Society of Gastroenterology have made substantial progress in establishing guidelines for referral based on sinister symptoms[11;19;105], the patients with Upper Gastro-Intestinal Cancer may not always present with an obvious combination of symptoms suggestive of cancer. On the other hand, taking into account a sinister symptom alone as a measure of inclusion criterion for referral may not always correctly identify only those patients at risk. Some patients will present with apparently benign symptoms and there is a balance to be struck between seeing only those who have 'sinister' symptoms on an urgent basis, and the overwhelming numbers that will need to be seen if benign symptoms such as simple dyspepsia are included; on the other hand, having a larger spectrum of inclusion criteria for initial referral might clutter the infrastructure created by the new services with possible knock-on effect upon the waiting times in general and ultimately detrimental consequence to the efficiency of these services. Beside the non-specificity of the onset symptoms, one needs to take account of the limitations imposed by the design of the study as a retrospective analysis; this issue is

playing an important role in establishing the symptoms at onset as predictable entities and, more than that, relies on records entries which are not always synonymous to the reality, as also noted by Malats[88].

It is therefore important to look to the population of patients with Upper Gastro-Intestinal Cancers that have been diagnosed through these services and establish if there is a certain pattern or combination of predictive ("sinister") symptoms that may be more suggestive of malignant pathology in the upper gastro-intestinal tract. This objective may be difficult to achieve and the validity of the data may be unreliable in a retrospective analysis based on pre-existent clinical records, unless there is adequate provision for adequate data recording. Thus, when interpreting the data for this particular subset of data certain limitations may apply such as subjectivity in data recording, variability of symptomatology thresholds, ability to identify specific symptoms, etc. Besides all these, it will be interesting to know if the patients with pre-existing digestive conditions might be more difficult to be diagnosed and therefore might present with a not so favourable stage of the disease.

The interpretation of the possible variation in waiting times needs to be looked at from other perspectives too: for instance, what is the influence of the new services upon the pre-operative staging of the disease or whether they can consequently improve the post-operative

staging too. Staging of the disease in this group of patients is a well-established modality to judge their prognosis and therefore a decrease in the waiting time to diagnosis and treatment may appear beneficial for better staging and possible better outcome. It is obviously the aim to diagnose these patients whilst in an earlier stage, but it is not clear yet if the methods of referral and services mentioned above might actually improve these patients' staging at diagnosis time or, indeed, at the moment of the definitive treatment. Independent of the survival study, I will therefore try to establish whether these services can have a direct influence on the stage these patients present with, either pre-operatively and post-treatment.

Another set of objectives to be followed up during the assessment of the potential benefits offered by these new services is related to the patients' outcome. Currently there are quite a few criteria established which may assist in the quantification of the outcome of cancerous patients following diagnosis and treatment. One of the most important remains the survival rate of these patients and therefore an analysis of the patients' survival data is mandatory if the efficiency of the new services is to be critically assessed. I will try to establish whether for those patients channelled through the new clinical services there is an improvement in the survival figures compared to the patients referred through conservative routes or indeed, if there are certain groups of

patients with this pathology that may have a different benefit from the new services.

The survival rate may represent the ultimate criterion for assessment of patients' benefit from these new and innovative services; however, there may be other outcome criteria to be discussed that may enjoy benefits too, such as operability or indeed patients' satisfaction with the speed of their treatment or cessation of their symptoms.

Introducing these new services may or may not introduce changes in the operability of these patients or indeed may or may not bring benefits in the adjuvant therapy deployment process. Although the relationship between operability, staging and survival is well defined in the medical literature, operability alone may remain a favourable factor of assessment not only because of the potential marginal improvement in life expectancy, but also because of the symptomatic relief that it may bring. Regardless of the improvement in the stage of the disease, it is therefore beneficial to know whether the new referral algorithms and innovative services can introduce any improvement in the overall operability figures for those patients channelled through the new route. All the afore mentioned factors seem at first glance to be influenced by the length of the waiting times between presentation and treatment and some of them might indirectly mirror the effectiveness of the services in question. Therefore it is only logical to

quantify the benefits of such services through the critical interpretation of these factors.

In spite of all these variables related with the epidemiological reality, presentation of the disease and referral pattern, a few questions remain clear: to what extent the new methods of referral and new innovative secondary care services can decrease the waiting times specifically for patients with Upper Gastrointestinal Cancers and whether reducing these waiting times - particularly to the target imposed by the so-called "two week rule" - can actually make a significant difference in patients presentation, TNM stage, operability and treatment outcome. The following pages will try to identify answers to these questions through critical assessment of the above mentioned variables and establish whether these new algorithms of referral and innovative services can make a difference in the early diagnosis and management of patients with diagnosed Upper Gastro-Intestinal Cancer.

Chapter V

SETTING, MATERIAL AND METHOD

Summary: *The setting for the study presents the two general hospitals and emphasizes their clinical services such as Open Access Endoscopy and Rapid Opinion Clinic in parallel with the conventional services such as Acute Admission and Outpatient Clinics. The material for the study is presented after the criteria of inclusion and exclusion are exposed. Based on these criteria, it is retained that a case mix of 440 patients are identified together with their complete data set. The sources for case identification are described and the assumptions used to isolate the relevant cases are enumerated. The mechanisms of data extraction, validation and analysis are also explained together.*

Subheadings in this Chapter:

Having established the aims and objectives of this study and bearing in mind its potential epidemiological and infrastructural implications for the structure and design of future medical services, it was paramount to choose an adequate model of study; this model had to reflect a populational area sufficiently representative for the objective chosen and comprehensive enough in respect of services and methods of referral offered to the patients eventually diagnosed with Upper Gastro-Intestinal Cancers. By the same token, this model had to feature several other important elements such as: reproducibility,

design based upon inclusion of all categories of gastroenterological patients, homogeneity of populational case mix, infrastructural similarities between sites as well as facilities for identification and follow-up of those patients who are diagnosed and treated within the same clinical setting.

A. Neath - Morriston Setting

In order to research the implications of various modalities of referral and clinical services offered to patients with potential Upper Gastro-Intestinal Cancer, as well as the consequences of these clinical services in respect of the speed of diagnosis, treatment and final outcome for these patients, I have chosen the case mix offered by Neath General Hospital and Morriston University Hospital in South Wales; these are two district general hospitals situated along the M4 Motorway corridor and on the outskirts of the City of Swansea, the second largest City in Wales in terms of population size and economic development. The area covered by the two hospitals offers an interesting socio-economic structure, containing pockets of favourable socio-economic deprivation index as well as areas of high unemployment and high morbidity, more recently associated significantly with the declining opportunities offered by the local British Steel industry.

Historically, the two hospitals were individual secondary care entities serving two different catchment areas, each having distinct

and specific primary care sector and featuring direct referral patterns to the allocated hospital. This feature was consistent throughout the period of the case identification exercise in respect of primary-to-secondary care sector referral pathways and medical investigation infrastructure, both for elective and non-elective referrals. During the period of time when the case identification process took place, each of the two hospitals belonged to the same Iiechid Morgannwg Health Authority as health care provider. Each was allocated to serve a population of an approximately similar structure and volume - cca. 130000 people -. It must be noted though that shortly after the commencement of the case identification period - i.e. 1994 - Neath General Hospital lost its acute surgical services in favour of Morriston University Hospital, thus unifying under one roof all surgical services for gastroenterological malignancies. Also, in 1999 a major reconfiguration of clinical services has taken place in South Wales when Neath General Hospital lost its status as an independent NHS Trust. These changes did not affect significantly the provision of service in the catchment area for upper gastro-intestinal patients as explained later in Chapter VIII.

Both hospitals offered the corresponding primary care sector all of the referral facilities and services that are under scrutiny in the present study. Beside the usual and traditional forms of referral - i.e. elective referrals to a consultant firm for Outpatient clinical appointments as well as emergency referrals to the Acute Inpatients

service -, both of the hospitals offered, in one form or another, new and innovative services designed to speed up the throughput of the gastroenterological patients in general; in spite of using various names, such as Fast Track Endoscopy, One Stop Endoscopy, etc., these new services were essentially represented by two different and specific modalities of medical appointments: Open Access Endoscopy and Rapid Opinion Clinic. Therefore, during the period of the case identification process, in both hospitals I have identified the following structured clinical services which were offered both to General Practitioners and in-house medical teams:

1. **Acute Emergency Admission**
2. **Elective Outpatients Clinic Appointment**
3. **Open Access Endoscopy**
4. **Rapid Opinion Clinic**

The clinical services number 1 and number 2 above represent the traditional services whereby the patients were referred by the primary care sector either to the outpatients department - in this case patients were seen electively after having an appointment scheduled on a "first come, first served" basis - or referred as acute inpatients - and seen immediately within the bedded area of the hospital -. The clinical services number 3 and number 4 were the new innovative services where patients were referred through a new route: in these cases the patients were seen either directly in the Endoscopy Suite where they were called readily prepared for an upper gastro-intestinal endoscopy, or were seen with priority in the case of the Rapid Opinion Clinic,

normally within an interval of a few days from referral date and benefited from a direct consultation with the gastroenterologist.

Both hospitals presented fully functional gastroenterological departments featuring designated endoscopic facilities and assisted by specific and dedicated supportive diagnostic departments such as Radiology, Histopathology, Immunohistochemistry and GI Surgery. Following the positive diagnosis of Upper Gastro-Intestinal Cancer, for each patient the pathway taken for treatment and palliative care in the secondary and tertiary care sector converged on the same point in both settings. The principal setting was Morriston University Hospital for patients' surgical management, Singleton Centre for Oncology for patients' adjuvant therapy and Ty Olwen Hospice for palliative and terminal care respectively. In other words, both gastroenterological settings used the same Upper Gastro-Intestinal surgical service and oncological tertiary centre for adjuvant therapy, even though the two sites were acting as independent entities of referral for diagnostic facility. Therefore, in these settings a particular diagnostic-therapeutic model has been observed, whereby there were two diagnostic units which converged towards one multi-disciplinary pathway for therapeutic, adjuvant and palliative care for upper gastro-intestinal cancer patients.

B. Material

Both hospitals offered an impressive case mix due to their position as secondary health care entities. Their case mix was generated by the referral process of gastroenterological cases at large and included both malignant and non-malignant conditions. For the purpose of this retrospective study and based on this large number of referrals, it was decided to take into consideration a period of time of *six calendar years*, from ***1st July 1993 to 30th June 1999***. To this decision contributed various factors, including the need for a sufficiently large case mix, possibility to cover various changes in the local healthcare infrastructure that may occur from time to time and last but not least, the necessity to allow time for the relevant referral algorithms and pathways of referral to be fully implemented within the primary and secondary care practice. To assist in the process of identification of suitable patients for the present study, it was mandatory to establish the patients' criteria of inclusion and exclusion as well as some assumptions since the research is a retrospective one based on past medical records.

a) Inclusion & Exclusion Criteria

The case identification process involved the scrutiny of all referrals for gastroenterological complaints followed by the isolation of only those patients with upper gastrointestinal cancers diagnosed and treated during the interval of time to be agreed to cover the study.

Soon it became obvious that some criteria for inclusion could be observed both in respect of the definition of histological malignancy as well as in respect of the anatomical topography of the gastro-intestinal segment involved. Also, due to the timing feature of the referral event, diagnosis through investigations, staging and actual treatment, the criterion of time was to be observed when deciding to include any patient in the study's time frame or not.

Although the definition of malignancy is not clearly defined on clinical grounds but perhaps more precisely defined in a histological context and, taking into consideration what various conceptual medical schools might include under the term of "malignancy", it was important to establish the boundary of what one may consider "malignant" in respect of the Upper Gastro-Intestinal Tract. First of all, the provisions of the International Classifications of Diseases ICD-10[1] were taken into consideration; secondly, the conceptual difference between primary and secondary malignancies was observed. Finally, consideration was given to both epithelial and non-epithelial originating tumours arising from the Upper Gastro-Intestinal Tract wall.

Therefore, from inception I have considered and observed throughout the following *criteria for inclusion*:

[1] ICD-10 codes used: Oesophagus = C15.9 & C78.8; Stomach = C16.9 & C78.8 Duodenum = C17.0 & C78.4

1. histological confirmation of malignancy; this confirmation had to be provided on a histo-pathological specimen - gained either by direct biopsy, brushing cytology or a resection specimen - and then validated by a histo-pathologist with interest in gastroenterological pathology;
2. the final diagnosis in the patient's clinical record consistent with malignancy in spite of histological uncertainty; such cases were only considered where the histo-pathological report was inconclusive and the clinical multidisciplinary consensus based upon clinical signs and progression of the disease was consistent with "malignancy" of the upper gastro-intestinal tract; the record's coding was therefore in accordance with the provisions of ICD-10 classification of diseases(254) and consistent with malignancy;
3. the malignant tumour must arise and involve as a primary tumour the wall of any of the segments of the gastro-intestinal tract; this criterion also includes the possibility of synchronous and metachronous primary tumours in the gastro-intestinal tract, as well as some metastasis from other cancers had not been diagnosed at the time of patient's initial referral for upper gastro-intestinal symptoms;
4. the malignant lesion must have originated in any structural component of the gastro-intestinal tract wall: epithelial, stromal, vascular neural, lymphatic, etc.; therefore both epithelial and non-epithelial cancers were included;
5. the segments of the gastro-intestinal tract taken into consideration were oesophagus, stomach and duodenum; adjacent or associated anatomical structures to these segments, such as papilla, head of pancreas, elements of porta hepatis or splenic hilum were excluded on anatomical grounds as not part of the upper gastro-intestinal tract;
6. any patient diagnosed as above was included in the study if either the positive diagnosis was established - i.e. histologically

reported - within the interval of time chosen or if the referral date or diagnostic episode occurred within the interval of the study;

7. all patients included must have been either positively diagnosed or submitted to treatment at either of the two sites chosen, irrespective of being referred from within or out with of the catchment area of the two hospitals.

In the context of inclusion criteria it is worth mentioning the following *changes in the provision* of services for the Neath General Hospital site:

1. *between 1st July 1993 and 30th June 1994 the name used for Open Access Endoscopy service was One-Stop Endoscopy; the Open Access Endoscopy name was used only after 1st July 1994;*
2. *the Rapid Opinion Clinic was formally introduced under this name on the 1st October 1995; previously, relevant referrals were channelled as in Morriston University Hospital setting;*
3. *the acute surgical services were moved to Morriston University Hospital on the 1st October 1995. These services related only to the admission facility for acute surgical intake and not elective and / or semi-elective work.*

There were a number of cases of Upper Gastro-Intestinal Cancer that were not seen fit for the purpose of this research; if included, they might have introduced a certain degree of bias and skewed the results and findings. It was therefore necessary to establish the exclusion criteria to be employed when identifying the unsuitable cases. The observed *exclusion criteria* were the following:

1. cancers arising from a nearby viscus - such as pancreas, papilla, porta hepatis, bronchial system, lungs, colon, etc - and only secondarily invading any segment of the gastro-intestinal tract;
2. the small gut, based upon its anatomical, histological and clinical features was excluded;
3. the histology reports on patients showing various degrees of dysplastic lesions of the gastro-intestinal tract; these patients were excluded based upon the use of the western definition of malignancy rather than the Far-Eastern one - e.g Japanese definition of cancer includes also severely dysplastic lesions such as polyps, ulcers, etc. -;
4. the absence of a confirmed histological feature of malignancy on either bioptic specimens or operative samples, as well as border-line cases where multidisciplinary consensus of malignancy was not achieved;
5. metastasis in the Gastro-Intestinal Tract arising from known primary cancers in other abdominal or non-abdominal viscuses; unless these patients were not observed or followed up during the usual process of clinical scrutiny for their original cancer, for the purpose of the current objectives of study these patients were not included in the case mix, even if they later presented with new symptoms or were referred as new clinical episodes;
6. those patients referred solely for the purpose of a second opinion but not treated within the sites mentioned earlier; although these patients were referred through with potentially positive diagnosis of malignancy and were subsequently submitted to the positive diagnosis algorithm, their staging and treatment was not accomplished within the originating setting; therefore, insufficient data for appraising the outcome of the services was achievable and they were excluded;
7. patients with incomplete data available; this could be due to lost, destroyed records or insufficient data available; however, patients with complete records available but who were geographically transferred to other sites during the follow up period were included in the study.

b) Assumptions

During the data extraction process it was apparent that there were several cases where the route taken by the patients was different; some referrals were addressed in the first instance to the Radiology Department or to various specialities like ENT, Rheumatology, etc. Also, although some patients were sometimes routed to one department or the other, the modality of referral was subject to the doctor's ability to recognize featured symptoms or even a possible diagnosis of malignancy. As these two conditions may influence the speed of referral and specialist care appointment the patients received, several assumptions were made a priori. In addition, the need to simplify the process of analysis of a quite heterogeneous collection of clinical data meant that, when data was introduced into the database, the following *assumptions* were used:

1. the initial diagnosis was considered to be negative at the moment of the first hospital appointment if there was no hint in the consultation letter/record or indeed, during the first Outpatients consultation, that a malignancy might explain the presentation symptom(s); if this assumption was correct, the medical practitioner failed to initiate the specific investigations and the patient had to be referred for the second time based on the same clinical picture; some delay in the referral process can occur on these grounds;
2. the diagnosis in respect of the Acute Admission modality was considered to be negative if no specific investigations were organised during that period of admission, even if these might have been organised after discharge from hospital; if this

assumption was correct, some delay in the diagnostic process might have occurred;

3. the diagnosis was also considered to be negative at the first hospital examination if the biopsy failed to positively diagnose cancer and another endoscopy was warranted; if this assumption was correct, then some delay could be explained during the diagnosis phase;
4. the modality of referral was considered to be Open Access Endoscopy when the patient's first contact with the hospital setting was at the endoscopy, irrespective of the referral's modality. This was particularly true in the case of Morriston University Hospital's site, as well as in the situation of re-routing in both sites of some referrals considered to be wrongly issued;
5. when Barium Meal was the first line of investigation, this situation was considered to be a referral to the Medical Department as an Outpatient modality; if this assumption was correct, a delay in the referral process can be explained in respect of these settings, due to the subsequent necessity for endoscopic confirmation;
6. cancer localisations at the interface between the oesophagus and stomach posed an important challenge in respect of topography; it was arbitrarily considered that cases involving the cardia do belong to the oesophagus - i.e. the bulk of the tumour situated in this area rather than eccentrically at the fundus of the stomach -; the reasons to do so are based on histological, anatomical and surgical criteria;
7. for a short period of time the modalities of referral directly to the endoscopy service were recorded with a different name, such as Fast-Track Endoscopy or One-Stop Endoscope; therefore these modalities of referral were grouped under the generic name of Open Access Endoscopy, a term which was used since mid 1994 for all these type of referrals;
8. it has been assumed that, irrespective of the four main modalities of referral - i.e. Acute Admission, Outpatients Clinic, Open Access Endoscopy or Rapid Opinion Clinic -, each referral was addressed

to the following grouped clinical services: gastroenterology, (other) medical specialties, (other) surgical services; grouping the targeted clinical services in this way makes sense based upon the internal collaborative features and differential diagnoses issues;

9. arbitrarily, patients' past co-morbidities were classed abdominal and gastroenterological; some patients might have had co-morbidities that may have altered their perceived symptomatology and as a consequence might have delayed their presentation or indeed the diagnostic algorithm; therefore, past medical or surgical co-morbidities may represent delaying factors of positive diagnosis and need to be observed when analysing the speed of diagnosis in Gastro-Intestinal malignancies;
10. recording the main presentation symptoms at GP level and / or main hospital consultation's symptoms is retrospectively unreliable; based on the assumption that each medical practitioner would describe in the clinical records the most significant symptoms in their respective order of magnitude, the same order of importance was preserved when introducing the symptoms into the database;
11. it has been assumed that several interval segments (see *Appendix A01: Natural History & Delay Intervals*) observed during the clinical progression of the disease are potential sources of delaying the management of these patients and they were a priori named herewith as "delay intervals". The assumed potential delay intervals and their substance were as follows:

- **"Onset Delay" = from the occurrence of the first symptom to the 1st GP examination**
- **"GP Delay" = from the 1st GP examination to the GP referral**
- **"Hospital Delay" = from the GP referral to the 1st Hospital appointment**
- **"Diagnosis Delay" = from the 1st Hospital appointment to the positive diagnosis moment**
- **"Treatment Delay" = from the positive diagnosis moment to the start of treatment**

12. the presentation delay is extremely difficult to quantify both during the direct history taking process and retrospectively in the clinical records assessment; therefore, the following ranges of delay in presentation were chosen to be more useful for the purpose of quantification:

- **less than 24 hours;**
- **less than 1 week but more than 24 hours;**
- **less than 1 month but more than 1 week;**
- **less than 3 months but more than 1 month;**
- **less than 6 months but more than 3 months;**
- **less than 12 months but more than 6 months;**
- **more than 1 year;**

c) Cancer Case Mix

Based on the inclusion criteria mentioned above, a total number of 462 cases of patients diagnosed with various forms of Upper Gastro-Intestinal Cancer have been identified in the two settings for the period of 6 calendar years, i.e. between 01 July 1993 and 30 June 1999. This represents approx. 2.36% of the total number of patients endoscoped for gastrointestinal symptoms or one case of cancer diagnosed for every 42.35 endoscopies performed.

However, 22 cases were excluded from the study based on the following reasoning:

- Incomplete data in clinical notes and/or electronic records = 15 cases;
- Destroyed primary and/or secondary medical records on several deceased patients = 6 cases;
- Diagnosis on Barium Meal alone without histological confirmation = 1 case;

A total number of 440 cases of Upper Gastro-Intestinal Cancer were therefore finally entered into the study after having fulfilled all the inclusion and exclusion criteria mentioned earlier. All these cases offered essentially complete clinical data sets and had positive diagnosis made by endoscopic and histological means.

C. Method

Bearing in mind that the period covering the study was significantly long and because the study covered essentially two different hospital sites, the following approach was used as a method of identifying the relevant cases and collecting the data:

a) Case Identification

The interval of time covering the case identification was chosen to extend between 1st July 1993 to 30th June 1999 inclusive and comprised of 6 calendar years. During this interval, the infrastructure of health care delivery in the two chosen settings for gastroenterological patients was stable and all the services were in place in one form or another. For the purpose of establishing the patients' outcome, the clinical results for these patients were monitored for a further 5 calendar years until 30th June 2004.

The case mix available was identified at the inception of the research from different sources, within or with direct connection to the two established sites. These sources were chosen in such a manner that they could offer:

1. speediness in the identification of each diagnosed Upper Gastrointestinal Cancer case;

2. thorough filtration of all gastroenterological malignancies within the two settings;

3. guarantee for accuracy and exhaustiveness of the clinical details to be collected.

The sources of data collection offered the facility for a thorough filtration of all cases of upper gastro-intestinal malignancy positively diagnosed within the two hospitals. These sources were:

1. The computerised records of the Histopathology Department; the identification of cases was based upon the coding system used by that department for various clinical entities compatible with the definition of malignancy and referring to the anatomical segments of the upper gastro-intestinal tract;

2. The Endoscopy Suite[1] records in both hospitals; the identification of cases was based upon a code-searching exercise against the macroscopic diagnosis registered by the examining endoscopist at the end of the examination;

3. The Electronic Patients Records ePR in both hospitals; a cross-reference process was employed based upon patients' demographic data;

4. The Coding Department; the identification process involved a code-searching exercise based on the International Classification of Diseases - ICD-10[2] - code of malignancy for the anatomical segments of the upper gastro-intestinal tract;

5. The Radiology Department; a search of all reports issued was carried out in order to identify potential cases which were missed from previous searches or perhaps not subjected to tissue diagnosis;

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[1] GeneCIS™ - ***Generic Clinical Information System***, Authors: Hayley Dickinson, Jayne Morgan, University of Wales Swansea, United Kingdom

[2] ICD-10 codes used: Oesophagus = C15.9 & C78.8; Stomach = C16.9 & C78.8 Duodenum = C17.0 & C78.4

6. The Singleton Centre for Oncology; the records of patients treated for upper gastro-intestinal malignancy in this centre were scrutinised and cross-referenced to previous findings;

7. CANTORIS[1] - the Cancer Registry Database for South Wales; this service had their records filtered for cases coded as upper gastro-intestinal malignancy as per reports received at their end;

8. The Iechid Morgannwg NHS Authority[2]; the information department of this health care provider was also queried for reported cases of upper gastro-intestinal malignancy coming from local General Practitioners;

9. All Wales Cancer Registry Cardiff; this registry was queried to obtain reported cases based on ICD-10 coding system and cases reported to the National Statistics Office.

Whenever necessary and possible, the data was cross-referenced with the computerized clinical system of various institutions and organisations involved in the respective patient's care, such as patient's general practice, local hospice, cancer registry, etc. There was no correspondence involved however with any of the patients or their families, nor any direct contact by phone or other means to obtain further clinical data other than that recorded in patients' clinical notes or in the electronic sources. On occasions the data extracted was completed with clinical details from the family practitioner's records or from nurses' records.

[1] CANTORIS Cancer Treatment & Outcome Registry, Singleton Hospital, Sketty Lane, SWANSEA, SA2 8QA;

[2] IMH *Iechyd Morgannwg Health Authority*, IT Department, 41 High Street, SWANSEA, SA1 1LT;

b) Data Extraction, Validation & Analysis Tools

To answer to the objectives previously established, a list of required data was compiled between the main researcher, the gastroenterologist and the statistician. It was decided that the set of information required needed to be structured in the following way:

1. **Patients' Demographic details;**
2. **Personal & Family History of gastro-intestinal malignancies;**
3. **Chronic use of gastroenterological-related medicines;**
4. **Presenting main symptom and other symptoms as they are specified, the order of recording as well as the estimate delay in presentation;**
5. **1st Examination details (primary care sector);**
6. **1st Hospital Examination (secondary care sector);**
7. **Positive Diagnosis and staging examinations;**
8. **Treatment instituted - both surgical and adjuvant;**
9. **Recurrence of disease (when present);**
10. **Death and cause of death (where applicable);**

As an intermediate tool in the data collection process, a proforma in paper format was designed (see *Appendix A03-A05: Data Collection Form*) and data was collected onto it from the clinical records. The data extraction process was carried out by the main researcher who accessed the medical records at source for each identified patient and also cross-matched the references in the clinical notes with other sources. To structure better the collected data and for manipulation and house-keeping purposes, the data was transferred onto a database using Microsoft Access[1] software. This

[1] Microsoft ACCESS 2000 in Microsoft OFFICE 2000 Premium®, Seattle, USA, 1999

was specifically in-house designed for this purpose (see *Appendix A06: Database Interface in Access 2000 format*). The accuracy of data collection and recording was validated with the assistance of an independent validator through a process of independent selection of 12% of the initially identified cases followed by scrutiny against the original recorded proformas.

Subsequently, the final data was imported into a statistical package (SPSS for Windows[1]) for statistical analysis. Data analysis and interpretation was assisted by a professional statistician. The statistical methods aimed to clarify the difference or relationship between the variables considered. These variables were established at the beginning of the statistical analysis process. They include demographic variables - such as age group, gender, hospital of referral, etc. -, referral variables - such as referral modality, clinical service -, pathological data - such as topography of tumour, tumour T stage, clinical TNM stage, histology, differentiation, etc. -, clinical variables - such as personal medical history, familial history, main/presentation symptoms, dates of presentation and diagnosis, staging procedures and treatment, etc. -, as well as outcome variables - such as recurrence episodes and individual survival -.

For the purpose of investigating the null hypothesis, the statistical analysis employed both parametric and non-parametric

[1] SPSS for Windows ver. 10, release10.0.7, 1 June 2000, Copyright© SPSS Inc. 1989-1999, USA

tests; the scope was *a) to investigate the differences* between the various groups of data considered as confounding factors, *b) to research fully the relationships* between various factors and *c) to draw sound conclusions* which could be used to ascertain whether the method of referral had any consequence upon the waiting times and upon the principal outcome characteristics of the case mix. In most instances the ***referral method*** and the ***department of referral*** were considered as independent factors because the chosen results aimed for were the waiting times as well as the various outcome factors resulted from the change in referral pattern. The other factors - such as demographic details, clinical data, histology, stage and other tumour related data, treatment variables and outcome data mentioned above - were introduced in the analysis in most of the cases as independent variables.

With the number of variables considered, a multivariate analysis was initially employed but this was abandoned soon after it was found that findings derived from this analysis were offering unstable results. This was due to the presence in many cells of low counts, for instance the case of the Rapid Opinion Clinic group of referrals where the overall method was used in only 12 patients.

I decided therefore to observe the relationship between the independent factors and the variables collected using a bivariate analysis where, in most instances, the method of referral was the independent factor. The results aimed to show the way in which the

waiting times and the patients' outcome were influenced by the method of referral. The frequencies and the instances of various factors such as age groups, gender, tumour size, TMN stage, etc., were analyzed in most instances using the cross-tabulation method - I have tried this way to summarize the intersections of independent and dependent variables and understand the relationship (if any) between those variables; by applying this method of analysis I have controlled the independent variable considered to be the method of referral (and as much else as possible and natural) and measure the dependent variables to test my hypothesis that there is some relationship between them. To test the nominal data a *Chi squared test* (χ^2)[1] was employed in most of the situations. The *statistical level of significance* was interpreted based on the *p-value* with a threshold of 0.5. The non-parametric *Spearman's Rank Order Correlation* test was also used. I have considered this approach because most of the data looked at was not categorical in nature.

To investigate the survival probability at the end of the study, the test of choice used was *Kaplan-Maier test.* The calculation of the survival proportion was observed deliberately at 1 year and 5 years as per current standard of reporting survival either following definitive treatment for treated patients or similarly after positive diagnosis only for non-treated patients respectively; the basis of the statistical

[1] Chi square or (χ^2) is a non-parametric test of statistical significance for bivariate tabular analysis

computation was the *Log Rank* and the *Breslow method*; the survival probability graphs were constructed based on this computations using the *95% Confidence Intervals*.

Once the aims, material and variables were established, a risk management and costing exercise have been carried out. It was found that - at the material time when the study was designed - there were no conflicts of interest or hazards envisaged, both for the patients and for the researchers alike. Also, no breach was noted with respect to the Data Protection Act[1] in force at the time and no other Disclosure of Information issues were to be observed. The research had no direct or indirect funding or grants either at the beginning or during the process of data collection and interpretation; no conflict of interests were known. The case identification and data collection exercises were carried out within the infrastructure already existent within the two chosen sites and not shared directly or indirectly with third parties. Approval from the regional Ethics Committee was sought and duly obtained.

This research was designed as a retrospective study based upon the auditing methodology. Making use of the algorithms, guidelines and new clinical services implemented at the beginning of the 1990's at Neath General Hospital, as well as the corresponding approach to the gastroenterological referral pathway in Morriston University

Hospital, the patients diagnosed with Upper Gastro-Intestinal Cancers in both settings were identified and their medical appointments, diagnostic pathway, therapeutic management and clinical outcome was scrutinised. The case mix required was not subjected to any selection process and all complete and validated records within the study interval were used for the analysis of data.

For all 462 upper gastro-intestinal cancer patients identified the clinical data set was obtained from their medical records and entered into the database. Each record consisted not only of demographic data, but also comprehensive clinical details of their first presentation at general practice level, including symptomatology and first line treatment, if any. Also, each record provided detailed referral pathway to the secondary care sector with positive diagnosis and staging events, treatment and outcome features. The data collected was analysed using the method described above and offered the results mentioned in the following two chapters. Subsequently, and in keeping with the auditing methodology, the results and conclusions which resulted following the analysis of the data were used to fine-tune the disseminated guidelines, criteria of referral and pathways of care for those gastroenterological patients presenting with symptoms suspicious of upper gastro-intestinal malignancy.

[1] Data Protection Act 1984, © Crown Copyright 1984, HMSO The Queen's Printer of Acts of Parliament, The Stationery Office Ltd.

Due to the complexity of data analysis, I considered it beneficial to look at the results in two separate parts: first approach refers to the speed of diagnosis alone in conjunction with a few variables seen to play an important role in the pre-treatment phase for these patients, such as demographic factors, anatomical organ, service and method of referral used, etc. The second approach looks to the results from the outcome and survival benefits standpoint, if any, resulting from the introduction of the referral algorithms and novel clinical services.

Chapter VI

RESULTS: INTERVALS & DELAYS

Summary: *This chapter presents the results of the study looked at from the perspective of the newly introduced clinical services and methods of referral. After briefly showing the possible confounding factors across the four methods identified as referral modality and presenting the distribution of the 440 cases from an epidemiological point of view - e.g. gender, age group, hospital setting, anatomical gastrointestinal segment involved and histological diagnosis -, the bulk of the chapter is dedicated to the quantification of the delay intervals established under the method of study. It is retained that the cohort includes 278 gastric cancers and 160 oesophageal lesions. The median age of the cohort is 73 years. Only 24 cases of non-carcinomas have been isolated compared to 416 carcinomas. The most frequent symptoms at presentation were dysphagia and weight loss. It was found that 42% of patients were initially referred to the Outpatients Clinic and only 21.4% to Open Access Endoscopy. Most patients have delayed their presentation with a minimum of 3 months; they faced a median delay of 11 days (mean delay = 15.96 days) before were examined in the hospital setting. The overall mean NHS Delay in this cohort is 117.88 days.*

Subheadings in this Chapter:

- ***A. Case mix presentation***
- ***B. Distribution of Cancer Pathology***
- ***C. Distribution of Services & Method of Referral***
- ***D. Speed of Referral, Diagnosis & Submission to Treatment***
  - ***a) Onset Delay***
  - ***b) GP Delay***
  - ***c) Hospital Delay***
  - ***d) Diagnosis Delay***
  - ***e) Treatment Delay***
  - ***f) NHS Delay***

The case identification exercise and data collection process offered a huge array of variables that may allow for an exhaustive scrutiny of the presentation, referral, diagnosis, treatment and outcome of those patients with Upper Gastro-Intestinal Cancer

diagnosed over a period of 6 calendar years. When looking at the raw results of this *uncensored cohort* from the perspective of the newly introduced clinical services and referral algorithms, there are essentially two areas of interest to be scrutinized: a) one refers to the speed of referral, diagnosis and in-hospital management of these patients and b) the second observes the consequences that the new services produced on the patients' outcome.

Due to the wide spectrum of the null hypothesis to be investigated as well as the complexity of data analysis, in this chapter I will only present those results with emphasis on the speed of patients' referral, positive diagnosis, staging and submission to treatment.

A. Case mix presentation

For the interval of 6 calendar years - i.e. 01 July 1993 to 30 June 1999 - a number of 440 cases of Upper Gastro-Intestinal Cancer have been entered into the database having fulfilled the inclusion-exclusion criteria established from the start under Method and having offered complete recorded clinical details. These cancers were diagnosed following an impressive number of referrals - more than 16000 - coming from the General Practitioners who were serving at the time a population in excess of 320,000 people. The distribution of cases positively diagnosed as upper gastro-intestinal cancers and picked up at the two sites was similar:

- **Morriston University Hospital = 224 cases (50.9%)**
- **Neath General Hospital = 208 cases (47.3%)**
- **Other referring Hospitals = 8 cases (1.8%)**

The cases originated from other units had the suspicion of cancer raised there, but positive investigations, staging procedures and clinical management still carried out in the two hospitals mentioned above.

Overall, there were 278 cases (63.1%) of gastric cancer, 160 cases (36.3%) of oesophageal cancer and only 2 cases (0.5%) of primary duodenal malignancy. All these cancers were primary malignancies arising from various structures of the Upper Gastro-Intestinal Tract wall (but excluding biliary/pancreatic structures), with four notable exceptions: these were the cases of primary tumours arising in other remote organs (lung, colon, kidney and melanoma respectively), but the patients were referred from primary care sector for upper gastro-intestinal symptomatology without prior knowledge of the primary tumour at referral time; as a consequence, from the beginning these patients were classed as upper gastro-intestinal patients until that moment in time when the primary tumour was identified.

B. Distribution of Cancer Pathology

Examining each suspected cancer patient, the general practitioner has chosen a method of referral or another based on his/her judgment and balance of probability between the patient's

symptomatology and several other elements with various degree of prediction for malignancy.

Parameter		Admi-ssion	OAE	OPD	RO	Total	Significance
Age	Mean Age	75.30 *n=149,*	68.62 *n-94*	71.76 *n=185*	72.50 *n=12*	72.31 *n=440*	
Gender	Male	89 (59.7%)	63 (67.0%)	114 (61.6%)	7 (58.3%)	273 (62.0%)	$\chi^2 = 1.411$ P = 0.703
	Female	60 (40.3%)	31 (33.0%)	71 (38.4%)	5 (41.7%)	167 (38.0%)	
Hospital	Morriston	93 (62.4%)	43 (45.7%)	88 (47.6%)		224 (50.95)	$\chi^2 = 24.202$ P < 0.001
	Neath	54 (36.2%)	50 (53.2%)	92 (49.7%)	12 (100%)	208 (47.3%)	
	Other Hosp	2 (1.3%)	1 (1.1%)	5 (2.7%)		8 (1.8%)	
Anatomical Segment	Oesophagus	36 (24.2%)	38 (40.4%)	80 (43.2%)	6 (50%)	160 (36.4%)	$\chi^2 = 15.547$ P = 0.016
	Stomach	112 (75.2%)	56 (59.6%)	104 (56.2%)	6 (50.0)	278 (63.2)	
	Duodenum	1 (0.7%)		1 (0.5%)		2 (0.4%)	
Clinical Depart.	Gastroen-terology	5 (3.4%)	88 (93.6%)	18 (9.7%)	12 (100%)	123 (28.0%)	$\chi^2 = 332.73$ P < 0.001
	Medical	117 (78.5%)	5 (5.3%)	97 (52.4%)		219 (49.8%)	
	Surgical	27 18.1%)	1 (1.1%)	70 (37.8%)		98 (22.3%)	
Age Group	<34						$\chi^2 = 34.300$ P < 0.001
	35 – 44	1 (0.7%)	2 (2.1%)	6 (3.2%)		9 (2.0%)	
	45 – 54	9 (6.0%)	6 (6.4%)	8 (4.3%)	2 (16.7%)	25 (5.7%)	
	55 – 64	10 (6.7%)	22 (23.4%)	28 (15.1%)		60 (13.6%)	
	65 – 74	41 (27.5%)	36 (38.3%)	66 (35.7%)	4 (33.3%)	147 (33.4%)	
	>=75	88 (59.1%)	28 (29.8%)	77 (41.6%)	6 (50.0%)	199 (45.2%)	
	Total	**149 (100%)**	**94 (100%)**	**185 (100%)**	**12 (100%)**	**440 (100%)**	

Fig. 6.01 – Synopsis of Confounding factors

These factors - namely the age group, gender, main symptom, anatomical segment and department of referral - are confounding factors

that might influence the adopted method of referral. There are other factors that will be discussed later – such as stage of the disease, suitability for adjuvant therapy, etc. - but this may not be confounding factors; they are not known at the time of initial referral and as a consequence they may not influence the practitioner's decision to adopt a route or another for referral. For this case mix a synopsis of the confounding factors for each separate method of referral is presented on the previous page (Fig. 6.01). When choosing the model of study to assess the null hypothesis it is essential that the groups of factors representing method of referral are comparable and well defined. The groups considered in these study present certain differences which are depicted in the synoptic table above and need due interpretation later in chapter VIII.

The predominance of male gender in this case mix was obvious - 273 cases (62.04%) males against 167 cases (37.95%) females -, giving an ***overall male/female ratio*** of 1.63 in favour of males. Yet, the same ratio appears to be smaller in the Morriston setting - 1.48 - than in the Neath setting - 1.73 -, signalling that female gender was less often diagnosed positively with cancer in Neath than in Morriston Hospital ($\chi^2 = 25.536$, $p<0.001$). The overall median age for all cancer patients was 73 years, whilst the overall mean age was 72.31 years (range 37 to 96). The distribution of cases in decades of age is shown in Fig. 6.02 below, according to the current pattern of reporting cancers based on risk prevalence.

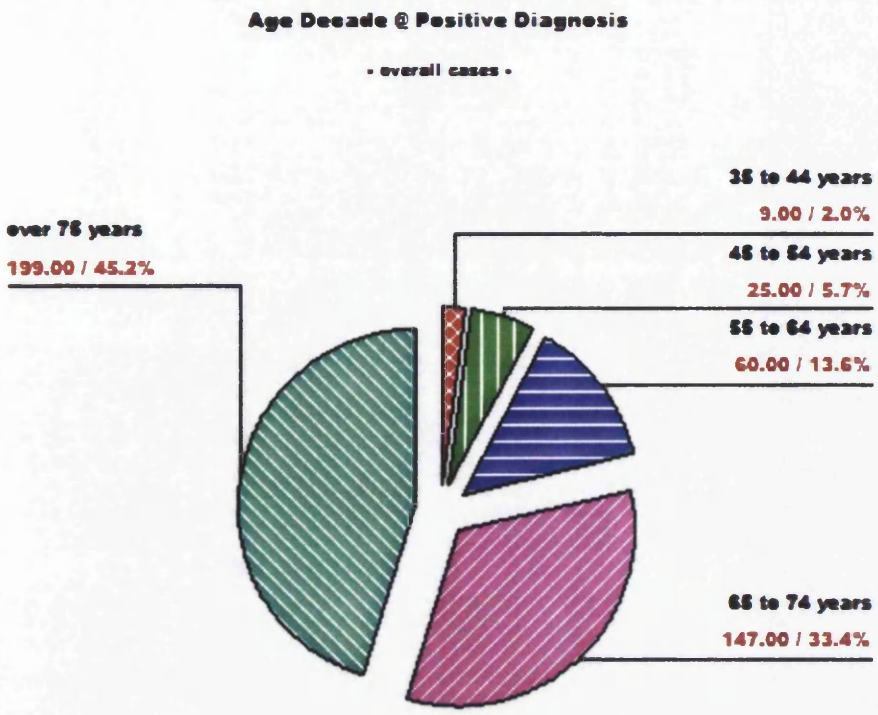

Fig. 6.02 - Case Mix Distribution per Age Decades

In this case mix the female gender seems to be diagnosed with Upper Gastro-Intestinal Cancer at an older age (females: mean age = 76.44 years, median age = 77, Std.Dev. = 10.94) than the male gender (males: mean age = 69.78 years, median age = 71, Std.Dev. = 10.55). However, there was no significant difference in respect of the patients' age between the two settings (mean age at diagnosis: Morriston = 73.72 vs. Neath = 71.40), nor between cancer localizations (mean age at diagnosis: Oesophagus = 71.21 vs. Stomach = 73.08 years).

As far as the anatomical segment is concerned, 160 cases (36.6%) were of oesophageal localization and 280 (63.63%) of gastro-duodenal topography - that is an ***oesophageal/gastric ratio = 0.571*** -. Tumours localized at cardia level - 147 cases (33.40%) - were considered, as per initial established assumptions, of either

oesophageal (93 cases at cardia/lower 1/3 oesophagus) or gastric-fundus origin (54 cases at cardia/gastric fundus), depending upon the localization of the bulk of the tumour on the endoscopic / laparoscopic / CT scan basis.

Fig. 6.03 below presents the distribution of histological types of cancers encountered:

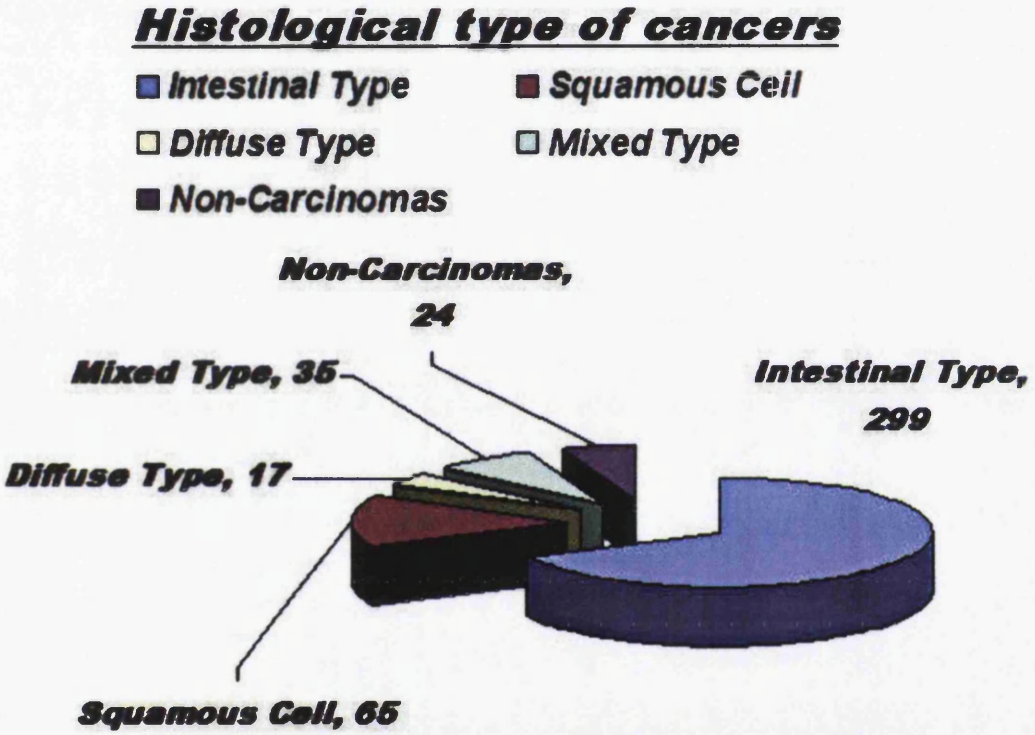

Fig. 6.03 - Histological Types of Cancers

Amongst the identified 440 cases, only 24 cases (5.50%) were non-epithelial tumours (i.e. 16 lymphomas / 4 carcinoid / 2 melanomas / 1 sarcoma / 1 myeloma) and 416 cases (94.50%) were carcinomas of various forms and differentiations. Amongst carcinomas, there were 3 cases of metastasis originating in other primary tumours which were unknown and/or asymptomatic at the

time of referral. Amongst the 24 non-epithelial cancers, 23 cases were localized in the stomach and only 1 case originated at oesophageal level (*oesophageal/gastric ratio = 0.043*).

Overall, 23 patients (5.3%) had a strong family history of malignancies, with 6 of them having more than one member of their family demised due digestive cancer; 17 patients had ancestors or siblings with gastro-oesophageal cancers and two of them had both parents demised with gastric carcinoma.

In 165 patients (37.5%) some form of past personal medical history – i.e. abdominal, gynaecological, metabolic, etc. - has been noted. These past conditions were multiple and various and can be grouped in:

- **Previous Digestive Pathologies - 134 cases (30.5%)**
- **Previous Surgical Abdominal conditions - 7 cases (1.6%)**
- **Other medical or surgical conditions - 24 cases (5.5%)**

Out of the total cohort of 440 cases, 157 patients (35.68%) presented previous digestive conditions that might have interfered with their presentation to the family doctor. These past medical conditions were as follows:

- ***In 7 cases other previous carcinomas and / or lymphomas***
- ***In 4 cases various previous abdominal surgical procedures***
- ***In 146 cases previous diagnosis and / or treatment for gastroenterological benign conditions (these include diagnosed conditions such as: Hiatus Hernia (20 cases), Gastro-Duodenal Ulcer Disease or Non-ulcer Dyspepsia (68 cases), GORD & Oesophagitis (13 cases), Chololithiasis (12 cases), Hepatic Cirrhosis (3 cases), various colon disorders excluding cancers (28 cases).***

All these patients had previous interactions with the health care system in one form or another, some of them being actually on regular follow-up lists for their medical problem. In 275 patients (62.5%) no past medical conditions were identified in their medical records.

The patients' records showed both at general practitioner's level and at hospital level a large array of symptomatology. A retrospective analysis of the symptomatology must take consideration of the limitations imposed by the current method of collecting data; this analysis is quite difficult because it relies on unstructured criteria for the recording of the patient's main symptom and/or associated symptom(s) at the time of their presentation.

1st Referral Symptom	Frequency	%
weight loss	219	16.6
dysphagia	148	11.2
abdominal pain	130	9.8
dyspepsia	96	7.3
anorexia	79	6.0
vomiting	74	5.6
lethargy	62	4.7
anaemia	59	4.5
chest pain	40	3.0
regurgitation	47	3.6
bleeding	41	3.1
other symptoms	85	6.4
No symptom 2 or symptom 3	240	18.2

Fig. 6.04 - Frequency of Symptoms at Presentation to GP

However, if recording of the first three symptoms took place in accordance with the magnitude of the sufferance each patient requested consultation for with his/her general practitioner, then the prevalence of symptoms that have been isolated are show the frequency seen in table Fig. 6.04 on the previous page. In 240 cases the patients complained of only one single symptom - at least as portrayed on the medical record -. Surely this must be dependent to many factors, including patient's threshold to discomfort, anatomical segment involved, previous gastroenterological history, etc.

Perceived Major Symptom	Frequency	%
dysphagia	103	23.4
weight loss	73	16.6
abdominal pain	73	16.6
dyspepsia	55	12.5
lethargy	35	8.0
chest pain	16	3.6
vomiting	14	3.2
anorexia	12	2.7
anaemia	12	2.7
bleeding	12	2.7
regurgitation	3	0.7
other symptoms	73	7.3
total	440	100

Fig. 6.05 - Perceived Major Symptom at Presentation to GP

When taking account of the assumptions made at the beginning that the first recorded symptom is also the most prevalent one, a list

of symptoms may emerge in which one can find a few symptoms recognized as indicators of malignancy; the frequency of the major symptom at presentation emerged from this analysis is seen in Fig. 6.05 on the previous page. Dysphagia and Weight Loss appear to be the most important causes of worry for the patient and they appear as the recorded dominant symptom in 40% of the cases, whilst dyspepsia concerns these patients in only 12.5% of the cases.

Perceived Major Symptom	Frequency	%
dysphagia	116	26.4
weight loss	29	6.6
abdominal pain	84	19.1
dyspepsia	31	7.0
lethargy	21	4.8
chest pain	23	5.2
vomiting	32	7.3
anorexia	3	0.7
anaemia	28	6.4
bleeding	29	6.6
regurgitation	2	0.5
other symptoms	42	9.5
total	440	100

Fig. 6.06 - Perceived Major Symptom of Presentation to Hospital

If we look to the symptom recorded as the most worrying for the patient at the time of his/her consultation in the hospital setting (see Fig. 6.06 on the previous page), dysphagia seems to be on the first position (in 116 cases - 26.4%) followed by Abdominal (Epigastric) Pain (in 84 cases - 19.1%). Other acute symptoms that might

precipitate patient's attendance at the specialist level - such as vomiting and bleeding - 61 cases, 13.6% - are completing the shift in symptomatology compared with the GP setting:.

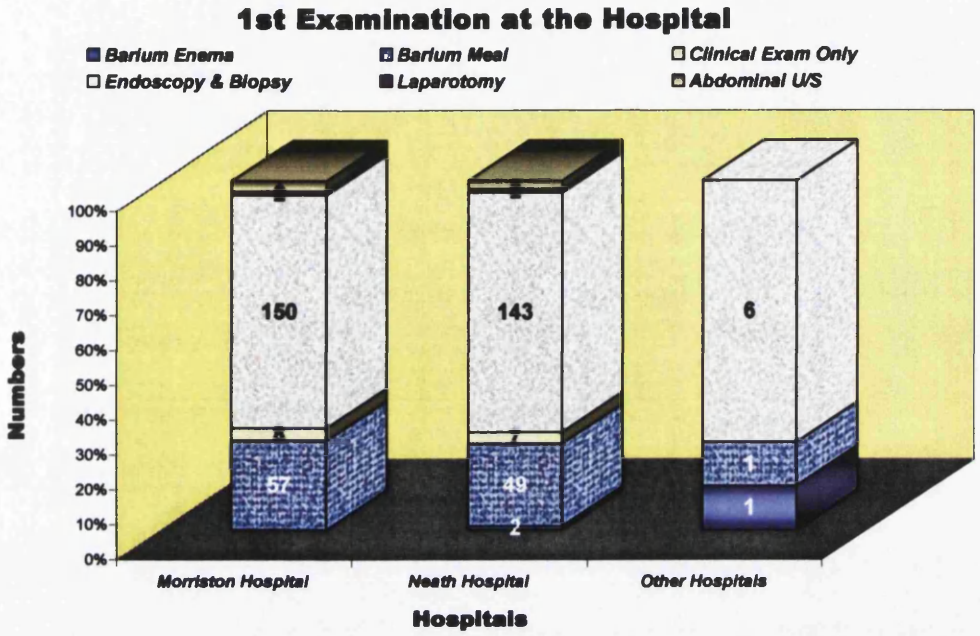

Fig. 6.07 – 1st Examination offered at the Hospital

The graph seen above (Fig 6.07) shows comparatively the first investigation undertaken at the both hospital sites; the majority of patients were channelled towards Endoscopy with biopsy; yet, approx. 3.4% were examined only by clinical means without any specific investigations arranged and, more disturbing, 107 patients (24.3%) were offered only a Barium Meal as a first line investigation. The implications of this approach to the investigation of the Upper Gastro-Intestinal Tract in this day and age merit some attention later The suspicion of malignancy with subsequent urgent scheduled investigations was obvious at the first examination in the hospital setting in only 310 cases (70.46%) whilst in other 130 (29.54%) the

required investigations were triggered without the expected degree of urgency.

All of the patients had Upper Gastro-Intestinal Endoscopy and multiple biopsies as a means of positive diagnosis. In 4 cases the positive diagnosis was made after the surgical treatment was performed as an emergency operation for various complications of the cancer itself - i.e. bleeding tumours, perforated tumours, etc. -. There were 8 other cases, emergencies as well, where the positive diagnosis was made during the laparotomy itself, either by frozen section histology or definitive histology on the operative specimen. In 2 patients the positive diagnosis has been reached only at necropsy. Various other investigations (e.g. CXR / U/S scan / CT scan / endoscopic U/S / laparoscopy / etc.) were undertaken for staging purposes as below:

Barium Meal	**undertaken in**	**139 patients (31.6%)**
Endoscopic U/S Scan		**280 patients (63.6%)**
CT Scanning		**225 patients (51.1%)**
Laparoscopic U/S Scan		**98 patients (22.3%)**
Laparoscopy		**98 patients (22.3%)**
Laparotomy		**10 patients (2.3%)**
Ba Enema		**10 patients (2.3%)**
Necroptic		**2 patients (0.5%)**

After positive diagnosis and staging investigations, the pre-operative T-stage distribution of the epithelial tumours is as shown in Fig. 6.08 on the following page; it refers at the "T" component of the TNM stage.

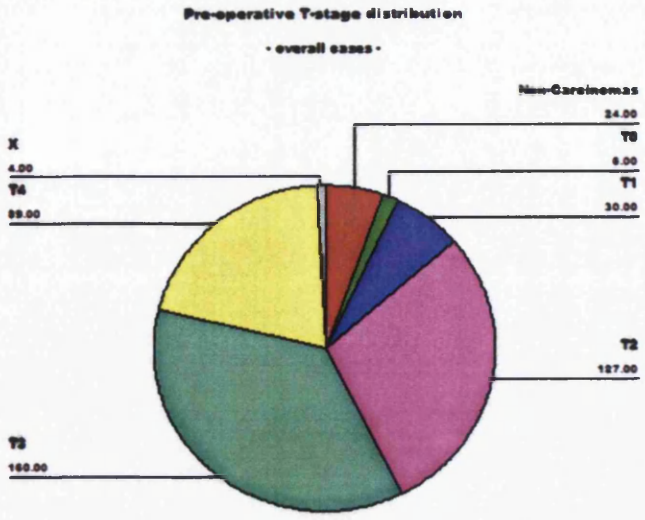

Fig. 6.08 - Overall T - stage Distribution

When taking into consideration the other elements of the clinical TNM stage, i.e. *N* = Nodes and *M* = Metastasis, the pre-operative distribution in clinical TNM stage of this case mix is presented in figure 6.09 below:

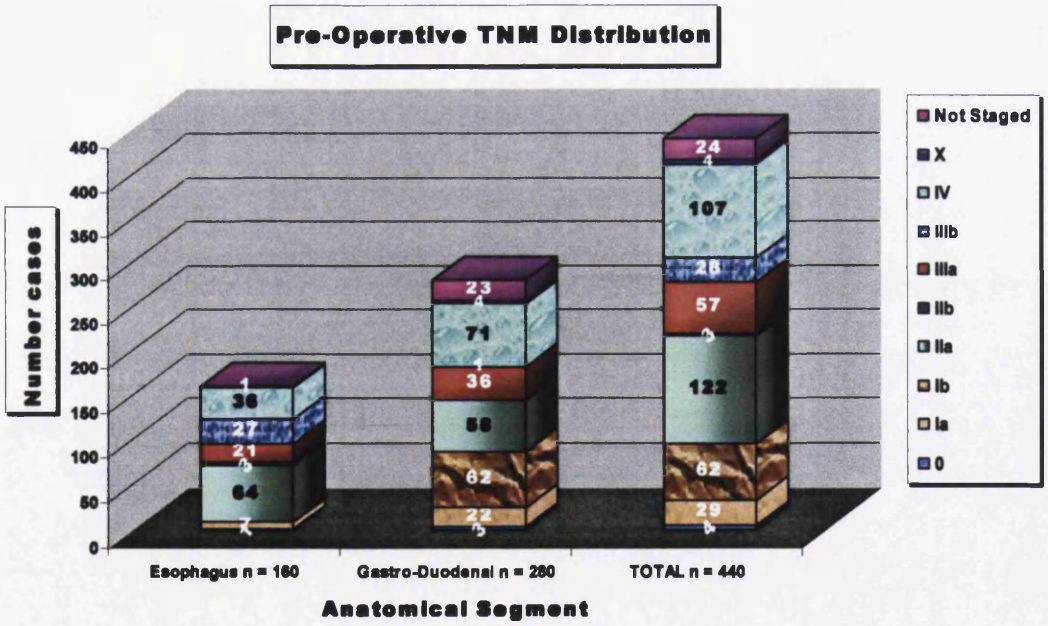

Fig. 6.09 - Overall Clinical TNM Stage Distribution

The overall pre-operative *early/advanced cancer ratio* for this uncensored case mix was 36/376 = 0.095 and the *differentiated/undifferentiated ratio was 170/218 = 0.779.*

C. Distribution of Services & Method of Referral

The two hospital settings made use of the various modalities of referral slightly differently, although the distribution of cases between the settings was approximately similar. The 440 patients have been referred initially to one of the following group of specialties / departments, as a referral from their General Practitioner to the secondary healthcare provider:

- **surgical (incl. General/ENT/Orthopaedic/etc.) 98 cases (22.3%);**
- **medical (incl. Cardiology/Geriatrics/etc.) 219 cases (49.8%);**
- **gastroenterology alone 123 cases (28.0%);**

The modality of primary referral included the following services, available to both hospitals:

- **Acute Admission 149 cases (33.9%);**
- **Elective Outpatients 185 cases (42.0%);**
- **Open Access endoscope 94 cases (21.4%);**
- **Rapid Opinion Clinic (Neath setting alone) 12 cases (2.7%).**

The two hospitals made use differently of the new clinical services created to serve the gastroenterological referrals - Neath Hospital = 62 cases, vs. Morriston Hospital = 43 cases (χ^2 = 7.050, p = 0.008). The *Appendix A07* shows the distribution of cases between the two settings based on the modalities of referral and clinical services used. It appears that for the Neath General Hospital setting a larger

proportion of cancer patients - 77 (37.0%) and 72 (34.6%) patients respectively - were referred almost equally to the medical and gastroenterological services, whilst for Morriston Hospital a larger proportion of referrals were channelled to medical services alone, nearly equally distributed between the Admission and Outpatient Clinic modality of referral - 142 (61.2%) patients ($\chi^2 = 25.727$, $p < 0.001$). It also appears (*see Appendix A08*) that the overall preferred department for referral was the medical department, particularly for the age group of above 75 years of age (113 patients out of 199), whilst for the modality of referral the preferred one was admission for the older patients (above 75 years 44.22%) and Outpatients Clinic for younger ones (55 to 64 years of age 46.66%).

D. Speed of Referral, Diagnosis & Submission to Treatment

Both of the hospitals made use of the new modalities of referral to channel the patients for a speedy resolution of their symptoms and to establish as urgently as possible the correct diagnosis and treatment. Since the interval of time taken by the patient to come forward for a consultation as well as the time spent for him / her to be examined and staged within the secondary care sector are potential sources for delay in the management of these patients, I have next looked at what has been named as "delay intervals" (see Chapter V - Assumptions).

a) Onset Delay

A certain amount of time elapses until the patient, already symptomatic, makes his way to the general practitioner or family doctor. This longer or shorter interval of time, which extends up to the day of the first GP Examination, is defining the "Onset Delay" in *Appendix A01*. This interval is the most difficult period to be quantified in a retrospective analysis and therefore the assumptions introduced in Chapter V apply very heavily here. Based on these assumptions, the data collected from patients' records shows for the overall case mix a net prevalence of a 3 months onset delay; in other words the majority of patients have waited on average up to 3 months before seeking medical advice (Fig. 6.10 below).

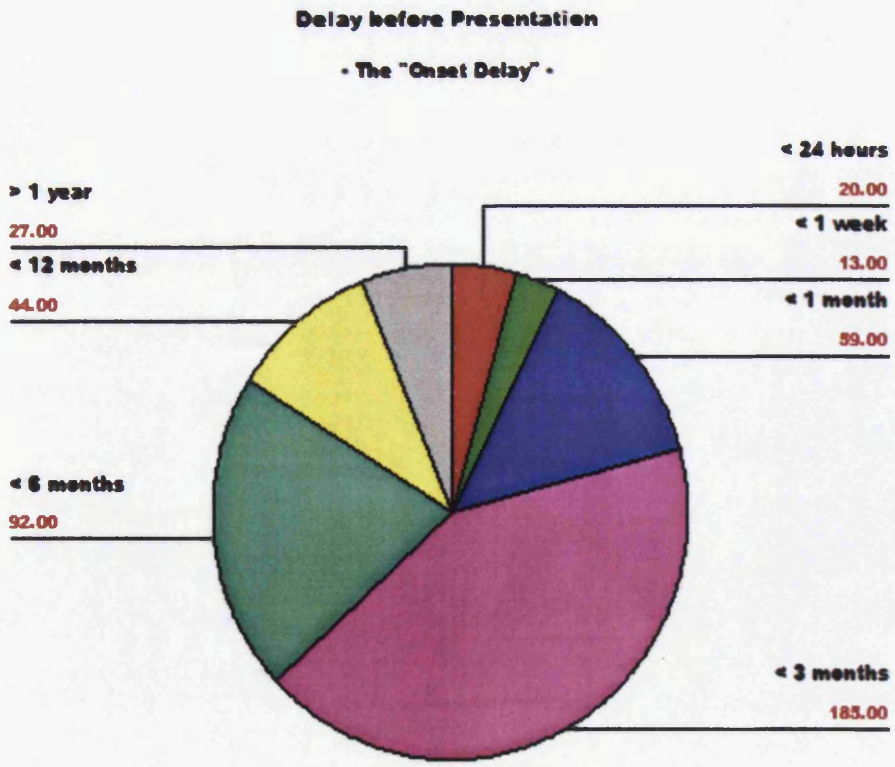

Fig. 6.10 - Overall "Onset Delay" Distribution

There was no difference in the Onset Delay between the patients diagnosed with involvement of different anatomical segments of the upper gastro-intestinal Tract: in the stomach group 64.0% of patients requested medical advice within 3 months of becoming symptomatic vs. 60.7% of patients in the oesophageal group ($\chi^2 = 0.463$, $p = 0.490$). Similarly, other variables such as: gender - 59.5% of females requested examination in the first three months against 64.0% of males ($\chi^2 = 2.837$, $p = 0.829$) -, age group ($\chi^2 = 17.828$, $p = 0.811$) and hospital setting, appear not to introduce any longer period of delay in seeking medical consultation with the general practitioner, although of note is the observation that the confounding groups are not comparable.

The relationship between the Onset Delay as an interval of delaying the presentation and the perceived prevalent symptom at presentation is difficult to assess due to the limitations of data collection imposed by the retrospective character of the study. In this case mix the first 5 major symptoms noted at presentation (see Fig. 6.05 above) - i.e. Dysphagia, Weight Loss, Abdominal Pain, Dyspepsia and Lethargy - were related to an Onset Delay of a minimum of three months in 42.04% of patients compared to an overall Onset Delay of a minimum three months in 62.95% of all patients (Pearson correlation = 0.309, $p<0.001$).

b) GP Delay

This interval equates with the time past between patient's first presentation to the general practitioner and the actual referral made for further investigation. This is related with the capacity of the general practitioner to assess the severity of a patient's symptoms and decide the appropriate modality of referral. The overall mean GP Delay interval was 17.09 days with a median delay of 0 days (Std.Dev. = 46.23). The age decade the patient belongs to is obviously a significant diagnostic aid which should trigger a certain degree of diagnostic suspicion within the clinical context.

Age Group	*n*	Mean *(days)*	Median *(days)*	Std. Dev.
35 -44	9	40.88	8	71.27
45 – 54	25	8.40	0	14.25
55 – 64	60	29.68	0	66.49
65 – 74	147	19.81	0	52.89
>75	199	11.31	0	31.71

Fig. 6.11 - "GP Delay" at various Age Decades

The age group, together with other confounding factors shown earlier, represent the only elements for guidance available to the general practitioner when he/she may decide to adopt a route or the other for referral purpose. Based on the combination of these factors the clinical judgement will dictate the practitioner to adopt an emergency route for referral or to adopt a more standard approach. Although the majority of cases were referred straight to the secondary care sector

for further investigation - median delay 0 days -, there is still a certain degree of delay in referral seen in certain age groups (Fig. 6.11 above).

Obviously, the general practitioner, based on his/her assessment of the case, may decide to issue the referral to one clinical service or another, using one method of referral or another. The table in Fig. 6.12 below shows the mean and median figures for the GP Delay interval relative to the various clinical services used and the modalities of referral employed to send patients to the secondary sector:

Clinical Service	*n*	Mean *(days)*	Median *(days)*	Std. Dev.
Surgical Dept.	98	15.44	0	38.83
Medical Dept.	219	17.17	0	51.68
Gastroenterology	123	18.26	0	41.40
Acute Admission	149	6.14	0	17.14
Outpatients Dept.	185	24.92	0	59.96
O A E	94	19.94	0	46.19
R O C	12	10.08	0	19.29

Fig. 6.12 - Mean & Median "GP Delay" and Clinical Services

The GP Delay interval seems to be slightly longer for the oesophageal patients - in days: mean = 18.46, median = 0, Std.Dev. = 45.90 - compared with the gastro-duodenal localizations - in days: mean = 16.43, median = 0, Std.Dev. = 46.62 -.

c) Hospital Delay

This is the time which spans between the dates of the general practitioner's referral letter to the first appointment the patient

attends at specialist level. The "Hospital Delay" is actually the interval targeted by the "two week rule" in cancer services and reflects primarily the ability of the system to provide for the patient; also, in some cases at least, this may be influenced by the patient's incapacity to take up the first appointment offered. The overall mean Hospital Delay was 15.96 days and the median value was 11 days (Std.Dev. = 18.68).

Variable	*n*	Mean *(days)*	Median *(days)*	Std. Dev.
Neath Hospital	208	16.73	13	17.91
Morriston Hospital	224	14.94	7	18.89
Other Hospital	8	24.62	16.50	29.81
Surgical Dept.	98	17.87	16	17.96
Medical Dept.	219	11.87	1	18.82
Gastroenterology	123	21.79	18	17.30
Acute Admission	149	1.44	0	6.57
Outpatient Clinic	185	24.37	20	19.81
O A E	94	23.17	18	16.26
R O C	12	10.25	9	4.99

Fig. 6.13 - Synopsis of the "Hospital Delay"

The table above (see Fig. 6.13) presents comparatively the mean and median figures for the Hospital Delay interval with respect to the hospital setting, clinical services and modalities used to refer patients. The demographic variables did not introduce any significant changes in the respective figures for the mean and median delay on this segment. However, it appears that the elderly group of patients above

75 years of age enjoyed the shortest Hospital Delay interval - mean = 12.67 days, median = 6 days (Std.Dev. = 16.13) - when compared with younger patients of 55 to 64 years of age where this interval was nearly double - mean = 24.13 days, median = 17 days, (Std.Dev. = 26.60) -.

It appears that the patients had their first appointment quicker at Morriston University Hospital and using the medical department. In respect of the method of referral used, the shortest Hospital Delay was accomplished by using Acute Admission and the Rapid Opinion Clinic respectively. As expected, the longest wait occurred for patients referred via an Outpatient Clinic appointment.

d) Diagnosis Delay

This interval mirrors the time required by the hospital to confirm endoscopically and histologically the positive diagnosis of Upper Gastro-Intestinal Cancer. Usually it is accomplished when the histopathological result is reported back by the pathologist. It follows that a number of days are automatically introduced for processing purposes. The overall "Diagnosis Delay" interval was surprisingly longer than expected - mean = 38.95 days, median = 10 days, Std.Dev. = 87.98.

Looking at each of the hospital settings, a quicker positive confirmation appeared to happen in other referring hospitals followed by Morriston and Neath settings; it also appears that a positive

diagnosis was reached quicker in the gastroenterology department and using the Open Access Endoscopy method of referral. As expected, the delay to positive diagnosis was longer if the patient was referred via the Outpatients Clinic as a method of referral (Fig. 6.14 below).

Variable	*n*	Mean *(days)*	Median *(days)*	Std. Dev.
Morriston Hospital	224	30.62	9.50	64.59
Neath Hospital	208	48.64	11.50	108.19
Other Hospital	8	20.12	0	31.28
Surgical Dept.	98	50.06	15.50	79.97
Medical Dept.	219	40.81	13.00	85.70
Gastroenterology	123	26.78	0	96.91
Acute Admission	149	26.18	8	60.41
Outpatients Dept.	185	63.29	22	116.20
O A E	94	13.34	0	38.92
R O C	12	22.83	0	55.61

Fig. 6.14 - Synopsis of the "Diagnosis Delay"

The Diagnosis Delay in conjunction with the demographic variables showed that in the elderly group of above 75 years of age the Diagnosis Delay was longer - mean = 42.78 days, median = 10 days, Std.Dev. = 106.37 - than for the younger patients - mean = 19.66 days, median = 8 days, Std.Dev. = 29.44 -. In respect of the anatomical segment involved in the malignancy process, oesophageal tumours seem to be positively diagnosed quicker - mean = 31.21 days,

median = 8 days, Std.Dev. = 90.89 - than the gastro-duodenal tumours - mean = 43.34 days, median = 13.0 days, Std.Dev. =86.37 -.

Based on the Lauren classification of carcinomas, it appears that the intestinal type of cancer took longer to be positively diagnosed - mean = 36.29 days, median = 11 days, Std.Dev. = 73.69 - than the diffuse type - mean = 19.76 days, median = 7 days, Std.Dev. = 55.23 -. This appears to be linked more significantly to the gastric localization than to the oesophageal one ($\chi^2 = 32.727$, $p<0.001$).

e) Treatment Delay

This is the interval of time elapsed between the moment of established positive diagnosis of malignancy and the beginning of definitive treatment. It normally incorporates both the time taken for staging procedures and the delay in actually commencing the treatment itself.

Not all 440 cases were submitted to some form of treatment: 140 cases (31.84%) were not given any form of treatment based on both their overall clinical picture and evidence-based appraisal of the stage of their disease and/or the patient's refusal of treatment, whilst 222 patients (50.45%) were subjected to one form of surgical procedure or another. In two cases the positive diagnosis was established after definitive treatment provided in emergency conditions. The overall Treatment Delay for those patients treated in one form or another - 300 patients (68.16%) - as well as its synopsis

for anatomical involvement as a variable is shown in table below (see Fig. 6.15 below):

Variable	n	Mean (days)	Median (days)	Std. Dev.
Overall Treated Cases	300	44.43	33.50	46.20
Surgical Cases	222	39.24	29	41.25
Chemo ± RxTh	78	55.50	49	37.88
Oesophagus	84	54.36	41	52.72
Gastro-Duodenal	188	38.97	28	41.50

Fig. 6.15 - Synopsis of the "Treatment Delay" (treated patients)

There was no significant difference (χ^2 = 25.536, p = 0.001) in the delay to treatment for both genders - mean = 38.42 days (Std.Dev. = 50.29) for males and mean = 42.56 days (Std.Dev. = 52.35) for females respectively, but it seems that the younger group of patients were submitted to treatment much quicker:

Age Group	n	Mean (days)	Median (days)	Std. Dev.
35 – 44	9	26.11	17	24.25
45 – 54	25	41.90	34	32.53
55 – 64	60	39.90	31.50	36.98
65 – 74	147	49.66	38.50	52.86
>75	199	42.99	28	46.17

Fig. 6.16 – "Treatment Delay" and Age Decades (treated patients)

Using the clinical services and the method of referral as variables, it appears that the Treatment Delay was shorter when patients were referred as a targeted department of referral to the

surgical department using an Acute Admission modality. However, there was no significant difference between hospital settings:

Variable	*n*	Mean *(days)*	Median *(days)*	Std. Dev.
Morriston Hospital	224	43.11	31	47.47
Neath Hospital	208	45.95	36	45.55
Surgical Dept.	98	37.38	26	36.43
Medical Dept.	219	42.20	28	54.03
Gastroenterology	123	52.03	42	39.24
Acute Admission	149	35.20	21	55.91
Outpatients Dept.	185	43.89	32	44.46
O A E	94	55.03	42	38.09
R O C	12	54.88	44	31.89

Fig. 6.17 - "Treatment Delay" and Clinical Services

The clinical stage of the disease – that is the stage of the T after quantification of the Tumour at the staging procedures - was significantly linked with a longer treatment delay (Pearson χ^2 = 589.535, p = 0.001). It appears that advanced cancers waited longer for the treatment than early cancers - T_4 tumours mean = 53.47 days - than early cancers - T_0 tumours mean = 23.66 days.

f) NHS Delay

Some authors use, as a measure of NHS efficiency, the interval from the first GP examination to the moment the treatment has commenced; this is variably named in the medical literature but most authors agree with the term NHS Delay; indirectly, it may signify the delay introduced at NHS infrastructure level in submitting the patient

to diagnosis and treatment. When taking into consideration the whole case mix, I found this global interval rather long - mean delay = 117.88 days, median = 82 days, Std.Dev. = 115.34 -.

The overall NHS Delay interval for the 300 cases treated in a form or another was significantly longer for early cancers than for advanced ones - in the sample of 280 cases of carcinomas, 20 cases of non-carcinomas treated with surgery or / and adjuvant therapy produced a mean NHS Delay of 191.60 days - although other forms of gastro-intestinal cancers had longer delays too -; it seems that the gastric localization required a longer mean NHS Delay interval (see Fig.6.18 below):

Variable	*n*	Mean *(days)*	Median *(days)*	Std. Dev.
Gastric Cancer	201	120.59	80	126.27
Oesophageal Cancer	97	113.27	91	93.41
Duodenal Cancer	2	101.50	101.50	109.60
Advanced Cancer	240	108.31	77	94.72
Early Cancer	36	144.81	95	163.66
Other Cancer	24	191.60	149	149.76

Fig. 6.18 - Synopsis of the "NHS Delay"

There was no significant difference between genders - mean delay = 117.13 days for males vs. mean delay = 119.31 days for females -, although again for Morriston University Hospital site the mean NHS Delay interval was significantly shorter (mean = 108.73 days), than for the Neath site (mean = 127.79 days).

Looking at the clinical services that the patients were channelled to, as well as to the methods of referral, it appears that referral to Gastroenterology as a service offered a shorter NHS Delay (mean delay = 110.88 days) than to the other clinical services; it was obvious that Admission as a method of referral offered patients the shortest route to treatment (see Fig. 6.19 below).

Variable	*n*	Mean *(days)*	Median *(days)*	Std. Dev.
Surgical Dept.	**98**	119.35	88	108.54
Medical Dept.	**219**	122.95	66	142.95
Gastroenterology	**123**	110.88	89	69.32
Acute Admission	**149**	66.67	33	98.72
Outpatients Dept.	**185**	155.47	109	136.41
O A E	**94**	109.37	86.50	67.50
R O C	**12**	101.88	52	78.12

Fig. 6.19 – "NHS Delay" compiled for Services & Referral Method

Before discussing the results mentioned above in the wider context of speed of referral and early diagnosis of upper gastro-intestinal cancer, the data collected permits a general look to the issues of clinical outcome and survival for these patients.

Chapter VII

RESULTS: OUTCOME & SURVIVAL

Summary: *Changes in the outcome are scrutinized in respect of a few variables such as staging of the disease, operability, recurrence and survival rates. Staging of the disease is looked at both from a pre-opera angle, where only 36 cases are noted to be in the early stages, as well as from a post-operative perspective where in the carcinoma group only 21% of patients appear to have early cancers. It is noted that only 222 patients were submitted to some form of surgical treatment, raising the crude operability rate in this series to 50.40%. Only 139 (31.59%) cases had radical surgery, whilst 168 patients (38.18%) were beyond any treatment means. Clinical records show only 92 patients (41.44%) with clear evidence of recurrence of the disease, although it is speculated that in many others the pattern of post-operative progression might also be suggestive of a recurrence. In this series the patients' survival, as a true measure of the implementation of clinical algorithms and services, is monitored as per current medical literature at 1 year and 5 years. It is noted that the overall 5 year survival rate is 15.06% and the mean survival is 472.87 days. Those patients who were referred to the gastroenterology department and had only surgical treatment as a method of definitive treatment yield the largest number of patients living for more than 1 year and 5 years respectively.*

Subheadings in this Chapter:

A. Staging & Treatment
B. Recurrence of Disease
C. Survival

It is expected that the innovative clinical services and the implemented methods of referral would have a certain impact upon the whole management of our patients diagnosed positively with Upper Gastro-Intestinal Cancer. The speed with which the patients have been eventually submitted to the referral process and open services appointments system may also have a certain impact in relation with their clinical outcome following investigation and

treatment. When judging these outcome results, it is paramount to look at several factors that might define in a quantifiable manner the potential benefit triggered by the implemented services and referral methods; variables such as staging of the disease, operability, adjuvant therapy, recurrence and not least survival parameters may be considered quantifiable variables suitable for this purpose.

A. Staging & Treatment

In this series of 440 patients, 416 cases (94.54%) presented with various forms of carcinomas; they were staged immediately after positive diagnosis according to the revised (1997) TNM[1] classification of cancers adopted by the UICC. The pre-operative TNM staging of these 416 cases is shown in Fig. 7.01 on next page. In four cases the minimum set of staging investigations needed to determine the pre-treatment values of T, N and M has not been achieved - therefore their stages were shown as stage X - all four cases belonging to the gastro-duodenal group -. 312 patients (75.0% in the carcinoma group) were noted to be diagnosed in stages not suitable for curative treatment; only 36 cases (8.65% of patients with carcinomas) could be labelled under the current standard as early cancers. Also, there were 24 cases (5.45%) of non-epithelial cancers - 16 lymphomas, 4 carcinoid

[1] TNM Classification of Malignant Tumours Sixth Edition, Union Internationale Contre Cancer (UICC), Geneve, Switzerland, Sobin,LH, Wittekind,CH, ISBN 0-471-22288-7

tumours, 2 melanomas, 1 sarcoma and 1 myeloma - and these cases cannot be staged under the TNM classification.

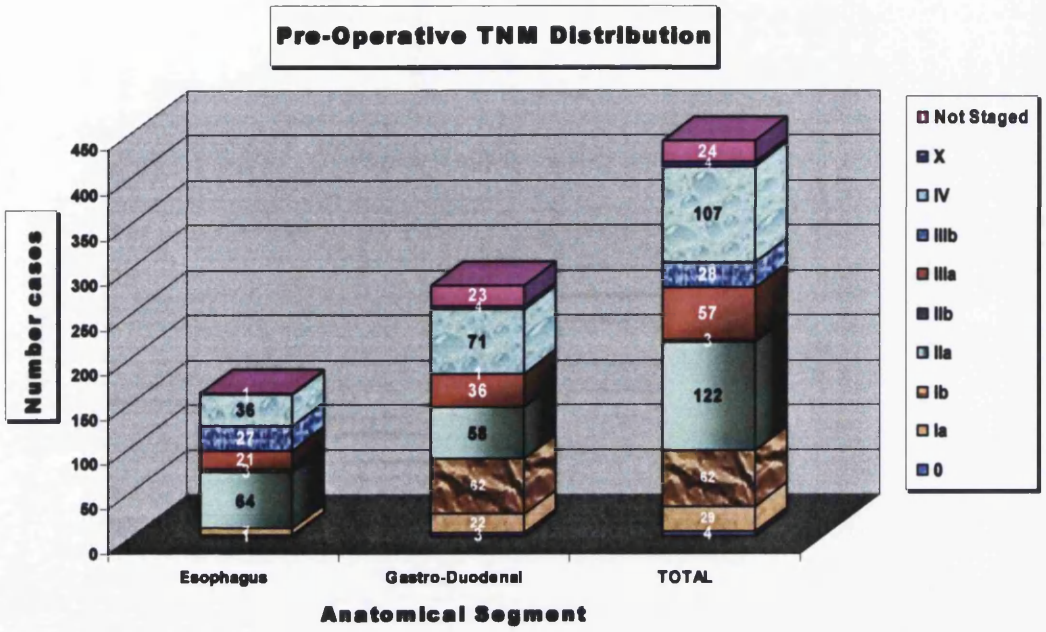

Fig. 7.01 – Carcinomas - Pre-operative TNM Stage Distribution

In this series I found only 12 cases where the Multidisciplinary Team (MDT) Meeting has agreed that pre-operative down-staging adjuvant chemo-radiation therapy might be beneficial - 8 cases of oesophageal tumours and 4 cases of gastric cancers -. In the oesophageal group, 7 cases presented with the bulk of the tumour within the lower third of the oesophagus and only one case within the mid third. 11 cases were adenocarcinoma and only one down-staged case was a squamous carcinoma of the mid-third of the oesophagus.

The following graph (see Fig. 7.02 on the next page) presents the modality of treatment the patients were submitted to; in 222 patients the surgical management of the disease was the chosen method of treatment, giving a crude operability rate of 50.45%. Following

surgery, 59 of these patients (26.57%) were submitted to further chemo +/- radiotherapy as adjuvant treatment.

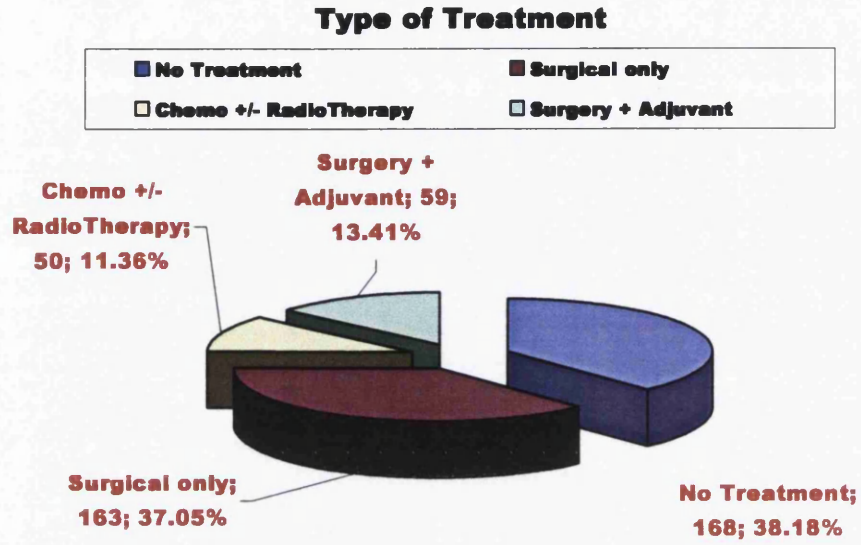

Fig. 7.02 - Overall Treatment Modalities

However, 168 patients (38.18%) were not deemed either fit for any sort of treatment (48 patients - 10.90%) or not envisaged to have gained any benefit other than symptomatic relief. In 50 patients (11.36%) chemo +/- radiotherapy was the only method of treatment.

The treatment modalities applied to each anatomical localization are shown in Fig. 7.03 on the next page. The localization of the neoplasm at gastro-duodenal level made the patient more susceptible to some form of surgery - 160 patients (57.85%) out of 280 cases had surgery - compared with the oesophageal localization - 60 patients (37.5%) out of 160 cases had surgery (Pearson $\chi^2 = 20.697$, $p = 0.002$) -. A larger proportion of the patients from the oesophageal group - 76

cases (47.50%) out of 160 - had no form of treatment compared to the gastric group - 92 cases (32.85%) out of 280 - This is largely due to the stage at presentation and the age group association (χ^2 = 132.49, p<0.001) .

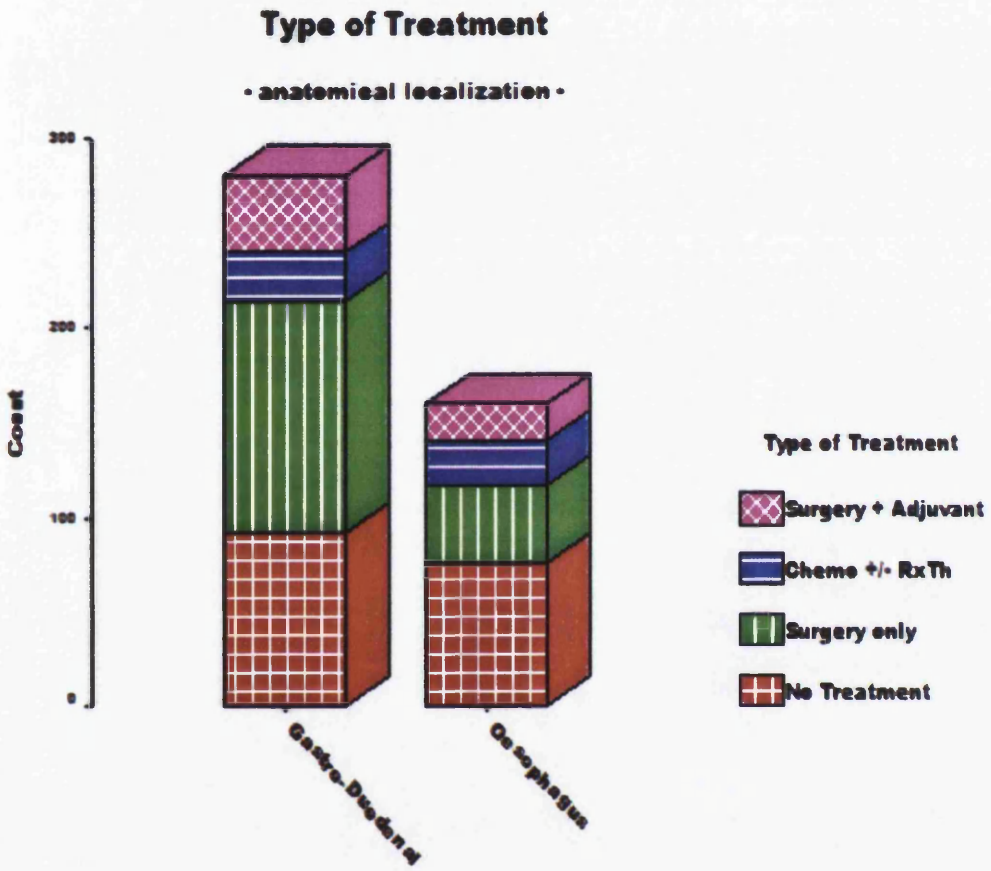

Fig. 7.03 - Treatment for Anatomical localizations

If we are matching the treatment method used for each of the anatomical parts of the oesophagus and stomach respectively (see Fig. 7.04 below), a pattern is noted by which the more the proximal the tumour is, the less likely would be the patient would be subjected to surgical +/- adjuvant treatment (Pearson χ^2 = 52.76, p<0.001):

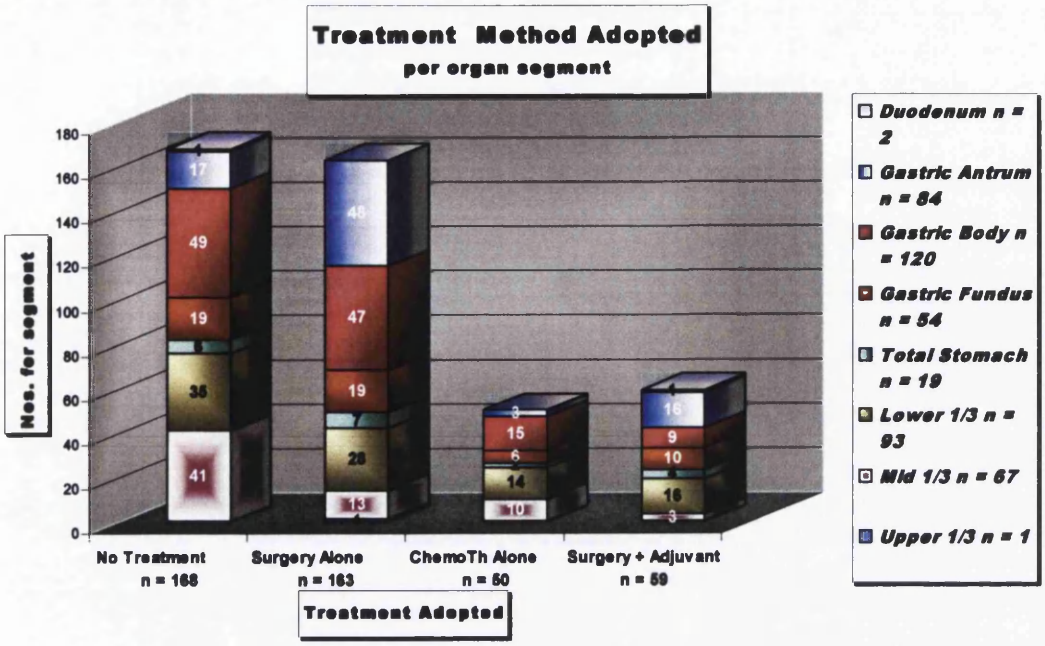

Fig. 7.04 – Oesophageal & Gastric - Segment-related Treatment

The distribution of patients who were subjected to surgical treatment relative to their stage of the disease is shown in Fig. 7.05 (for the oesophageal group) and Fig. 7.06 for the gastro-duodenal group.

Surgery Per-formed	0	I	IIa	IIb	IIIa	IIIb	IV	X	Total
no		2 (2.0%)	35 (35.0%)	2 (2.0%)	11 (11.0%)	18 (18.0%)	32 (32.0%)		100 (100.0%)
yes	1 (1.7%)	5 (8.5%)	29 (49.2%)	1 (1.7%)	10 (16.9%)	9 (15.3%)	4 (6.8%)		59 (100.0%)
Total	1 (0.6%)	7 (4.4%)	64 (40.3%)	3 (1.9%)	21 (13.2%)	27 (17.0%)	36 (22.6%)		159 (100.0%)

(Pearson χ^2 = 18.67, p = 0.005)

Fig. 7.05 - Oesophageal Cancers & their pre-operative TNM stage

74 patients (34.4%) of the 218 non-surgical ones were in TNM stages I and II of the disease or were non-carcinomas (7 cases). In the surgical group of 222 patients, 74 of them (33.40%) belonged to TNM

stage III and IV as advanced cancers where curative therapy is not expected.

Surgery Per-formed	0	Ia	Ib	II	IIIa	IIIb	IV	X	Total
no		2 (1.8%)	13 (11.7%)	20 (18.0%)	17 (15.3%)	1 (0.9%)	57 (51.4%)	1 (0.9%)	111 (100.0%)
yes	3 (2.1%)	20 (13.7%)	49 (33.6%)	38 (26.0%)	19 (13.0%)		14 (9.6%)	3 (2.1%)	146 (100.0%)
Total	3 (1.2%)	22 (8.6%)	62 (24.1%)	58 (22.6%)	36 (14.0%)	1 (0.4%)	71 (27.6%)	4 (1.6%)	159 (100.0%)

(Pearson χ^2 = 68.88, p<0.001)

Fig. 7.06 - Gastro-Duodenal Cancers & their pre-operative TNM stage

However, it appears that the elderly group of 74 years of age and above was subjected to no treatment what-so-ever in 57,8% of the cases, whilst the younger patients belonging to the decades of 55 to 74 years of age were subjected to some form of surgery in the proportions of 75.0% and 55.1% respectively (χ^2 = 99.047, p<0.001). From a gender standpoint, 77 patients (46.1%) from the female group had no treatment against 91 patients (33.3%) in the male group. It also appears that male patients - 140 patients (51.3%) - were subjected more often to some form of surgery compared with the female group where only 82 cases (49.1%) had surgery(χ^2 = 17.012, p = 0.001).

Chemo +/- radiotherapy as a form of palliation was given more often to male patients - 42 males (15.4%) - than to female patients - 8 females (4.8%) -. In those 222 cases where surgical management was

deemed beneficial, the following types of surgical procedures were deployed (Pearson $\chi^2 = 61.65$, $p<0.001$):

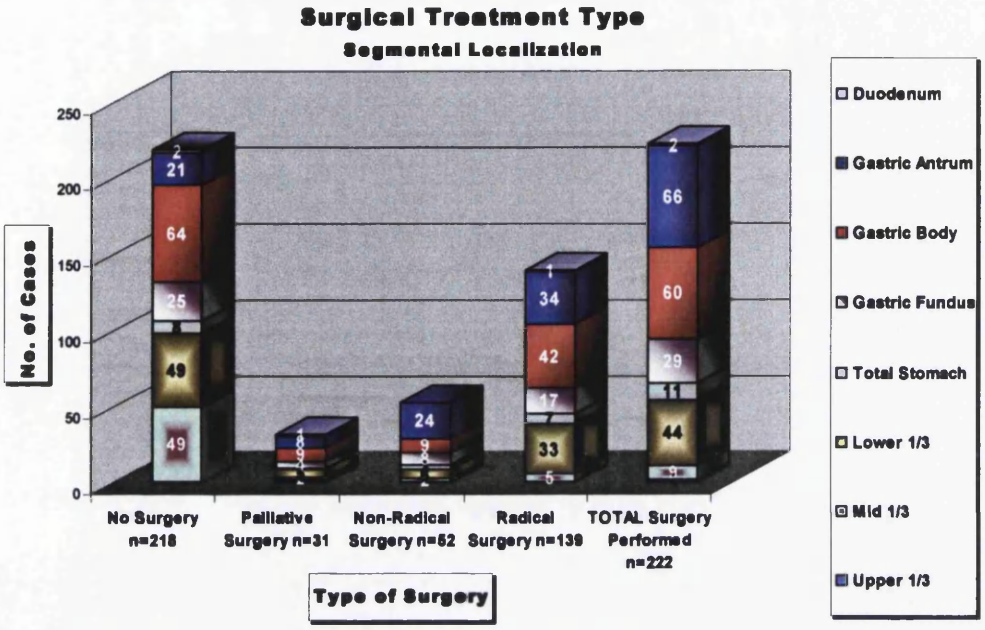

Fig. 7.07 - Type of Surgical Procedures Performed

Mean corrected age for surgical patients was 68.80 and median age was 69.50 (Std.Dev = 10.73). The procedures addressed gastro-duodenal cancers in 162 cases (72.97% of the overall surgical episodes) and oesophageal localizations in 60 cases (27.02%). As expected, the operability was higher at younger decades - 77.8% and 64.0% at the decades of 35 to 44 and 45 to 54 years respectively - rather than in the elderly people - 36.7% operability beyond 74 years of age -. The graph below (Fig. 7.08) shows the type of surgery undertaken with respect to the pre-operative assessment of the clinical TNM stage; it emphasizes the relationship between equivalent TNM stages in both oesophageal and gastric localizations (2 = 32.07, p = 0.022) and treatment strategy adopted. As expected, the more

advanced the stage of the disease, the less radical the surgical treatment is.

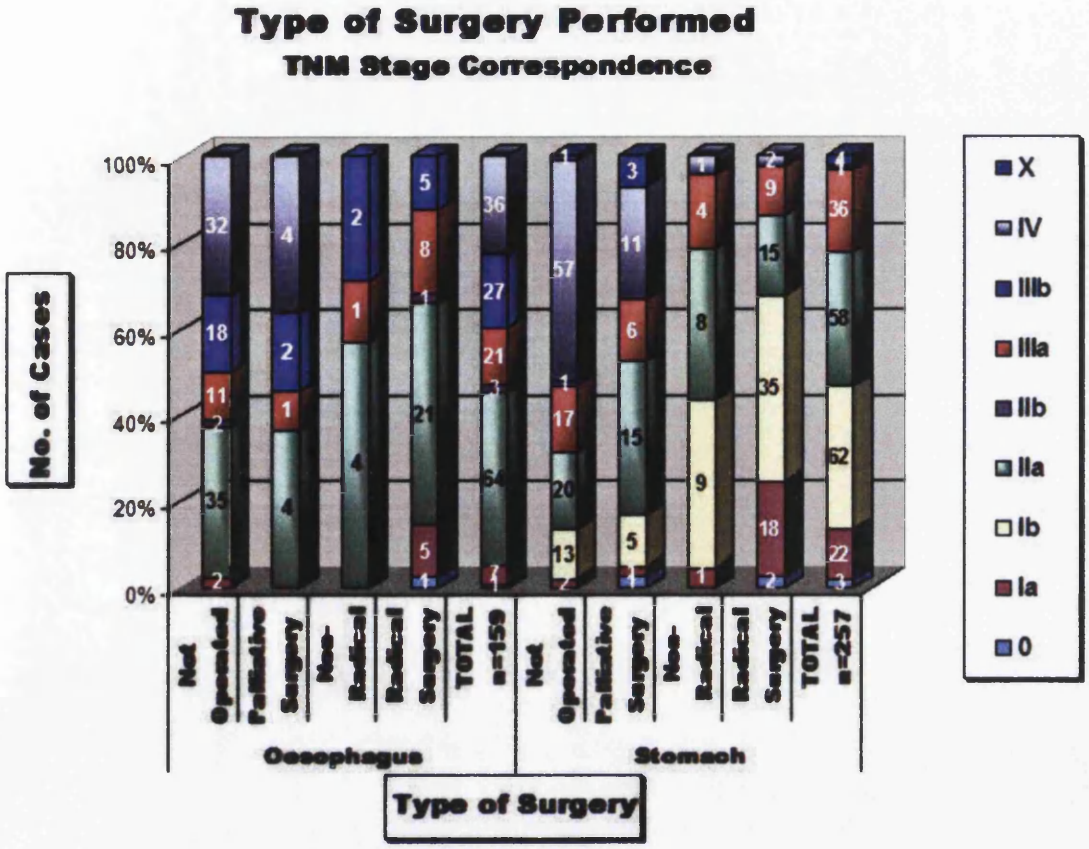

Fig. 7.08 – TNM Stages & Types of Surgical Procedures

The postoperative pathological pTNM staging - i.e. the T, N and M stage based on clinical "T", "N" and "M" grouping and concluded after definitive surgical treatment - is shown in the graph (see Fig. 7.09 on the next page). Among the surgical cases, 17 (7.7%) were non-carcinomas and they were not staged. Within the carcinoma group, the majority of cases - 145 cases out of 222 (65.30%) - were found in stages III and IV beyond potential curativity and only 21 patients (9.50%) were found with early cancers.

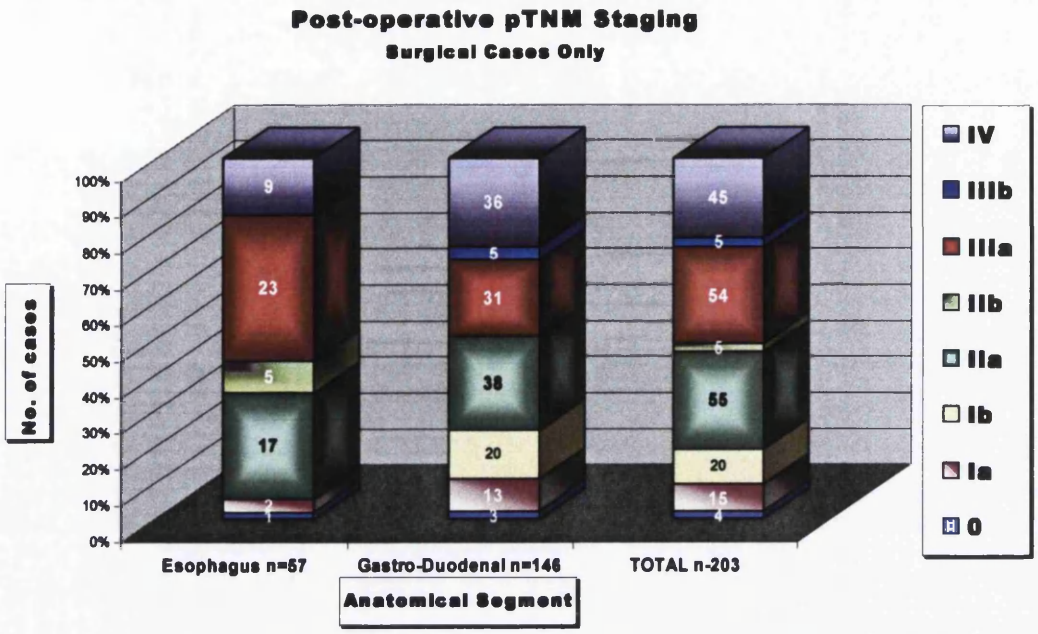

Fig. 7.09 - Post-operative pTNM Stages

In 66 cases (15.0%) included in the study some form of palliation was used, other than surgical palliative resection or adjuvant therapy. These forms of palliation were:

- Gastric by-pass	-	1 case (0.2%)
- Gastrotomy	-	2 cases (0.5%)
- Dilatation	-	9 cases (2.0%)
- Stenting	-	54 cases (12.3%)

There were only 2 complications of oesophageal rupture with demise following stent insertion. Overall postoperative mortality - i.e. mortality occurring within 30 days following surgery - was 13.51% (30 cases). For each anatomical localization of cancer the mortality was:

- operated oesophageal cancer	-	10 cases (4.5%)
- operated gastro-duodenal cancer	-	20 cases (9.0%)

Mortality in these cases was due to several pathological entities, some of them being a mirror of the background co-morbidities:

- **anastomotic leak - 7 cases**
- **bleeding complications - 5 cases**
- **cardio-vascular cases - 13 cases**
- **pulmonary embolism - 1 case**
- **infective causes - 4 cases**

Severe postoperative morbidity was noted in another 7 cases and was represented by:

- **anastomotic leaks - 3 cases**
- **bleeding - 1 case**
- **ischemic complications - 1 case**
- **cardio-vascular complications - 2 cases**

B. Recurrence of Disease

Recurrence of the disease is usually an indicator for the efficacy of the treatment received by patients in the appropriate stage of their disease, rather than a measure of how speedy the patient was passed through the healthcare infrastructure. However, due to the particularities of the neoplastic spread, often impossible to obviate, recurrence may sometimes represent an indicator of the early diagnosis and management of cancer; therefore, one could argue that recurrence may also represent an indirect mirror of the patient's speedy management when looked at in association with other more quantifiable variables, such as staging and operability. In this series only the surgical group of patients - i.e. 222 patients - in which a more or less radical exeresis of the cancer took place can offer quantifiable results related to the recurrence of the disease as an outcome factor.

Out of the 222 patients submitted to some form of surgery, in 92 patients (41.44%) recurrence of the disease was eventually diagnosed at some point in time during their follow up; their clinical records showed clear evidence of this fact based on various examinations and investigations. The mean interval between surgery and diagnosis of recurrence in these patients was 459.66 days (median = 318,50 days, Std.Dev.= 411.22). The rest of 130 patients subjected to surgery had no recorded evidence of recurrence diagnosed by clinical or para-clinical means, although some of them passed away peacefully in a manner which was highly suspicious of recurrent disease.

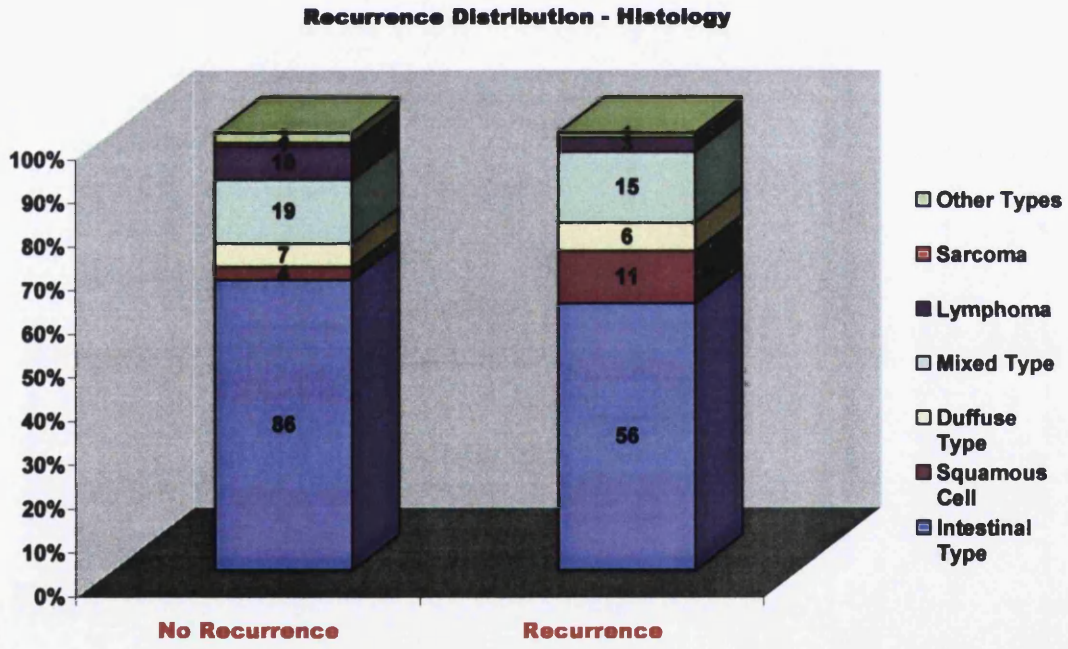

Fig. 7.10 - Recurrence Distribution & Histological Types

It seems that for the follow up interval of time of 5 years that we monitored the clinical records, the younger group of patients - decades 35 to 44 and 45 to 54 years of age - presented with a lesser

susceptibility of developing recurrence of the disease (14.3% and 37.5% respectively) compared with the elderly group (41.1% of over 75 years of age). The graph in Fig. 7.10 above presents the distribution of recurrence related to the histological type of cancer. In a bivariate analysis between the recurrence occurrence in the treatment group and various other factors, I have found no significant correlation between recurrence after treatment and the pTNM stage of the disease (Spearman's rho = 0.205, $p<0.001$), or chemotherapy alone as method of treatment (Spearman's rho = 0.178, $p<0.001$). It appears that the highest incidence of recurrence was observed in the cases of squamous cell carcinomas - 11 patients out of 15 or 73.3% - and the lowest for lymphomas - 3 patients out of 13 or 23.1% -.

	Type of Treatment		Total
	Surgery only	Surgery + ChemoTh.	
No Recurrence	102 (62.6%)	28 (47.5%)	130 (58.6%)
Recurrence	61 (37.4%)	31 (52.5%)	92 (41.4%)
Total	163 (100.0%)	59 (100.0%)	222 (100.0%)

Fig. 7.11 - Recurrences & Treatment Modalities

When looking at the recurrence rates within 5 years after treatment from the perspective of the main method of treatment (Fig. 7.11 above), the cases treated only by surgical means recurred in proportion of 37.40% of cases compared with those who had chemo +/- radiotherapy associated to the clinical management, which recurred in proportion of 52.50% of cases.

When the recurrence was suspected, the diagnosis of recurrence has been established using the following investigations:

Clinical exam	**89 cases out of 92**
Ultrasound	**32 cases out of 92**
Biopsy / Tissue Dg.	**31 cases out of 92**
Endoscopy	**27 cases out of 92**
CT Scanning	**21 cases out of 92**
Barium Meal	**4 cases out of 92**

Fig. 7.12 - Investigations for Recurrence Diagnosis

The following table (Fig. 7.13) shows the treatment decided for in these 92 cases where the recurrence of the disease has been noted:

No treatment	**59 cases out of 92**
Palliative Treatment	**24 cases out of 92**
Surgical palliation	**8 cases out of 92**

Fig. 7.13 - Treatment of Recurrences

Either the treated and non-treated groups of patients had their survival quantified both at 1 year and 5 years. The findings are presented below.

C. Survival

When introducing new clinical services or referral pathways for potential cancerous patients, the ultimate aim is to improve their life span. Survival length after early diagnosis and adequate treatment is therefore recognized as one of the most accepted tools for assessing oncological measures of diagnosis, treatment and palliative care. All patients introduced in the study were followed up as per current standard for 5 years. The follow-up period was closed for calculation

purposes at 30th June 2004, or for earlier patients still alive, at five years from the date of treatment date which must have been coincidental with an Outpatients Clinic follow-up episode.

Two cases would have been introduced with negative values in the survival study - these cases refer to patients who were dealt with as emergencies and the positive diagnosis was established after the surgical event or necropsy respectively; for the purpose of breaking down the figures, although with little influence on the end result, these two cases were excluded and the total number of patients discussed for survival assessment was kept at 438. Since the patients in this case mix were followed up for 5 calendar years, the results concerning the patients' survival will be presented for both 1 year and 5 years, consistent with the current accepted pattern of reporting clinical oncological outcome.

In this series of 440 patients, there were 62 patients still alive (14.09%) at the end of the interval allocated for follow up - i.e. 5 calendar years -. However, 66 patients survived a minimum of 5 years following treatment, making up a 5-year survival rate of 15.06%. At 1 year following the treatment date there were alive 151 patients (34.30%) from all recorded cases) or 121 cases (54.50%) from the 222 cases surgically treated. Following the null hypothesis of this study, it is noted that the mean survival figures for the uncensored case mix is varying with the method of referral used (see Fig. 7.14 below):

Method of Referral	n	Mean Survival	Median Survival	Std. Dev.
Admission	148	379.34	101.50	598.28
Outpatients Referral	184	436.75	199.00	564.25
Open Access Endoscope	94	622.30	336.50	619.33
Rapid Poi-nion Clinic	12	743.91	711.50	616.18
Total	438	465.59	204.00	595.98

Fig. 7.14 - Mean Survival & Method of Referral

It is also noted, as per our expectations, that younger group of patients had presented longer survival intervals (see fig. 7.15 below): and the survival data were far better for the gastro-duodenal group of patients compared to the oesophageal group (see Fig. 7.16 next page):

age group at diagnosis	mean *(days)*	median *(days)*	Std. Dev.
35 to 44	599.66	257.00	940.39
45 to 54	779.00	459.00	711.90
55 to 64	702.78	310.50	721.07
65 to 74	468.77	265.00	568.34
>=75	361.26	127.00	540.07
Overall	472.87	204.00	609.53

Fig. 7.15 - Mean & Median Survival for Age Decades

	Oesophagus			Gastro-Duodenal		
pTNM Stage	**Mean**	**Median**	**Std.Dev**	**Mean**	**Median**	**Std.Dev.**
0	1189.00	1189.00	214.68	1584.66	1552.00	286.40
Ia	51.50	51.50	9.19	1193.61	1300.00	883.16
Ib				1049.15	1016.00	721.25
IIa	932.29	1047.00	630.77	880.86	679.50	709.85
IIb	460.20	199.00	481.11			
IIIa	518.17	350.00	489.11	540.58	302.00	552.85
IIIb				228.80	181.00	231.44
IV	321.11	201.00	336.70	302.44	210.00	461.22
Total	**600.87**	**350.00**	**554.84**	**709.02**	**436.00**	**702.96**

Fig. 7.16 - Mean Survival @ pTNM stages

The overall mean value for survival following positive diagnosis of cancer was 472.87 days with a median of 204.00 days (Std.Dev. = 609.53). The table in Fig. 7.15 above details the mean and median survival figures for various decades of age. It appears that the decade of 45 to 54 years of age enjoyed the longest survival, whilst the elderly over 75 years of age did not live much longer than a year, on average.

The overall survival figures at 1 year and 5 years following presentation or definitive treatment respectively are seen below:

interval	n	% of 438 cases
12 months survival from 1st GP examination	**186**	**42.46**
12 months survival from positive diagnosis	**151**	**34.47**
5 years survival from treatment	**66**	**15.06**

Fig. 7.17 - Crude Survival Rates at 1 year & 5 years

A breakdown of survival figures at 1 year and 5 years for patients undergoing various forms of treatment is presented in the table below (Fig. 7.18).

Interval	*n*	Survived days after:			
		No treatment	Surgery alone	Surgery + Adjuvant	Chemo +/- Radiotherapy
12 months survival from 1st GP Examination	186	30	89	44	23
12 months survival from positive diagnosis	151	16	83	38	14
5 years survival from treatment	66	2	48	13	3

Fig. 7.18 - Treatment modalities & their Survival Ratio

Surgical treatment and surgical treatment + chemotherapy yielded the largest number of patients surviving beyond 1 year or 5 years from the definitive treatment, respectively.

	n	Age Group				
		35 – 44 (9 cases)	45 – 54 (25 cases)	55 – 64 (60 cases)	65 – 74 (147 cases)	>75 (197 cases)
12 months survival from 1st GP Examination	186	3	16	31	69	67
12 months survival from positive diagnosis	151	2	14	28	55	52
5 years survival from treatment	66	2	9	15	21	19

Fig. 7.19 - Survival Breakdown for Age Decades

There was however no significant difference in the numbers of patients surviving 1 year or 5 years respectively in relation to gender or hospital of origin. Patients belonging to the decade of 45 to 54 years of

age seem to survive in larger number than the other decades for the same period of time (Fig. 7.19 on the previous page). The number of patients surviving at 1 year and 5 years respectively varies largely subject to the method of referral used:

Survival	*n*	Method of Referral			
		Admission *(148 cases)*	O P D *(184 cases)*	O A E *(94 cases)*	R O C *(12 cases)*
12 months from 1st GP Examination	186	43	86	50	7
12 months from positive diagnosis	151	41	60	43	7
5 years from treatment	66	17	23	22	4

Fig. 7.20 - Method of Referral & Survival

It appears that a larger number of patients survived at 1 year and 5 years respectively when the referral was addressed to the Gastro Department - 68 cases out of 123 at 1 year after presentation to the GP and 29 cases out of 123 at 5 years following treatment (Fig. 7.21):

Survival	*n*	Department of Referral		
		Surgical *(98 cases)*	Medical *(217 cases)*	Gastroenterology *(123 cases)*
12 months from 1st GP Examination	186	39	79	68
12 months from positive diagnosis	151	31	61	59
5 years from treatment	66	13	24	29

Fig. 7.21 - Department of Referral & Survival

These are the overall (crude) figures and not corrected in any way for various confounding factors such as age, gender, anatomical segment, clinical department of referral, etc. Although the survival raw figures mentioned above are obviously influenced by other factors as

well, such as stage of the disease, co-morbidities of the patients, treatment instituted, etc., they are not directly linked to the method of referral and speed of diagnosis which represent the hypothesis of this study. The survival ratios can however be corrected in the light of the above entities should one wish to quantify every aspect of the survival ratio. From the study standpoint though, the confounding factors were considered only those which influenced in a form or another the decision to refer the patient using one of the methods of referral and subject to the initial assessment made by the referent General Practitioner. As a matter of interest though, it appears that the survival at 12 months following the initial referral is not influenced by the site of the malignancy (Pearson $\chi^2 = 6.170$, $p = 0.046$, Spearman's Coefficient = 0.048) or by the clinical pTNM stage (Pearson $\chi^2 = 8.770$, $p = 0.119$, Spearman's Coefficient = 0.129). In case of the stomach localization, the clinical pTNM stage can influence the survival ratio at 12 months (Pearson $\chi^2 = 26.885$, $p<0.001$) but the correlation is poor (Spearman's Coefficient = 0.070).

In the next chapter I will discuss the implications of these results and how they have been influenced by the clinical services or referral algorithms introduced specifically to improve these figures. It would also be interesting to see if the current model described in previous pages, with a dichotomy in diagnostic vs. therapeutic services can improve outcomes and whether it can be replicated to other healthcare providers.

Chapter VIII

DISCUSSION & INTERPRETATION

Summary: *In this chapter I am discussing the implications of the results found earlier. Firstly, the strength and weakness of the method and chosen model is scrutinized, the pros and the cons for adopting such a model of inter-specialty collaboration are discussed and the validity for other health providers is favourably argued. Using this model reveals a continuous trend in the volume of endoscopies performed without being followed by a similar trend in the rate of cancers diagnosed. The interval of delays are scrutinized and is found that their median figures are compliant with the "two week rule" in cancer services, but mean values suggest a number of cases delayed due to unrecognized clinical presentation. The statistical analysis of the presentation symptoms confirms the presence of "alarm symptoms", but fail to stigmatize any combination of them as prevalent for cancer suspicion. There is certain benefit in using open access services as clinical setting which is demonstrated by slight benefit in operability ratios and probability of survival. The open access services did not pick up either significantly more early cancers or improved better TNM ratios.*

Subheadings in this Chapter:

Irrespective of their clinico-pathological particularities, Upper Gastro-Intestinal Cancers represent a significant pathological entity

which is present with variable incidence and prevalence throughout the world and affecting generally people from all ethnic origins[22;23;67;79;148]. It is of undisputed notoriety that the incidence is higher in the Eastern hemisphere and somewhat smaller in the Western World, whilst in the African continent the incidence is quite low[79].

Japan has overtaken the rest of the world in the rapid diagnosis of early stages of these cancers, as well as in respect of multi-disciplinary management and survival rates for their patients. It appears that the secret for these survival rates, in excess of 90% at 5 years in some specialised centres, is the diagnosis of early Upper Gastro-Intestinal Cancer, which in Japan exceeds 50% for TNM stages 0 and I [18;43] in the majority of reports during 1990's. It is mentioned earlier that one of the ways by which the Japanese have achieved these results in the early 1990's was broadening patients' access to imaging and diagnostic facilities - i.e. one-stop centres, expansion of radiological, and more recently endoscopic services, with direct "access from the street", etc. -.

As a direct consequence of this early diagnosis, the 5-year survival rate in Japan can exceed 45%[15;79] for patients with early Upper Gastro-Intestinal Cancer; papers from some specialised centres - for instance Axon and Lambert cite in 1999 the Tokyo Cancer Institute reports - quote ratios close to 86% for T_0 and T_1 gastric cancers. In America the survival rates at 5 years varies between 7%

and 22%[35;79;112], whilst in the European Union these rates are between 9% and 27% depending on the report and case mix[27;72;101;102]; some other authors[101;111] may even give figures of up to 54% for selected cases, depending whether the case mix refers to a hospital-based study or epidemiological population-based research. In a population-based statistic, the average European Union 5-year survival rate is 13% in the EUROCARE I Study[22;79], with a poorer figure of 5% for the oesophagus and 19% for the stomach. In the UK[1;3;79] the relative 5-year survival rate is around the figure of 9% again with poorer values of 7% for the oesophagus and significantly better values for the stomach at 19%[27]. It appears clear that the survival expectancy in Japan is twice than the average Western world rate; this is mainly due to early detection of these cancers, although some other factors can contribute as well, such as: different biology of tumours, gender and age group distribution, more aggressive standardized care, etc. At the same time, Britain's survival figure at 5 years is lower than the average for the whole of Europe; however, patients in the UK with gastric cancer appear to have "a better deal" than their European counterparts.

Having said that, due to increased collaboration and standardization of care, almost all Western and Japanese authors are now reporting 5-year survival rates of over 90% for early gastric

cancer - stages 0 and Ia under the TNM classification[1] - if relative survival for these cases are considered alone[43]. Experience (backed up with research) shows that early cancer detection represents the key to better results. It has been reported that when the Japanese community-based system of identifying these patients and the subsequent Japanese surgical technique is applied to Western patients diagnosed with early gastro-intestinal cancer, the results appear to be similar in terms of outcome and survival[90]. It appeared logical under these circumstances to try to copy - or apply - the Japanese methodology in diagnosing gastro-intestinal cancer to the Western population, as a vector for diagnosing these cancers at an early stage. It is hypothesized that early diagnosis associated with oncological standardized care can identify patients in the early stages of their disease and therefore much fitter from a surgical standpoint and with higher chances of sustaining aggressive multifactorial treatment.

In the United Kingdom these cancers are considered a real problem for health care providers and medical professionals alike due to their late diagnosis, poor survival rates and financial implications for early diagnosis and comprehensive management. In a recent document issued by the Department of Health [40], the incidence of

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[1] TNM Classification of Malignant Tumours Sixth Edition, Union Internationale Contre Cancer (UICC), Geneve, Switzerland, Sobin,LH, Wittekind,CH, ISBN 0-471-22288-7

these cancers in England and Wales is assessed as in the table below (Fig. 8.01). In Wales alone the total number of patients affected by the upper gastro-intestinal malignancy was in decrease during the previous decade, i.e. from 16259 cases to 15816 cases registered in 1992[114]. According to the figures released by the Office of National Statistics in London, there appears to be a slight increase in the incidence of oesophageal carcinoma over the previous 10 year-period – i.e. 1981 to 1990 - (from 9.8 to 13.8 per 100000 population) and a slight decrease in the incidence of gastric cancer (from 29.8 to 24.9 per 100000 population)[1;2;114].

Localization	**New cases p.a.**	**No. p.a. / 100 000 population**
Oesophagus	5736	13.8(♂) / 9.0(♀)
Stomach	10227	24.9(♂) / 14.7(♀)

Fig. 8.01 - Incidence of Upper gastro-intestinal cancers (adults 15 years+ in England & Wales)[40]

This high incidence is associated with a high prevalence of the disease in the community, followed by significant economic costs, psychological implications for the patient and the family and pressures at every level of the NHS upon the medical staff responsible for the care of these patients.

Numerous attempts have been made, not least at political[80] and professional[5] level, to find ways to improve the speed of diagnosis and treatment for these cancers, as well as the outcome of the patients treated for these conditions. Observing the recommendations from NICE, many trusts have embarked on a relatively costly exercise to

provide the adequate infrastructure to ensure compliance with the "two week rule" requirement for referral resolution and 62 days cancer waiting times from presentation to treatment of all referrals[1] .

Observing the experience of these hospitals trusts in which clinical services were able to make use of general endoscopic direct access pathway and referral algorithms that were functional from the beginning of 1990's, the aim of this retrospective analysis was firstly to establish whether these services can achieve the target of the "two week rule" in Upper Gastro-Intestinal Cancer and secondly if there are any clinical benefits for the patients' outcome that would follow the implementation of these services. To answer these questions it would be essential to find a model for the study that:

1. **features all of the services and referral algorithms in question;** ***and***
2. **subject to clear benefits being noted, the infrastructure allocated for these services could be replicated to other settings.**

A. Internal Validity

Based on the established objectives set aside for this research and bearing in mind the potential epidemiological and infrastructural implications for the structure and design of future medical services, the chosen model had to reflect a populational area sufficiently representative and comprehensive enough in respect of services and methods of referral offered to the patients eventually diagnosed with

[1] DoH 2001 - Cancer waiting times. Maintaining the "two week target", DoH, London

Upper Gastro-Intestinal Cancers. Such a setting must offer the general practitioners good guidance on patients' pre-selection for referral pathway, all the possible options for getting the patient investigated at the right speed in the secondary care sector, as well as supported services by all specialties that may influence the outcome study. By the same token, this model had to feature several other important elements such as: reproducibility, design based upon inclusion of all categories of gastroenterological patients, homogeneity of populational case mix, infrastructural similarities between sites as well as facilities for identification and follow-up of those patients who are diagnosed and treated within the same clinical setting.

a. Neath - Morriston Model of Study

In order to research the implications of the various modalities of referral upon the waiting times and their consequences upon the outcome of the patients with Upper Gastro-Intestinal Cancer, I have chosen the case mix offered by Neath General Hospital and Morriston University Hospital; these are two District General Hospitals situated in South Wales (United Kingdom), along the M4 Motorway corridor and on the outskirts of the City of Swansea, which is the second major city in Wales. The area covered by the two hospitals offers an interesting socio-economic structure, containing pockets of favourable socio-economic deprivation index around the City of Swansea, as well as areas of high unemployment and poor income translated by a low

depravation index around the towns of Neath and Port Talbot and associated with the declining opportunities offered by the scaling down of the local British Steel Industry.

At the time of the end of the study, i.e. 1999, both hospitals were part of the same Iechyd Morgannwg Health Authority[1] as individual NHS Trusts and each one was serving a population of an approximately similar structure and volume; the NHS reconfiguration process beginning in April 1999, which changed the structure of trusts in Wales, did not affect the patients' flow and therefore did not influence the validity of the data collected within the study. In fact, the re-organisation of trusts in South Wales made the provision of gastroenterological services even more inter-twined than before: the acute surgical services were already established for years in Morriston University Hospital and the flow of the patients for out-of-hours service was known to everybody within the health establishment. As a bonus, even before the re-configuration of services and continued afterwards, the endoscopic team at Neath General Hospital was attending on a regular basis the Multi-Disciplinary Team meetings in Morriston Hospital where cases were debated and direct referrals to the Upper Gastro-Intestinal surgical team were made.

The use of the Neath-Port Talbot and Morriston model presented me with several benefits which contributed to the homogeneity of the

[1] IMH Iechyd Morgannwg Health Authority, 41 High Street, SWANSEA, SA1 1LT;

dataset and as such, to the scientific validity of the collected data. Briefly these benefits are:

1) Epidemiological benefits

Both hospitals are situated in close proximity to each other; this means that the population within their catchment areas will tend to be homogeneous, based on cultural background, ethnicity and geographical access to health services; this setting allowed a thorough monitoring of the case mix, based not only on the Secondary Care sector access to medical records, but also the possibility to engage some population-based research methods through the use of the medical records from the local health care provider and the regional cancer registries. Some inevitable socio-economical differences can be perceived between the two settings at populational level, translated in different rates of the socio-economic depravation indexes[6].

2) Structured healthcare benefits

Both hospitals had similarly organized services. During the interval of the study both units were running Acute Medical Services in General Medicine (i.e. medical & surgical emergency admissions) plus the usual Outpatients Clinics, based on the standard referral request open to practitioners from the primary care sector; also, both of the hospitals each had a dedicated gastroenterological team interested in Endoscopy and gastrointestinal malignancies, as well as

a dedicated up-to-date Endoscopy Suite for diagnostic and therapeutic procedures.

Most importantly for the purpose of this study, both hospitals and both gastroenterological teams had from the early 1990's put in place, in a more or less formal manner, various modalities for patients' access to the diagnostic facilities; these modalities were open to all primary care practitioners to facilitate direct referral of their patients with gastroenterological symptoms in general and were assisted by algorithms for easy guidance. Essentially, these modalities were: One-Stop Clinics, Open Access Endoscopy and Rapid Opinion Clinics, although for some short interval some of them carried different names, such as Fast Track Endoscopy or One-Stop Endoscopy Clinic.

Since the beginning of the 1990's the setting in Neath General Hospital was one of the fewest in the country to establish in a more formal way both new clinical services as well as more structured clinical recommendations for the referral pathway of gastroenterological patients; these were in the form of guidelines to the primary care sector associated with proformas for structured reasoning of the referral (see *Appendix No. A03 to A05 - Referral Proforma*). As in many other UK hospitals, these guidelines, and particularly the proformas for referral, were designed to serve the population of gastroenterological patients in general and not the potential cancer patients in particular. Whilst Neath General Hospital

employed these specific proformas in the process of accepting referrals, based upon guidelines and algorithms which were distributed in advance to local General Practitioners, Morriston University Hospital achieved, in essence, the same end-result for channelling its patients to the appropriate service, with the difference that the interpretation of the severity or association of symptoms was done at the hospital level rather than by the referring doctor. Also, the Neath General Hospital setting enjoyed a more formal infrastructure dedicated to these new services, in the form of support staff and IT infrastructure. Instead of this, Morriston University Hospital used a system of triage for channelling referrals based upon the perceived clinical severity of the described symptoms in the practitioner's referral letter.

It is also worthwhile to note that in both hospitals there were radiological services with similar technical facilities, staffing levels and direct access by means of referral from both the primary and secondary care sector, as well as a single Pathology Department which served both units.

And finally, to complete the similarities, it should be noted that during the time of this study both settings were linked with the same tertiary Centre for Oncology[1] situated in close proximity and accepting all patients for assessment and necessary adjuvant therapy. The units

[1] Cancer Treatment Centre, Singleton Hospital, Sketty Lane, SWANSEA, SA2 8QA;

also shared the same network of voluntary services for palliative and terminal care: e.g. the Macmillan Nurses Service and The Hospice for the Care of Terminally ill patients.

However, there were some structural differences between the two settings, the main one being the loss of Acute Surgical Services at Neath General Hospital during the first part of the study, with the immediate transfer of all acute surgical intake to Morriston University Hospital; this change happened relatively soon after the starting point of the study - 1st October 1995 - and hypothetically was possible to affect a certain proportion of the patients' flow. The change in services provisioning did not negatively affect the inclusion-exclusion criteria issues, nor did it introduce further delays due to referral patterns.

The NHS re-configuration of services and health care providers in Wales, which began in the autumn of 1999 and changed the structure of the NHS Trusts in Wales, also had no effect upon the case identification criteria; logically however, the consequences of this change were probably diminished by the fact that the surgical team involved in the management of the patients with Upper Gastro-Intestinal Cancer was essentially based at Morriston University Hospital anyway and all multi-disciplinary conferences, other diagnostic facilities and inter-specialty consultations took place in Morriston University Hospital as well. The provision of all multi-disciplinary oncological collaborative activities on one site had significant implications for the quality of care for cancer patients; this

was beneficial not only in respect of the speediness of the decision-making process, but also in respect of standardized care, adoption of algorithms for practice and educational purposes.

Another important difference between the two settings is related to the logistical organization of certain services, such as Open Access Endoscopy service and Rapid Opinion Clinic service in respect of the modalities of referral from the primary care sector and from within the hospital itself. Whilst Neath General Hospital had started a clearly structured Open Access Endoscopy referral service at the beginning of the 1990's and Rapid Opinion Clinic at a defined point in time during the study – 1st October 1995 -, with a dedicated, in-house produced, electronic patient record software[1] and specifically designed referral algorithms for patients with sinister symptoms, Morriston University Hospital in contrast used a less structured approach but with much similar effects: the elective referrals were vetted by the gastroenterological team and fast-tracked straight to the Outpatients Department or to the Endoscopy Suite, as necessary; this created in effect an Open Access Endoscopy service, but with the absence of dedicated referral algorithms and pathway of referral. There was however no Rapid Opinion Clinic service formally organised in the Morriston Hospital setting and the software to record the endoscopic

[1] GeneCIS™ - Generic Clinical Information System, Authors: Hayley Dickinson, Jayne Morgan, University of Wales Swansea, United Kingdom

episode was less clinically centred at the beginning, but adequate for timing purposes and diagnostic criteria.

3) Specialized staffing benefits

Patients attending, diagnosed and treated for Upper Gastro-Intestinal Cancer in both Neath General Hospital and Morriston University Hospital in broad terms had been assisted throughout the study period by the same surgical and oncological teams of specialists. This feature conferred uniformity to the dataset in terms of: algorithms of treatment, approach, criteria applied for selection of patients, expertise in staging and surgical management. As such, with only minor exceptions, all patients were dealt with by the same team in a Multi-Disciplinary Team type of approach:

- in more than 95% of cases the positive diagnosis and final histology result, irrespective of the endoscopist concerned, was dealt with by the same pathologist who specialized in gastro-intestinal pathology; all of the specimens and reports were again reviewed by the same pathologist in a Multi-Disciplinary-Team (MDT) meeting together with the upper gastro-intestinal surgeon, gastroenterologist and oncologist throughout the progress of the study;
- radiological support was provided by a radiologist with special interest in Digestive Radiology, including radiological staging procedures such as CT scanning and Endoscopic Ultrasound;
- surgical assessment, surgical treatment and follow-up in more than 85% of the cases was the responsibility of two teams of upper gastro-intestinal surgeons who performed nearly all the elective procedures; only in less than 15% of patients the surgical team was different due to emergency work and work undertaken in Neath General Hospital before moving the Acute Surgical Services to Morriston University Hospital;
- the adjuvant therapy was decided, administered and assessed by the same oncological team at the Swansea Oncological Centre in Singleton and

closely linked with the surgical team through the collective Multi-Disciplinary-Meeting (MDT) and medical correspondence;

- supportive specialised medical, nursing and technical staff were used in all settings and these were briefed whenever necessary about changes occurring in the algorithms and protocols;
- for the patients being in the terminal phase, palliative care was ensured by a Hospice in close proximity to Morriston University Hospital and adequately staffed with support nurses and palliative care physicians;
- finally, the clinicians involved in the patients' assessment and care - gastroenterologists, surgeons and oncologists - did maintain constant correspondence during follow-up with the patient's general practitioner responsible for each individual patient's care in the community.

However, there were several notable differences between the two sites and these were related to the staffing level and expertise of the two gastroenterological departments: the Endoscopy lists in Neath General Hospital, including the referrals for Open Access Endoscopy and Rapid Opinion Clinic, were manned by two experienced endoscopists - one physician and one Fellow Research Registrar with interest in Endoscopy -, although the department as a whole and the outpatient clinics were conducted and monitored by a Consultant Gastroenterologist with concomitant Academic involvement. In contrast, the Endoscopy lists in Morriston University Hospital were provided by a Consultant Gastroenterologist and a middle grade endoscopist and, with rare input, by the Specialist Registrars in training in General Medicine allocated to the firm and constantly supervised throughout. The medical staff in both units were assisted by dedicated nursing staff with extensive training in running Endoscopy procedures. All these, together with regular circulation of,

and easy access to algorithms and advice, made the differences between the settings minimal, whilst ensuring a constant increase in throughput of patients and maintaining appropriate safeguards for rapid diagnosis and staging protocol.

Based on the above observations, one can conclude that the model of two adjacent hospitals comprising two different teams of physicians endoscopists who can triage and process the referrals for primary diagnosis and with one single team of specialists responsible for the staging, therapeutic, follow-up and palliative care process may represent a homogeneous model; this model may be extremely beneficial not only in respect of understanding epidemiological issues, uniformity in management of patients and pathways of care, but also for retrieval and analysis of evidence-based data.

b. Overall Trends in Referrals

The possibilities for investigation of the upper gastro-intestinal tract have evolved over the years. These possibilities, generally speaking, address two large areas of upper gastrointestinal pathology: morphologic changes and functional disorders, with some degree of commonality between the two in a few of the clinical entities. In general it is accepted through consensus that any gastrointestinal diagnostic algorithm should always investigate firstly the potential morphological changes in the upper gastrointestinal tract; therefore, the Upper Gastro-Intestinal Endoscopy has made recently significant

in-roads in any algorithm of investigation. It is no surprise that the use of Gastro-Intestinal Endoscopy has therefore extended in recent years, becoming the gold standard for starting the investigations in any patient with upper gastroenterological symptoms. It follows that any medical service in receipt of referrals of such patients would normally rely on this particular investigation to start off the diagnostic algorithm.

1. Gastroenterological referrals

For the period of time considered in this study - i.e. 01 July 1993 - 30 June 1999 - both of the two hospitals offered an impressive case mix of patients with gastroenterological symptoms referred to their medical and surgical services. Although the referral reason was not always deemed to be related to an upper gastro-intestinal pathology, in the majority of cases the clinicians at the receiving end of the referral algorithm were convinced that some form of gastro-intestinal investigation might be necessary. These hospitals made no exception to the general rule of investigating patients with upper gastrointestinal symptoms referred to their services and a huge number of upper gastro-intestinal endoscopies were performed in the two settings, as shown in Fig. 8.02 on the next page. Obviously, the procedures outlined below were required based on a very large range of indications, from simple dyspepsia to cases where the possibility of a gastro-oesophageal malignancy was strikingly obvious; these figures

also include endoscopies as therapeutic indications for other pathologies, remotely related with the upper gastro-intestinal tract, such as insertion of Percutaneous Endoscopic Gastro-Enterostomy feeding devices or even endoscopic echographic investigations employed in the diagnosis of extra-gastroenterological pathologies.

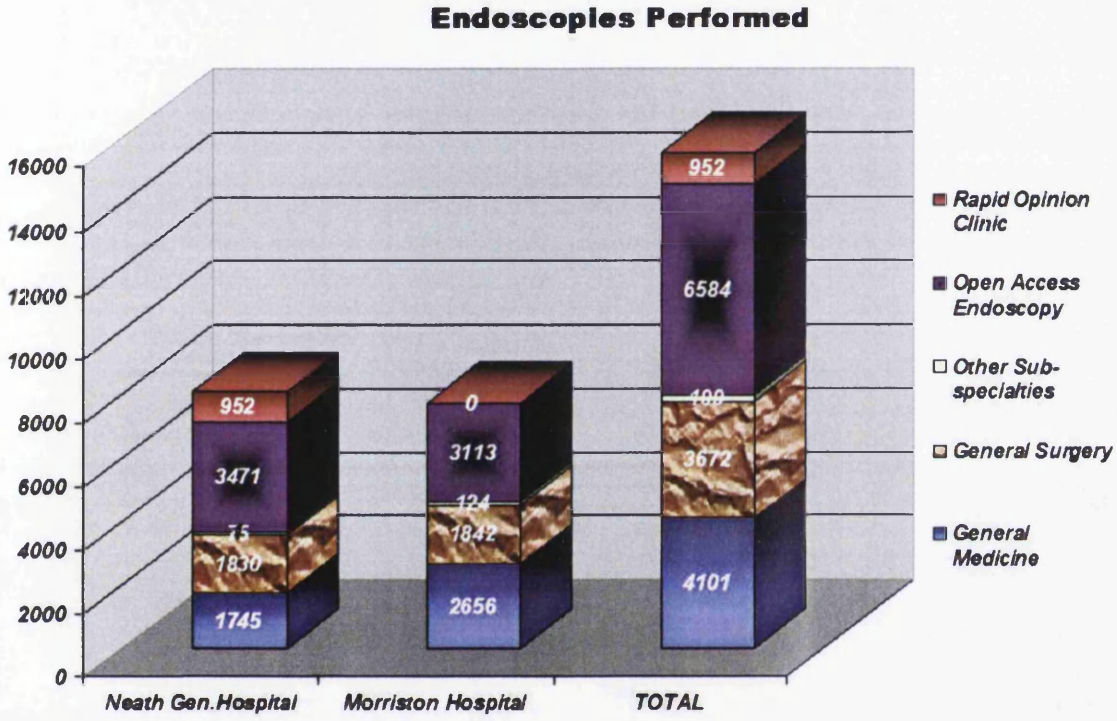

Fig. 8.02 - Number of Endoscopies performed

However, even under these circumstances, the concomitant potential diagnostic yield for upper gastro-intestinal malignancy was significant and these procedures may be included in the general pool of endoscopic examinations for the purpose of cancer detection. Obviously a number of endoscopies were repeat procedures in aid of the initial diagnosis or follow-up and staging.

These procedures are, however, not symmetrically distributed in time and locality between the two settings. The variable distribution is

related not only with the provision of endoscopic services in the two hospitals, but also with the differences between the sites in respect of acute admissions, variability in disseminated guidelines to the primary and secondary care sector, as well as other infrastructural capabilities.

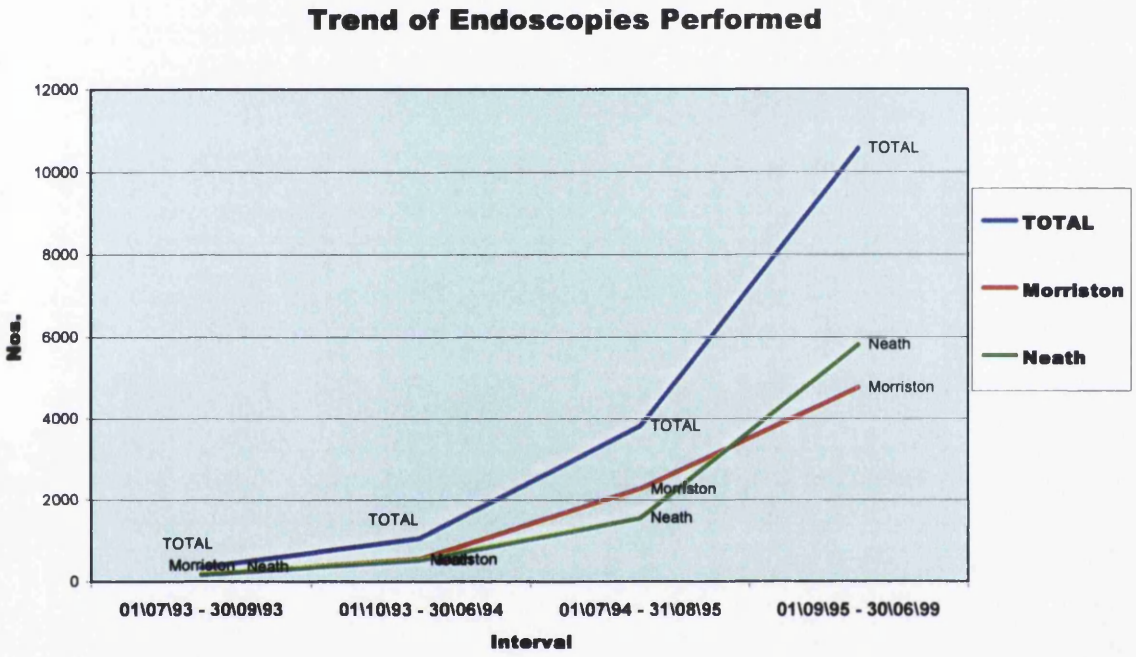

Fig. 8.03 - Trend of Endoscopies performed

For both hospitals, and particularly for Neath General Hospital, several moments can be identified in respect of the introduction of new services or reconfiguration of the current ones, as described above. Considering the above events and matching the number of endoscopies performed for each interval, there was an obvious ascending trend in the overall number of examinations performed (Fig. 8.03). The graph on the previous page shows this trend in time; the X axis refers to certain events, such as reconfiguration of acute clinical services or introduction of new services.

It becomes obvious that there is a progressive increase in the number of procedures performed in the two settings which equally mirrors the trend in referral pattern. This result was contributed to not only by epidemiological factors, such as ageing of population, increased local population or increased awareness elicited by the socio-mediatic factors, but also the disseminated algorithms of referral which guided general practitioners in deciding who should get referred for further investigations. It must be noted though that the increase in the number of procedures is not associated with any change in the infrastructure allocated for running these services.

The question arises whether the increase in the number of requested procedures would have any detrimental effect upon the overall speed of patients' throughput; this may affect not only the Endoscopy service per se, but also related services such as radiology, histopathology, etc. The consequences of progressive surge in referrals based upon certain guidelines and the capacity of the infrastructure to absorb these referrals is not yet fully explored and only anecdotal evidence exists in this respect. Although this issue is outside the remit of this study, it is obvious that the relation between the infrastructural provisions offered by the health care provider and the volume of referrals needs to be explored further.

It seems at first sight that the increase in the number of endoscopies performed may offer a chance to pick-up more cancers; and not only that, these cancers may have the chance to be picked up

at earlier stages than before. It follows that the trend seen in the two settings - see Fig. 8.03 on page 164 - might be followed by a similar trend in the number of cancer cases diagnosed, or indeed, a progressive lowering of the advanced cancers in favour of the early ones. Therefore I will be looking below at the cancer case mix alone offered by the two settings.

2. Cancer cases

During the exercise of identification and collection of data, a number of 440 cases have been isolated and their clinical details introduced in the database. The study was designed to collect data for an uncensored case mix during a six year period and, as a consequence, the cases were not filtered in respect of any variable. Observing the objectives and declared aims of the study, it was paramount to establish the independent factors to be monitored, as well as the confounding factors which would permit the correct interpretation of the results.

Since the objective of the study was the impact of the newly implemented methods of referral used in the referral pathway of those patients subsequently diagnosed with upper gastrointestinal cancer, it followed that the main independent factor would be the method of referral - i.e. *Admission, Outpatients, Open Access and Rapid Opinion* -. This would also mirror the real life environment whereby the General Practitioner would end up sending the patient to one of the hospital

departments using one or another of the methods of referral described earlier, subject to his assessment of the patient's case. Therefore, according to the design of the study, the results will need to prove or disprove the benefits of using the newly introduced methods of referral compared to the traditional ones.

However, from the General Practitioner's standpoint, the decision to refer patients suspected of cancer involves a process of taking account of several factors which, individually or in association, may raise the suspicion of malignancy. Since these factors represent the main instruments the practitioners have to hand during their decision process, it is worthwhile to consider these ones as confounding factors in establishing the homogeneity of my case mix. Thus, the main confounding factors are in my opinion the *age* of the patient and his/her dependence to an *age group* of recognized risk of malignancy, the *gender* of the patient, the *anatomical segment* of the upper gastro-intestinal tract involved - which is sometimes indirectly mirrored by the onset symptom(s) -, as well as a few other factors which could also influence the decision of the General Practitioner to use any method of referral, such as the *hospital* where the patient would be referred or the *department of referral.*

Examining the cohort from the perspective of the confounding factors, it appears that there are significant differences between the allocated groups matching the referral methods. This is surely the consequence of using a case mix which, consequent to the method

described in an earlier chapter, is not filtered in any form or shape. The question which arises is whether this lack of consistency of some of the confounding factors would alter the results and compromise the validity of my conclusions.

There are confounding factors such as *mean age* at presentation which are clearly limiting the consistency of the 4 referral method groups; it follows that I cannot draw any conclusions in which the factor age group might have significance for the speed of referral or outcome measures relative to the referral pathway. However, if the mean age at presentation is looked at from the perspective of a broader approach, such as the inclusion into *age groups of increased risk of malignancy*, it appears that this confounding factor is actually bracketed within the same age decade of 65 to 74 years of age, with the notable exception of the Admission group (mean age = 75.30 years). Based on this cohort and from statistical standpoint, any conclusion which associates the age at presentation to a specific method of referral may need to be interpreted in relation with the age group the patient belongs to rather than the age of the patient itself. This does however have a connotation of practicality since, within the algorithm of referral, the age group the patient belongs to may be considered a confounding factor; in this cohort, the association between the age groups of malignant risk and the four methods of referral was consistent ($\chi^2 = 34.30$, $p<0.001$).

There are other confounding factors noted in this study which return consistent association with the four groups of referral methods. Both the *hospital site* where the 1st referral was made (χ^2 = 24.20, p<0.001) and the *anatomical segment* of the upper gastro-intestinal tract (χ^2 = 15.54, p = 0.016) appear to show only limited differences across the four referral groups. Since the hospital site as a confounding factor tests the healthcare provision in an area with direct implication to the referral pathway to be chosen by the medical practitioners and since the anatomical segment involved may indirectly test the patient's clinical presentation, consistency of the association with the referral groups is paramount for the validity of my conclusions. A particular note must be added later in relation to the effect these confounding factors and their differences may place upon the outcome results, such as stage of the disease, associated treatment or survival.

One mention needs to be made in respect of the Rapid Opinion method; although the number of cases grouped under this method is quite small and suggest disparity, the statistical analysis would gain even more significance when the Rapid Opinion Clinic and Open Access Endoscopy groups are considered under a single spine as One-Stop method of referral.

The differences between the four referral groups are clearly obvious and have been highlighted above. In answer to the question as to whether these inconsistencies across the four groups of referral

would compromise the study, one may need to take account of the fact that the study was designed from the start as a longitudinal observational study based on an uncensored case mix and the limitations of the data collection and interpretation process was set from the beginning. As such, there are set of results and areas of interpretation which may not be duly influenced by the inconsistency of the factors observed; I am thinking here at the global delay intervals and the stage of the disease at presentation and positive diagnosis. There are however other areas – such as mean survival or even survival probability - which would be clearly influenced by the lack of comparable distribution of the case mix.

The cases of Upper Gastro-Intestinal Cancer diagnosed in the two settings during the six calendar years the study refers to did not follow the dynamics of referral pattern described above. In other words, there was no notable dynamic increase in the overall number of cancer cases picked up that parallels the increase in the number of referrals / endoscopies performed. For example, for the Neath General Hospital site, with its more structured approach to referral pathway and clinical services offered, the number of cases diagnosed have not increased from period to period, as the graph below (see Fig. 8.04) is showing based on 6-monthly interval pick-up rate:

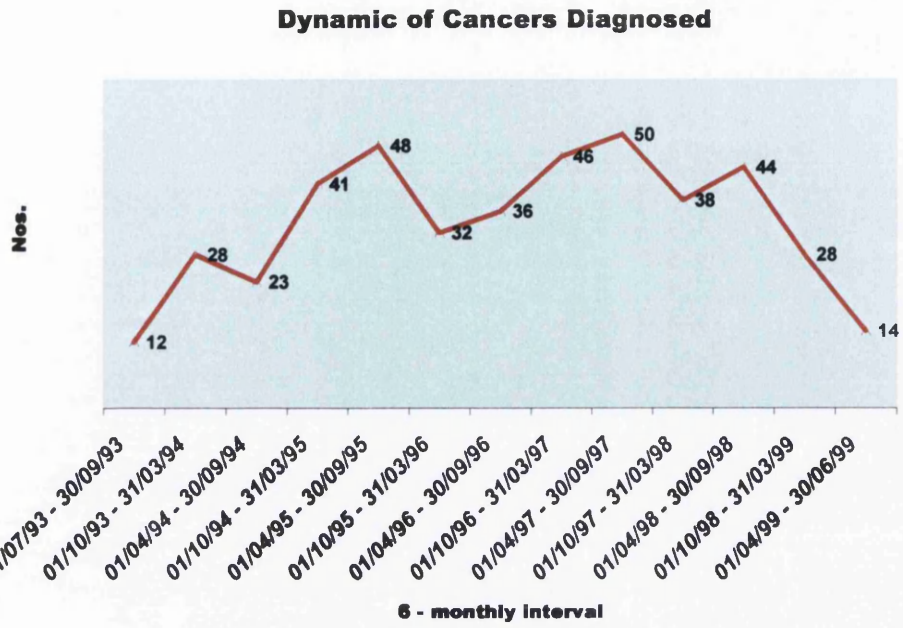

Fig. 8.04 - Dynamics of Cancer Pick-up Rate - 6-monthly intervals

However, the progressive increase in the total number of cancer cases diagnosed subsequent to the increase in the referrals number represents only one face of the coin; the other aspect, which is extremely relevant to the substance of the present study, refers to the possibility to diagnose a progressively increased ratio of "early" cancers, i.e. more and more stage 0 and stage I cancers compared to stage II to IV cancers as classified by the TNM system.

The case mix material highlighted above in brief offers a large pool of quantifiable data in respect of the number of patients, their clinical presentation, as well as the clinical services and referral methods used to diagnose their cancers. Because the main purpose of the current study is to assess the implications of new services and referral algorithms upon the speed of diagnosis and outcome of these

patients, I will discuss next these implications in relation to the introduction of these services.

B. External Validity

There are however certain views that need to be aired in this context. There are advocates for this type of approach, based on the need to increase the input of skills and expertise in the management of these patients. It is easy to understand the need of a unified approach, in a multi-disciplinary manner, since the standardized care of these patients is far from being achieved and plenty of scope is still left for refining the management of the individual patient. Also, the management of these patients require certain specialized facilities, such as endoscopic and anaesthetic-surgical; the provision of these facilities is not always a "one-way street", but also requires the collaboration of the clinicians involved in the care of these patients. Finally, from a surgical perspective, it is much easier and beneficial at the same time to have all the specialists involved in the critical phase of patients' care on the same site.

There are however people who found certain disadvantages to this approach. One of these is of socio-political connotation, involving the decision to agglutinate many clinical services on one site; the consequences are that, in contrast with the expectations of population at large, some medical local infrastructural facilities would have to be slimmed down in favour of expansion of the main centre ones; this

issue attracts criticism from those who advocate "a hospital on the doorstep", since the patients and their relatives would have to travel more to benefit from specialist services. Another criticism is the financial burden induced by the reconfiguration of services, with all that this expenditure entails: staff re-training and re-deployment, financial investment in infrastructure, change in communication and collaboration patterns between the primary and secondary care sector, expansion of local services to enable them to deal with increased need and/or magnitude of after care issues, etc.

The question arises whether this model is viable. Before seeing the evidence, it appears that many Health Authorities have already embarked on this direction[27], based on financial and staffing constraints. Throughout the UK many acute services have agglutinated their work under the term "special interest" and therefore the patients' stream started to be guided towards larger centres. This way, specialist upper gastro-intestinal teams have been formed and the management of upper gastrointestinal patients started to become more structured and standardized[43].

The qualitative and economical benefits of such a model for distributed specialised work are still to be seen; however, the situation is slightly different when scrutinizing its interaction with the diagnostic facilities and referral pathways. Here, the evidence started to trickle slowly into the medical press and seems to be related with the influx of patients towards the endoscopic services[20;119;136;159]. The

experience encountered at our two settings in South Wales showed without doubt a clear trend in increasing the number of referrals (Fig. 6.02). Beside the issue of costs - although not within the scope of this study, I am aware of Delaney's findings[39] that endoscopy is a cost effective method of intervention even for the management of dyspepsia in patients over 50 years of age -, the ever increasing trend in referral pattern may have a rebound effect on the speed with which the service is delivered and therefore negating the specific reason for which the open access services have been introduced; Jones et al.[65] already found that, in general, urgent referrals treated under the "two week rule" have led to a doubling of the waiting time for routine cases.

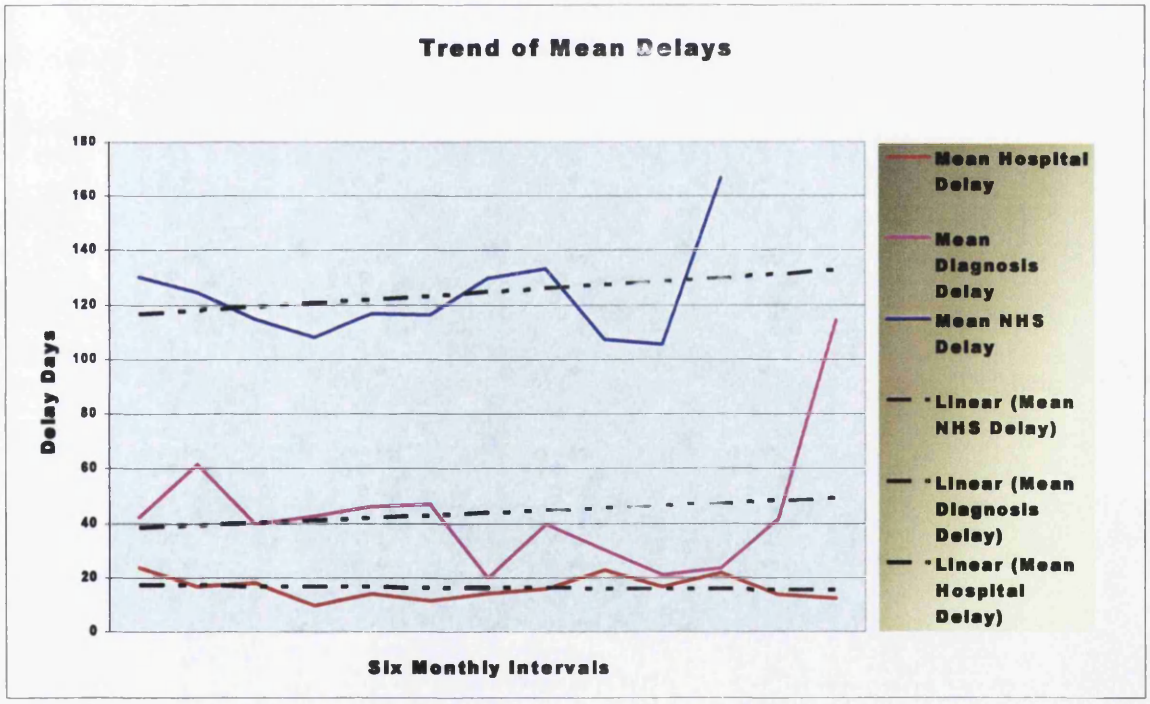

Fig. 8.05 - Linear Trend for Delays

By the same token, Thomas[149] argued that transferring resources from routine cases to fast-track urgent referrals would be followed by ever increasing waiting times. When looking to the benefits

of the new services for rapid diagnosis of gastro-oesophageal malignancies it is therefore important to take account of this reality as well. Based on the cohort of cases presented here, it appears difficult to endorse the above view. In an analysis of the mean intervals of delay encountered for all cancer patients, the 6 monthly trend in delay increase is not immediately obvious. The graph (see Fig. 8.05 on the previous page) shows the variation and linear trend of the mean delay for the Hospital Delay, Diagnosis Delay and overall NHS Delay.

There was no evidence that the Hospital Delay encountered an ascending trend; this would normally be the interval which is facing firstly the effects of increased referral rates and the first to progressively change. Since the referrals sent to the open access service are not filtered and potential cancer cases are not clearly earmarked - although referrals are based on algorithms that suggest selection of "sinister" cases -, and because the incidence of cancer cases within the catchment area is not fluctuating largely for a given period, it was expected that the mean Hospital Delay would parallel the increase of the referral numbers. The cohort in this study does not support therefore the view that increased referral numbers associated with the "two week rule" for suspected cancer may be followed by a progressively increased delay to the first appointment at open access services.

The same does not appear to be true for the Hospital Delay and the overall NHS delay to treatment intervals; here, there is an evident linear ascending trend, suggesting the increase in mean delay figures. Since these delay intervals refer only to the timing when the patient was fast-tracked within the specialist setting, this trend may not be explained by the increased throughput of patients in open access services; the patients suspected of cancer at hospital appointments were fast-tracked as per previous arrangements and there was no evidence that diversion of Programmed Activities took place in the timetable of the medical staff in order to support increased activity within the open access services. It is difficult to explain the basis of this progressive increase in mean hospital-based delays other than agreeing with Thomas and Burnet[149] that diverting resources from routine activity might produce a discrepancy between demand and capacity offer with ever increasing waiting times. However, it is not less true that certain measures need be contemplated to deal with the eventual increase in demand on the open access services generated by other factors, such as population-based changes, dynamic changes in pathology, etc.

Based on the observations above I can conclude that the model chosen to investigate the waiting times, referral pattern, trends and outcomes in the management of the upper gastrointestinal cancer patients has sufficient strengths to be representative for the purpose

and is robust enough to be able to replicate in other hospital settings in order to obtain the same results.

C. Delays in presentation, referral, diagnosis & treatment

Conscious of the discrepancies between Britain and the rest of the European countries in relation to the waiting times and post-treatment outcome for some of the cancer localizations, the British government has promised a change in the approach to this issue. The targets set out in The NHS Cancer Plan 2000[80] for dealing with cancer pathology in general and waiting times in particular, introduced time constraints on the referral process and on the period taken for each patient to be submitted to definitive treatment. The NHS Cancer Plan[80] states in its preamble that "the ultimate goal is that no one should wait longer than one month from an urgent referral for suspected cancer to the beginning of treatment except for a good clinical reason or through patient choice"; also, The Government's White Paper[40] entitled "The new NHS - Modern, Dependable" guaranteed that everyone with suspected cancer will be able to see a specialist within two weeks of their GP deciding that they need to be seen urgently and requesting an appointment. In 2004, The National Institute for Clinical Excellence NICE recommended that all NHS cancer services should urgently consider the endoscopic services they provide as a tool in speeding up the cancer diagnosis sequence and expand them wherever necessary[11].

Therefore, the importance placed by various political and non-governmental bodies on the waiting time issue becomes evident for every clinician, although there is only anecdotal evidence in the medical literature that reducing waiting times to the current target of the "two week rule" may bring any palpable benefit in staging and outcome for these patients.

Beside a huge number of medical reports concerning various methods of treatment and staging of the disease, the medical literature is quite scarce in evidential papers looking at ways to improve the early detection and speed of diagnosis for this particular group of patients, i.e. Upper Gastro-Intestinal Cancer patients. This fact is more evident in the United Kingdom where, due to historical reasons, the health care system seems to take more time in referring and submitting patients to the appropriate treatment. A quick browse of the work published in the last 10 years alone shows a net prevalence of papers [41;47;65;68;91;115;124;149;158] dealing with the rapid diagnosis issues, early diagnosis or indeed the issue of the "two week rule" in cancer referral for many of the cancer localizations, such as breast, colorectal, etc., but with the notable exception of the gastro-intestinal cancer. Based on the experience of the these two neighbouring NHS trusts described above, the following pages are designed to fill the gap noted in the literature by referring to the gastro-intestinal cancer localization in particular and by assessing the

efforts and results in these two trusts in complying with the "two week rule" in cancer services in South Wales.

The open access services described earlier were not initially designed to "filter" referrals for potential cancer cases, but this started to change once the available algorithms of referral were adapted to serve the more sinister pathology. Progressively, the concept of reducing the waiting time to conventional clinical services for gastroenterological cases at large has been overtaken by the need to speed up the referral process for potentially malignant cases. The trend we have noticed in these two hospitals was not singular in the UK; it was noted in approx. half of the hospitals by mid 1990's and some of them even started to use open access services offered to the general practitioners for identifying early gastric cancer as Hallisey and Heatley[59] wrote in 1993. Therefore, with the advent of the "two week rule" in cancer services, the two hospitals like many others in the UK, were ready to implement and at the same time monitor the implications of the required changes. It would be interesting to scrutinize how the two hospitals used the implemented services to address the ever rising needs of appointments for those patients with gastrointestinal malignant disease alone; the results shown earlier in chapters VI and VII will need to be interpreted according to the new requirements addressed to cancer services and establish whether these services can improve cancer detection without delay and if this is followed by improvement in outcome.

a) Traditional vs. Rapid Referral Pathway

It is already known that the patients with upper gastro-intestinal carcinomas are experiencing the progression of their disease in several phases, two of which are quite well demarcated: pre-symptomatic and symptomatic phases. Whilst it is agreed that the pre-symptomatic phase is longer, measured in years and difficult to obviate, unless targeted screening is employed, the symptomatic period appears much shorter in time and, more importantly, easier to highlight in a retrospective history-taking exercise. What is more obvious is that, once the symptoms appear, the patient becomes the main focus of the diagnostic algorithm; as a consequence, clinical records may be able to obviate, with more or less accuracy, certain events that mark the progression of the disease on one hand and diagnostic, staging, and treatment processes, where appropriate, on the other hand.

Certain landmarks in time are therefore present in the clinical history of each patient and may mirror various events such as: onset of symptoms, first presentation to the family doctor, referral to secondary care sector, first examination by the clinician, positive diagnosis, staging episodes, treatment and occasionally outcome related events. Placed on a timescale bar as in *Appendix A01*, these landmarks may identify several time intervals; they can be longer or shorter and in conjunction with the natural history of cancer

progression could represent a potential delay in the patients' diagnosis and clinical management; it is on this basis that they were named "Delay Intervals". As a consequence they may be used to indirectly quantify the effect of the referral methods and clinical services introduced in the clinical practice to manage these patients. The definition and substance of these intervals is shown below (see Fig. 8.06) and graphically emphasized in *Appendix A01*:

Appendix A01 Mapping	Interval Name	Significance
1	**Onset Delay**	Time elapsed between occurrence of 1st symptom AND Presentation to the General Practitioner
2	**GP Delay**	Time elapsed between Presentation to the General Practitioner AND Referral made by the General Practitioner
3	**Hospital Delay**	Time elapsed between Referral made by the General Practitioner AND 1st Hospital Examination
4	**Diagnosis Delay**	Time elapsed between 1st Hospital Examination AND Positive Diagnosis
5	**Treatment Delay**	Time elapsed between Positive Diagnosis AND Beginning of Main Treatment (where appropriate)

Fig. 8.06 - Definition of Delay Intervals

It is worth mentioning in the above context the following:

- *the "Onset Delay" mirrors the speed with which the patient comes forward to seek medical advice;*
- *depending upon the GP practice involved, the "Onset Delay" as an interval may incorporate not only the delay related to the patient himself/herself, but also a longer or shorter period of time required for offering an elective appointment to the patient;*
- *on a retrospective basis it is quite difficult in the vast majority of cases to isolate the precise moment in time when the first symptom occurred;*

therefore, it is more common to establish the length of this "onset delay" interval arbitrarily as blocks of time which may be more transparent to the patient when taking history and more certain to be found highlighted in the patient's medical records;

- *the "GP Delay" interval is larger than 0 days only when the general practitioner did not refer the patient at the first encounter and recalled the patient after instituting some form of treatment;*
- *the "Hospital Delay" interval is always 0 days when the patient was referred as an Acute In-Patient Admission;*
- *the "Diagnosis Delay" is always incorporating the necessary time to process the histo-pathological diagnosis of the bioptic / operative specimen; it can be 0 days only in emergency situations where a frozen section examination is employed;*
- *the "Treatment Delay" interval refers only to patients who were submitted to some form of treatment such as surgical, chemotherapy, radiotherapy, stenting, etc.; it is always 0 days when patient had his / her treatment administered as an emergency procedure;*
- *the "Treatment Delay" interval must incorporate the time elapsed after the positive diagnosis which is used for staging procedures and examinations.*

Before discussing the practical results of the introduction of referral algorithms and new clinical services in the two hospital settings, it is important to note that:

- *based upon the patients' interaction with the healthcare infrastructure, the above intervals can be consolidated in two global intervals that have been used by several authors[90] to explain better the reasoning behind delays in presentation and clinical management of these cancers: Presentation Delay - attributable essentially to the patient - and NHS Delay - for which the health care infrastructure is assuming responsibility - (Fig. 8.07 on the next page);*
- *the referral algorithm which was disseminated to the general practitioners and other hospital doctors aimed to guide the appropriate channelling of the patients to the most efficient service; it may influence the length of the interval 2 - i.e. GP Delay interval -;*
- *the new clinical services implemented at the two hospital sites may influence interval 3 - i.e. Hospital Delay - by eliminating the potential extra time*

required by the patients to pass through the conventional clinical services such as Outpatients clinics;

Appendix A01 Mapping	Name	Significance
1	**Patient's Delay**	Time elapsed between the occurrence of 1st symptom AND Presentation to the General Practitioner
2 + 3 + 4 + 5	**NHS Delay**	Time elapsed between Presentation to the General Practitioner AND beginning of the definitive Treatment

Fig. 8.07 - Definition of Global Delay Intervals

- *irrespective of the method of referral used and the clinical services introduced, the time elapsed after the implementation of the main treatment defines the outcome period which historically is equated for these patients with survival interval; it is agreed by consensus in the medical literature to discuss survival at 1 year, 5 years and 10 years respectively. Sadly, this survival interval may end abruptly at any time with the demise of the patient due to recurrence of the disease or, in some occasions, due to other medical conditions. Only for statistical and calculation purposes I extended this interval to the end of the follow up date only for the patients still alive at that particular date.*

I found the overall picture of these delay intervals as shown in table at Fig.8.08 on the next page. It is evident that neither the overall mean Hospital Delay nor the mean Diagnosis and Treatment Delay intervals complied in retrospect with the requirements of the "two week rule" or the requirements for commencement of treatment of a malignant case within 30 days from the initial referral. However, their respective median delay figures show that the majority of these patients were seen, diagnosed or treated respectively within the timescale imposed by the current required standards.

Interval	Mean *(days)*	Median *(days)*	Std. Dev.
"GP Delay"	17.09	0	46.23
"Hospital Delay"	15.96	11	18.68
"Diagnosis Delay"	38.95	10	87.98
"Treatment Delay"	44.43	33.50	46.20
"NHS Delay"	117.88	82	115.34

Fig. 8.08 - Overall Mean & Median Delays

Out of the 440 patients with cancer I found, only 245 patients (55.68%) were seen at the hospital level within two weeks from referral date; as a matter of fact, this figure includes 139 patients who were seen on the same day of referral made by the General Practitioner which implies that they were referred as inpatient emergencies.

On the same note, it must be added that, despite of distributed algorithms and availability of open access services, still a large number of patients were diagnosed using the outpatients referral modality: 42.0% of diagnosed cancers were referred initially to the Outpatients Clinic and only 21.4% were initially channelled to the Open Access Endoscopy. These figures may explain the length of the Hospital Delay interval as well as the differences in mean Delay figures between the various modalities of referral. The figures are reproduced in a statistical analysis for individual hospitals and various delay intervals; the results show that the Hospital Delay is longer than 14 days in Morriston University Hospital in 40% to 45% of cases and in Neath General Hospital in 45% to 50% of cases. It

appears that the "two week rule" for referrals works slightly better in the Morriston University Hospital than in the Neath General Hospital.

I have also calculated for each method of referral the outliers to the "two week rule"; in a χ^2 test, the breakdown for cases seen beyond the 14 days target interval is as follows:

- ***for Acute Admission 6 patients out of 149 or (4.02%) seen after 2 weeks***
- ***for Outpatients Clinic 94 patients out of 121 or(77.68%) seen after 2 weeks***
- ***for Open Access Endoscopy 66 patients out of 185 (35.67%) seen after 2 weeks***
- ***for Rapid Opinion Clinic 3 patients out of 12 or(25%) seen after 2 weeks***

In Fig. 8.09 below a comparative look to the mean and median values of Hospital Delay for various methods of referral reveals little difference between the Open Access Endoscopy and the Outpatients Clinic method of referral - mean delay = 23.17 days compared to 24.37 days respectively -.

Method of Referral	*n*	Mean *(days)*	Median *(days)*	Std. Dev.
Admission	**149**	1.44	0	6.57
Outpatients	**185**	24.37	20	19.81
Open Access Endoscopy	**94**	23.17	18	16.26
Rapid Opinion Clinic	**12**	10.25	9	4.99
Total	**440**	**15.96**	**11**	**18.68**

Fig. 8.09 – "Hospital Delay" & Methods of Referral

Not all of the patients referred to the Open Access Endoscopy were seen within the "two week rule" timescale and in fact the improvement comparative with the conventional method of referral to

Outpatients Clinic was minimal. However, the median delay figure is 11 days and this is below the required threshold for the two-week standard. However, if we associate the figures from the χ^2 test with the slightly lower value for mean Hospital Delay in the Open Access Endoscopy group compared with the Outpatients Clinic group, we may conclude that the cases seen after the two weeks deadline in the Open Access Endoscopy group had a shorter wait compared with the patients from the Outpatients Clinic group. This may signify that the Open Access Endoscopy, although not always complying with the "two weeks rule", may offer shorter delays for these patients compared to the more traditional referral method.

When taking account of the fact that the two sites had a slightly different mechanism of accepting referrals and Neath General Hospital had algorithms distributed locally to General Practitioners emphasizing the need for urgent referral, the figures above seem to be at least disappointing. The reasons behind the increased delay are difficult to identify. This picture may be explained by a number of factors, including patients' decision to attend appointments according to a timing suitable to them - for instance Flashman[47] in 2003 quoted in his series a compliance for colorectal appointments to urgent referrals of only 91.68% for the "two week standard" -; another factor that might have prolonged the interval could indeed be the large throughput induced by the referral pattern which may clog up the

service to certain extent with non-cancerous cases. Ultimately, this situation relates to the impossibility of distinguishing either an obvious sinister symptom and/or a combination of symptoms highly suggestive of malignant pathology which may ultimately guide the decision to refer to the appropriate service. There was no mechanism in place to verify whether the date given for an appointment was chosen by the individual patient or the appointment was scheduled based on filling up free examination slots within the session's timetable.

The Acute Admission method of referral was the second most used amongst the four methods (149 patients out of 440 or 33.86% and after Outpatients referrals for 185 patients or 42.0%) and offered the lowest mean Hospital Delay as per our expectations. It is expected that this method should be used for acute emergencies, even though in the case of the surgical department as a recipient for referral this may not mean automatic surgical management of the patient's condition. It is difficult to scrutinize the reasons behind an urgent referral or indeed to correlate the need for emergency admission with the recorded symptoms. This interval certainly correlates better with the Diagnosis Delay as it is expected that the patients using this referral method will be examined quicker - sometimes this is what is expected at local surgeries - and will have a positive diagnosis quickly established. Unfortunately this is not the case in this cohort of

patients where the Diagnosis delay was longer for the Admission method (mean Diagnosis Delay = 26.18 days, median = 8 days) compared with Open Access Endoscopy (mean Diagnosis Delay = 13.34 days, median = 0 days). This way I may explain what all medical practitioners may have previously thought: some patients are admitted and only their acute symptoms are dealt with, whilst investigation to reach a positive diagnosis may on many occasion take the conventional route through the Outpatients Clinic system.

It is only the Rapid Opinion Clinic method that complied with the required rule; this may be an endorsement of the need to have more precise referral criteria[29;149], since patients were referred to this clinic with quite serious symptoms or complaints. When a balance is struck between the provision of service and correct interpretation of patients' symptoms based on accurate and updated guidelines and algorithms, the Rapid Opinion Clinic may be the example to follow in dealing with potential Upper Gastro-Intestinal Cancer patients. High attendance rates associated with provision of service for "on the spot" upper gastrointestinal investigation may be the answer in reducing both the Hospital Delay interval and the Diagnosis Delay interval as well.

One can also question the benefit of the Open Access Endoscopy pathway, since the mean Hospital Delay difference is not so much reduced compared with the Outpatients Clinic pathway; in

fact, the two hospitals were already operating in one way or another some form of Open Access Endoscopy at the time the study was commenced and local practitioners were already used to channelling patients via this quicker route of access to specialist care. This way the traditional long waiting time for outpatients appointments is not negated and the benefit of an open access service is re-endorsed. However, considering the report given by Spurgeon[139] for the waiting times of gastric and oesophageal patients in a national retrospective survey, our figures are encouraging; for both stomach and oesophagus the urgent referrals were seen after a median delay of 9 days in our case mix comparative with a median of 10/11 days shown in the national survey. The non-urgent referrals are more difficult to assess, since the majority of the papers[139] class them as outpatient clinic appointments and data for Open Access Endoscopy waiting time in the Upper Gastro-Intestinal Cancer group of patients is difficult to identify; even so, our figure of median delay at first appointment of 18 to 20 days is lower than the national average - median 24 and 27 days respectively -.

Another interesting aspect is related to the level of interaction in the grey areas between specialties. It is obvious from day-to-day practice that patients with certain suspicious symptoms are referred by their practitioner to various specialties or departments without a certain guidance being available. In this case mix there was a

significant shift in referrals towards the medical referrals at the Morriston University Hospital site and approximately equal distribution at the Neath site between surgical, gastroenterology and medical departments respectively. I believe that this is a direct consequence of the profile held by each hospital and their recognized status for acute admissions. Since the Open Access Endoscopy lists were manned in the Neath General Hospital by gastroenterologists, the majority of referrals for the Neath site were addressed in this direction; in Morriston University Hospital the situation was different and the bulk of referrals were addressed to the medical department, most likely due to acute symptoms.

In fact the Hospital Delay was the shortest for Medical Department - mean = 11.87 days, median = 1 day - and the longest for Gastroenterology - mean delay = 21.79 days, median = 18 days -; this result is contributed to by the large number of emergency admissions that used this route for the first referral. Paradoxically, these figures appear to negate the benefit of introducing Open Access Endoscopy and Rapid Opinion Clinic services which traditionally are functioning under the umbrella of the Gastroenterology Department. However, I believe that this result is in fact related to the surge in acute admissions that the medical practitioners saw fit to request, which shifted the balance in favour of the Acute Admissions method of referral.

This referral pattern may also explain why Morriston University Hospital complied better in a bivariate analysis with the "two week rule" - mean Hospital Delay = 14.94 days compared to 16.73 days for the Neath General Hospital - and endorses the opinion of Cann[29] that the referrals under the "two week rule" or urgent ones should be made in a single pool of referrals, rather then in a departmental manner.

Another delay interval closely associated with the Hospital Delay interval is the delay in referral occurring at the General Practitioner level. I have noted that compared with the overall mean GP Delay value for this interval of 17.09 days and median = 0 days, the patients with previous digestive conditions were referred slightly quicker - mean GP Delay = 16.70 days - than those with surgical abdominal history - mean GP Delay = 34.14 days -. However, for the majority of the patients - 292 patients (66.4%) - the medical practitioner deemed necessary to refer the patient same day rather then attempting some form of treatment. I have noted another 110 patients (26.36%) who were not referred in the first 14 days after presentation and recalled for further examinations or even given some form of medication. One must assume that the symptoms elicited by these patients were atypical since they were not recognized at practice level. However, a ratio of non-referrals of 26.36% seems rather high when the medical practitioners were already alerted of the availability of the diagnostic fast track pathway.

In a statistical analysis using the non-parametric Spearman's Rank Order Correlation it appears that the picture looks better for the Morriston University Hospital site - in 20%-25% of cases the GP Delay is more than 14 days - compared with the Neath General Hospital site - in 25%-30% of cases the GP Delay is more than 14 days -. However, the correlation is poor. These figures are particularly alarming since the Neath site had already implemented at that material time fully structured algorithms of referral and the patients belonged to the high risk group irrespective of presenting sinister symptoms or not.

The above picture may raise some questions with reference to the correct identification of patients for each referral pathway; since all the services were fully functional at the time of the case identification exercise and the patients suspected of cancer already benefited from priority in receiving appointments, staging and pre-treatment assessments, one area that remains to be addressed is that of the symptomatic structure of patients' presentation and correct interpretation of worrying symptoms.

b) Presentation - still the key to late diagnosis

The patients in this cohort requested their consultation with the general practitioner after a long delay. This is not surprising, since many reports raise the same issue in relation with late diagnosis and poor outcome. 42% of our patients delayed their presentation for up to 3 months whilst 6.1% of them for even more than one year. It must be

stated though that, as a retrospective study based solely on data retrieved from medical records, the validity of these figures - some authors rate this to 40% and above - are questionable[88]. It is therefore difficult to make precise correlations with other variables such as staging or survival rate as the results may be quite imprecise. However, the onset interval may be substantiated as range of delays and correlated with a symptom or combination of symptoms the patients presented with.

I have looked at the range of symptoms the practitioners considered to be the most relevant for the individual patient's complaint. It appears that the first three most relevant symptoms are Dysphagia (309 cases), Weight Loss (219 cases) and Abdominal Pain (219 cases). I found it interesting to note that in the third position as frequency stands Dyspepsia (165 cases) followed by other worrying symptoms such as Lethargy (105 cases), Vomiting (42 cases) and Anaemia (36 cases). These symptoms are on the list of common symptoms in adult patients with cancer[40] and have been endorsed by the British Society of Gastroenterology. In the referral letters we looked at the associated symptoms as well, since 311 patients were reported to present them. Interestingly, for the second line symptom - i.e. the symptom with less weight in doctors' referrals - we found the first five most frequent symptoms better correlated with the BSG's guidelines. This aspect is difficult to interpret and the correlations we can make are very poor. We wonder if some of the symptoms do not

"impress" the practitioners more than others or indeed the practitioners at large are not sufficiently aware of the possibility to judge the high index of suspicion for malignancy based on less prominent and obvious symptoms.

In this case mix dyspepsia was in the seventh position of frequency. I have decided to observe the combination of dyspepsia associated with one or more "sinister" symptoms since in the daily gastroenterological practice more than 30% of referrals are based on this symptom[79;84]; I found that in only 44 cases (10%) non-ulcer dyspepsia was present either alone (18 cases) or in combination with other less "sinister" symptoms; in these cases the suspicion of cancer was less obvious. Like many other authors[107] I could not find dyspepsia alone an indicator for malignancy and in the majority of cases dyspepsia was either absent or associated with "alarm symptoms" which could trigger investigation of the gastro-intestinal tract on their own merits. Therefore, the question arises whether the referral should be placed under the "two week rule" or not.

In a non-parametric statistical analysis of the main symptoms I did not find sufficient evidence to suggest that more weight should be put on a certain combination of symptoms that might be more suggestive of malignancy. However, there are many authors[14;32;54;79] who are strong advocates for using dyspepsia as a triggering marker for endoscopy, even when it appears unassociated with other symptoms, but occurs in high risk age groups. Since the majority of

our patients were above the age group of 45 I have to agree from this point of view with the opinion of Lambert[79] that endoscopy is promptly recommended for dyspepsia in patients over 45.

One interesting aspect observed was the combination of previous abdominal history and onset of symptoms. I have noted in our case mix a number of 165 patients (37.5%) who had past medical history such as gastroenterological disorders of benign type (i.e. Barrett's, gastro-duodenal ulcers, GORD, etc.), abdominal surgical events (i.e. cholecystectomies, gastrectomies, hysterectomies, etc.) or other abdominal conditions or general diseases with abdominal expression.

I have compared the Onset Delay interval in these patients with the overall figures. Whilst the overall figures show that roughly 73% of patients presented to their doctor for consultation within the first three months of the clinical onset, in cases of patients with pre-existing or past abdominal medical conditions these figures were significantly lower: those patients with previous surgical abdominal events presented within three months from onset in proportion of only 57.2% of cases and those with pre-existent gastroenterological conditions presented within the same interval in only proportion of 68.6% of cases. The patients with other conditions in their past medical history and previous symptoms related to the abdominal cavity had a higher than average threshold of presentation within 3 months of onset (87.5%). These figures may suggest that the threshold

for triggering a request for consultation might be more elevated in this group of patients than in the overall population who did not experience digestive and/or abdominal symptomatology earlier in life. The fact that the threshold of consultation request was much higher for patients with abdominal and/or digestive conditions may confirm that the patients in this group may know how "to live with the symptoms" and may distinguish with greater difficulty the change in the pattern of symptoms. This effect may also be affected by the self-medication issue so much discussed in the literature in conjunction with the delay in presentation.

In a χ^2 test analysis for past personal medical history and pre-operative clinical TNM staging, I have found that for those patients with other previous abdominal conditions the stage of the disease was much more favourable but the correlation was poor (Pearson χ^2 = 4.843, p = 0.184):

- **16.7% of patients with other medical history had early cancers**
- **8.2% of patients with previous gastroenterological history had early cancers**

I searched this case mix for any correlation between the prolonged Onset Delay interval and other variables. I did not find any correlation between the length of the symptomatic interval before presentation and stage of the disease; irrespective of the length of onset, there were approx. 7.4% of patients with early cancers in each range of onset interval, suggesting that for this length of delay there is not enough

evidence for disease progression. This seems to endorse the view[78] that it might take at least a year of progression for the malignant tumour to induce symptoms.

Not even in terms of operability the Onset Interval had statistical significance. A χ^2 test did not show any significant association between the Onset Delay and the type of operation performed, be it radical, non-radical or palliative. Operability was the highest when the Onset interval was recorded at less than 24 hours (20% of cases) - most likely this is related to emergency surgery - and smallest when the length of this interval was less than 1 month. The results confirm the impression of many authors that the longest segment of delay in the management of these conditions occurs before the patient is referred to the hospital. Although I have not been able to quantify accurately the presentation delay the patient is responsible for, there is strong indication that our case mix would match the opinion of Sue Ling et al.[90] who found that the pre-hospital delay accounts for more than 50% of the patients' cancerous history?

c) Specialist care related delays

Normally the Diagnosis Delay and Treatment Delay intervals are not influenced directly by the methods of referral in use at the two hospital sites, nor by the pattern of referral from General Practitioners to one department or another. However, in this model of two hospital sites used for the diagnostic side of patients' pathway and a

subsequent one hospital site with convergent surgical and oncological pathway for the therapeutic side of patients' management, some delays may occur if the referral pattern has changed and more patients are using the admission method or the surgical department as a choice of referral. Having said that, in normal circumstances the number of cases addressed by the Upper Gastro-Intestinal Surgical / Oncological team does not explain any major delay in managing these patients. The delays are generally explained by the infrastructural deficit as a whole rather than pressure coming from this group of patients alone.

In this cohort of patients the mean Diagnosis Delay was rather long at 38.95 days. However, a median delay of 10 days is quite acceptable since the majority of the patients had a positive diagnosis within this timeframe. It is difficult to lower further this delay interval as time is needed for tissue diagnosis - i.e to process the bioptic specimens and read the slides -. Examining the method of referral I was pleasantly surprised to see that the Open Access Endoscopy was the method of referral to allow the quickest positive diagnosis (mean Diagnosis Delay = 13.34 days, median = 0 days). However, the prolongation of this Diagnosis Delay is linked in most circumstances with false negative results which warrant a repeat of the endoscopy. This is surely an area where improvement in skills and training can bring the delay down further.

Surprisingly I found the Diagnosis Delay longer at the Neath site (mean Diagnosis Delay = 48.64 days, median = 11.50 days) compared with the Morriston one (mean Diagnosis Delay = 30.62, median = 9.50 days); comparing the diagnostic delays between the two hospital sites I have noted that within the 10 days timescale for the Neath site only 49.04% of allocated patients were positively diagnosed whilst at Morriston University Hospital 51.79% of allocated patients were positively diagnosed; since the same pathology department was processing the specimens on both sites, I find it difficult to interpret this finding. One explanation could be related with the increased number of false negative biopsies delivered. It must be added that the 10 days interval is arbitrarily chosen and is related only with the time needed to process the tissue samples.

Another explanation is related to the algorithm used for establishing the positive diagnosis. Since the current standard is that one of a tissue diagnosis, any other attempted method to refer and diagnose these patients through alternative methods may only prolong the Diagnosis Delay interval. I was not surprised to observe that, in spite of having referral algorithms distributed widely as well as the knowledge that the local Radiology waiting list was quite long, 107 cases (24.31%) were referred to Barium Meal as a first line investigation and even more than that. 15 cases (3.40%) were examined only through clinical examination. The table in Fig. 8.10 below shows the Diagnostic Delay interval for each type of the first

examination the patients were subjected to when attending the hospital setting for the first time; it must be added that the first examination is the one the patient attended irrespective of the method of referral employed and reflects how the medical staff - General Practitioner or Specialist Hospital staff - considered to investigate the patient.

First Examination requested @ Hospital	***n***	**Mean** *(days)*	**Median** *(days)*	**Std. Dev.**
Barium Enema	**3**	63.00	55	20.22
Barium Meal	**107**	41.03	19	63.97
Endoscopy	**299**	30.98	6	86.37
Clinical Exam	**15**	163.20	97	168.17
Abdominal Ultrasound	**12**	66.25	13	84.99
Laparotomy	**4**	12.75	5	17.15
Overall Diagnosis Delay	**440**	38.95	10	87.98

Fig. 8.10 – "Diagnostic Delay" & 1st investigation requested

The table shows clearly the extent to which the Diagnostic Delay interval is prolonged simply by abating from the distributed guidelines. For an overall mean Diagnostic Delay of 38.95 days, simply by using Clinical Examination alone extends the positive diagnosis moment to 163.20 days and by choosing Barium Meal this interval extends to 41.03 days. A Chi-Square test (χ^2 = 9.57, p = 0.002) shows that:

- **20% of cases examined by clinical exam only were early cancers**
- **4.6% of cases examined by Barium Meal were early cancers**
- **9.7% of cases examined firstly by Endoscopy were early cancers**

All these situations, as well as a few cases where ultrasound or Barium Enema was the first line examination based upon patients' symptomatology, have prolonged the positive diagnosis interval. There is anecdotal evidence that some hospitals may enjoy a shorter radiological waiting list; however, there is wide spread agreement that for gastroenterological symptoms Upper Gastro-Intestinal Endoscopy is the investigative method of choice.

There is a progressive increase in the Treatment Delay from the 35 to 44 years of age group upwards. However, it must be stressed that a number of patients, particularly the over 75 years of age, would fall outside the bracket imposed for this interval and this relates mainly with the staging and medical assessment investigations which are required for the surgical / oncological management, where necessary. On a bivariate analysis of the Treatment Delay, I found no correlation between the Treatment Delay interval and the method of referral.

A note must be introduced about the global delay interval named by many authors as the "NHS Delay". This offers a more general view on the speed with which the patients are diagnosed and treated, without offering details as to where the bottlenecks are. In our case mix the NHS Delay interval was quantified for treated patients only and offered a slightly higher ratio than expected: mean NHS Delay = 117,88 days, median = 82 days for overall treated patients

and mean NHS Delay = 105,52 days, median = 71 days for surgical patients alone. The significance of these figures is two fold: firstly, once presented to the General Practitioner, the patients are waiting much too long to have their treatment commenced; secondly, surgical patients are waiting shorter time than average, meaning that the bottleneck is related to the oncological services.

Many authors[29;47;149] coming from a variety of specialties argued that based on clinical evidence the resources may be more effectively targeted at reducing the waiting times from diagnosis to treatment rather than reducing the time from referral by the general practitioner to diagnosis. There are a multitude of studies centred on the waiting times assessment and compliance with the "two week rule" in cancer services. The majority of these belong to certain subspecialties which benefited from structured screening programs, such as breast[66;106;138] or colon[46;157]. Very little evidence is found related to the investigation of waiting times and "two week standard" for cancer services in relation to the upper gastro-intestinal pathology.

D. Outcome & Survival

There are a few other variables that I looked at briefly when discussing the Diagnosis and Treatment Delay. These are only tangentially related with the scope of this study and are used mainly for quantification of the possible consequences of using the new methods of referral and algorithms presented in earlier chapters.

Some of them have been indirectly discussed in the results part of this study and refer to pre- and post-operative stage, operability, etc.

The clinical TNM stage of these patients is one of the most important indirect tools in assessing whether the algorithms and the new referral methods have made any improvement in the way our patients had a positive diagnosis earlier during the natural history of their disease. Should these clinical services make any inroads into the early diagnosis of upper gastro-intestinal cancer and pick up an increased number of early cancers, one would expect to find the early/advanced cancer ratio tilted in favour of early cancers. Based upon the clinical T component of the TNM classification I found an *early/advanced cancer ratio of 36/376=0.095.* It is obvious that this ratio is very unfavourable from prognosis point of view and compares much less favourably with other reports available in the medical press[10;62;72;90]. If the prognosis of these patients is to improve, this figure should increase dramatically towards the unit, which is roughly where the Japanese expertise is at best these days.

I have also looked at the dynamics of the early/advanced cancer ratio using a χ^2 test and tried to identify whether the new services have made any difference between the first year and last year of the study. Whilst in the first year the ratio was 0.16, in the last year this ratio diminished to 0.12 (Pearson χ^2 = 10.69, p = 0.469). The correlation of the test however was poor. The same picture applies if we look at the variable T of the TNM stage alone. It appears that in the

last year of the study the proportion of cases picked up in stage T_3 and T_4 were more frequent than in the first year (80% compared to 54.2%).

In this cohort of patients 12 cases were submitted to down-staging radio/chemotherapy - 8 of oesophageal origin and only 4 of gastric topography. An analysis of the outcome of these cases shows that the *pre-operative / postoperative correlation* was favourable only in three cases, all of them referred as Open Access Endoscopy referral method: one was converted from TNM stage I to stage 0 and two cases from TNM stage III to stage II; however, in the rest of 9 cases there was either no effect noted - one remained in TNM stage II and two cases remained in stage III - or progression of the disease was observed from TNM stage II to stage III in 5 cases. The result of 7 out of 12 cases with no effect or positive effect is encouraging but the data in the literature is so heterogeneous due to different trials and their interpretation in this case mix makes a valid conclusion impossible.

Although a comprehensive analysis of the surgical management of these patients is beyond the remit of this study, I would mention only a few facts related with the surgical outcome as part of our quantitative assessment of the services and methods of referral used. Beside the operability issues mentioned above, it is sufficient to point out that the 222 cases were subjected to the following types of surgical procedures:

- palliative procedures - 53 cases

- non-radical procedures	-	30 cases
- radical operations	-	139 cases

The ratio of radical procedures of 31.55% of the whole uncensored cohort (or indeed 62.61% of all 222 cases deemed suitable for some sort of surgery) is quite high compared with the standards seen in the medical literature. It is obvious that this situation refers to an uncensored cohort of patients; the figures therefore cannot be compared with those from specialised centres in a "like-to-like" manner where both referral pattern and standardized aggressive approach may be different. In a χ^2 cross-tabulation test (see Fig. 8.11 below), although with a poor correlation, the cases referred through Open Access Endoscopy and Rapid Opinion clinic had a higher chance to be subjected to a Radical procedure ($\chi^2 = 33.63$, $p < 0.001$):

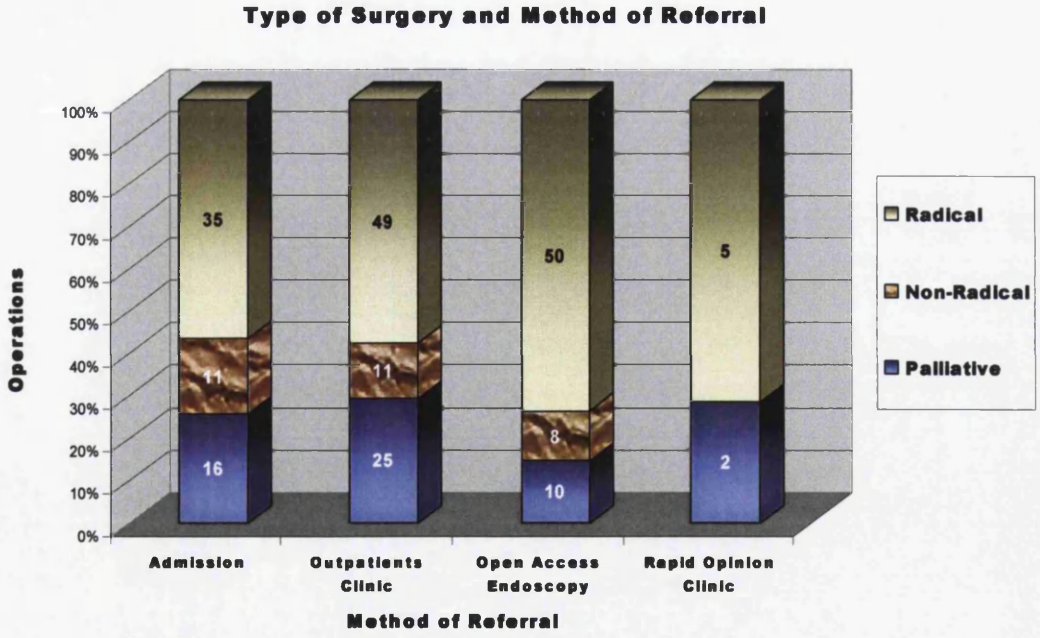

Fig. 8.11 - Surgical Treatment & Method of Referral Distribution

- **73.5% of 68 patients referred to Open Access Endoscopy had Radical operations**

- **71.4% of 7 patients referred to Rapid Opinion Clinic had Radical operations**
- **57.6% of 85 patients referred to Outpatients Clinic had Radical operations**
- **56.5% of 62 patients referred to Acute Admission had Radical operations**

The largest group of patients who were subjected to palliative procedures came from the Outpatients Clinic group. This is a significant finding which endorses the idea that the patients referred to Open Access Endoscopy had a slightly more favourable stage of the disease. Whether this is due to rapid referral or due to less symptomatic disease which encourages general practitioners to refer to a department with a minimal waiting time but no immediate admission, is difficult to speculate. However, these findings are not significantly correlated with the stage of the disease.

Survival remains the most important outcome factor in assessing the benefits brought in by various new diagnostic algorithms, therapeutic techniques and after care measures. Alongside other variables such as staging and operability, we used the survival figures to assess whether the new referral methods and new clinical services provided an improvement in the life span of these patients. The crude survival figures were dealt with in earlier chapters and have shown that overall survival is quite reduced when compared with the current standard. An overall survival rate following positive diagnosis of 34.31% at 1 year and 15.00% at 5 years is quite low. The Japanese report figures in excess of 55% in non-specialized centres[43;44]; for Wales Pye et al.[114] reported in a Welsh survey a

mortality at 1 year of 34%, which makes us think that these results are equal with the Welsh median survival.

I have looked further at the survival figures from the perspective of the changes introduced in early 1990's with the advent of the new referral methods and open access services. Since all these services aimed and, partially achieved as previously shown, a substantial reduction in the waiting time the patients faced between presentation, diagnosis and treatment, I have tried to establish if survival as a variable was influenced by these services. It would be interesting to know if the overall survival has been influenced, and how, by the various intervals of delay considered in the study. For this purpose I have run a non-parametric correlation test using Spearman's Rank Order between survival and the following intervals:

- *GP Delay Interval: I have found that there is no correlation between this interval and survival as more that 50% of the cases return a delay of 0 days; it seems that in our case mix and at the extent that this delay interval was shortened or perhaps lengthened by the distributed algorithms, the survival was not influenced;*
- *Hospital Delay Interval: there is only weak correlation between this delay and the median survival (Spearman's Rank = 0.203); this is the only interval with significant impact on survival ($p<0.001$) but the correlation is weak; it may suggest that the longer the interval of delay is, the shorter the survival would become; the test showed also that 50% of the patients waited 16 days or more to be seen by the specialist in the hospital setting.*
- *Diagnostic Delay Interval: there is poor correlation because in more than 50% of the patients the delay to reach a positive diagnosis is less than 12 days (i.e. 11.5 days).*
- *Treatment Delay Interval: this interval has a small impact on the survival in the sub-group of the treated patients; more than 50% of the treated patients are*

waiting more than the required 30 days between the positive diagnosis moment and start of the definitive treatment; however, the correlation between this delay interval and survival is quite weak (Spearman's Rank = 0.205, p<0.001).

On the same note, the Spearman's Rank Order Correlation test showed some areas of possible improvement; for instance, the GP Delay interval is longer in 25% of the cases suggesting that these cases were referred 2 weeks later than expected. Also, in 65 out of 440 cases the GP Delay interval is 37 days or more and 45% of patients are waiting for their first hospital appointment more than 14 days in both Neath General Hospital and Morriston University Hospital. In respect of the positive diagnosis, the Spearman's Rank Order Correlation test showed that 40% of the patients are waiting more than 14 days for their positive diagnosis.

I was intrigued by the long Onset Delay noted in the study, even if the absolute values were impossible to be collected. Using the *Kruskal-Wallis test* I found that there was no correlation between the onset delay and the survival at 1 and 5 years after the presentation to the General Practitioner.

The same *Kruskal-Wallis test* was employed to ascertain whether there is a relation between the modality of referral and survival. For the purpose of temporality in this test, I closed the episode for each patient at the date when the patient was last seen alive either at the Primary Care setting or in the hospital/outpatient. The test returned significant differences (p<0.001) in the median survival of those

patients referred to the open access services (see table in Fig. 8.12 below):

Method of Referral	Median overall survival *(days)*
Acute Admission	100
Outpatients Clinic	189
Open Access Endoscopy	333
Rapid Opinion Clinic	711

Fig. 8.12 - Median Survival & Referral Pathways

However, if some patients actually live longer than the time introduced in the test, which is quite likely, the significance of the test would be even stronger and the correlation with the method of referral would be emphasized.

Since the introduction of the referral guidelines and the subsequent modification of referral pattern at Primary Care level was a dynamic process, it would be interesting to find out how this adaptation process worked out and whether there was any difference between the first and the last year of the study; in a *Mann-Whitney test* I found no significant difference ($p = 0.52$) between the two sites in relation to the survival.

Continuing the investigation of the impact these referral modalities have on patients' survival, I looked further at the issue of whether the survival probability for these patients is actually influenced by the various modalities of referral. Due to the constraints of the statistical computation imposed by the reduced numbers in

some cells – i.e. Rapid Opinion Clinic independent factor – I considered useful to amalgamate both the Open Access Endoscopy and Rapid Opinion Clinic pathways in a single spine as One-Stop Clinic; although at first sight this may deviate from the initial structure of the hypothesis, it will however test better the results of the new pathways of referral for the overall case mix.

	Admission *(days)*	**Outpatients** *(days)*	**One-Stop (O A E + R O)** *(days)*
Mean	496.63	661.59	985.13
Median	130	326.00	385.00
95% C I	367.53-625.73	265.37-386.63	771.43-1198.83
Total	**147**	**180**	**105**
No. Events	131	161	80
No. Censored	16	19	25

Fig. 8.13 - Survival Analysis & Referral Method

The Survival analysis using the Kaplan-Meier test (see Fig. 8.13 above) returned significant difference in survival rates between those patients referred to the Outpatient Clinic and the whole group referred as One-Stop Clinic (Log Rank = 22.88, Breslow = 45.22, $p<0.001$); there was a slightly higher probability for the patients in the one-stop group to live longer based on their median survival rates.

Finally, using a Kaplan-Meier test I looked at the probabilities of survival for these patients subject to the referral method used (see Fig. 8.14 below) and the treatment method employed in their clinical management (see Fig. 8.16 on the next page); in my opinion these may

be the two major factors which may influence the survival outcome in a way or another.

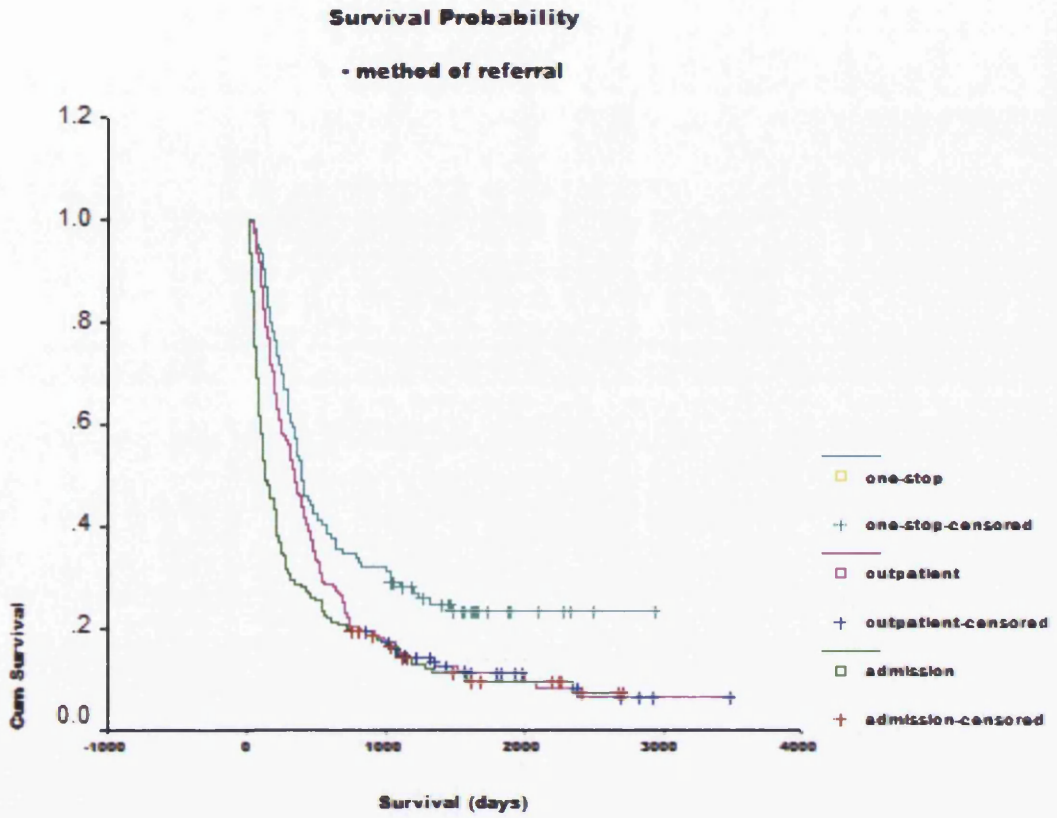

Fig. 8.14 - Survival Probability & Referral Method

The survival function shows a larger probability in survival for those patients referred to the "one-stop services" (i.e. Open Access Endoscopy and Rapid Opinion Clinic). The smallest probability, as expected, is linked with the patients referred to the Outpatients Clinic, where the graph shows a dramatic steep downwards trend; this can be correlated with reduced mean survival figures.

It is however difficult to postulate that these statistical figures are solely the consequence of the referral pathway and the "hospital delay"; there are obviously other factors which may intervene in the equation, such as the stage of the disease at the time of treatment, co-

morbidities, aggressivity of surgical treatment, etc. On the other hand, there is too much to be left to the element of chance by accepting that, on balance, the patients in the Outpatients Clinic group have already been in more advanced stages of their disease at the referral time and the onset symptomatology in their case was more silent than in the other groups.

Looking at the survival figures in conjunction with the treatment methods used, it appears that surgery offers the best overall survival in this group. The table below (see Fig. 8.15) represent uncorrected figures that refer to overall cases.

	No Treatment	Surgery alone	Surgery + ChemoTh	ChemoTh alone
Mean	160.15	995.42	884.74	364.13
Median	66.00	387.00	568.00	236.00
95% C I	118.90-201.40	822.79-1168.06	678.80-1090.68	245.53-482.73
Total	**166**	**163**	**59**	**50**
No. Events	164	118	46	48
Censored	2	45	13	2

Fig. 8.15 - Survival Analysis & Treatment Method

The graph below (see Fig. 8.16) refers to the survival probability related to the method of treatment used. It clearly shows that the patients treated by surgery associated with chemotherapy have a higher probability to live longer and, for the same interval of time, in larger number, than the patients subjected only to surgical management; in the long run, however, the patients subjected only to surgery seem to stand a higher probability of survival.

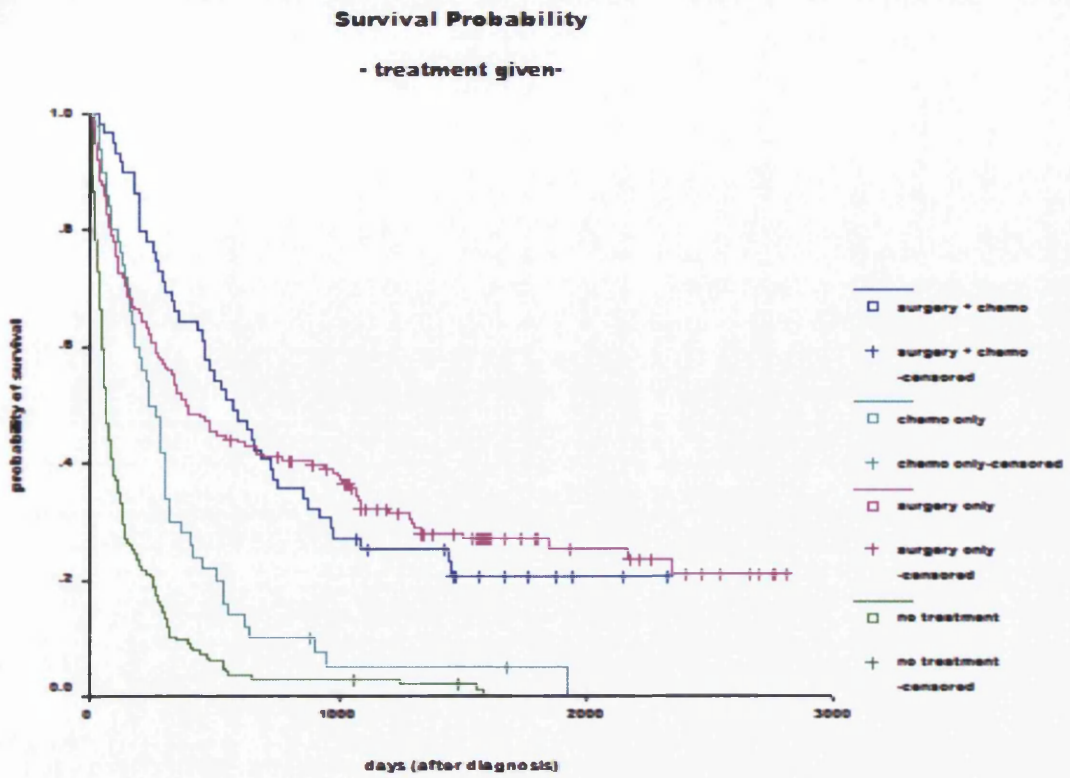

Fig. 8.16 - Survival Probability & Treatment Method

It is quite difficult to accurately interpret the above graphs. They represent only a potential statistical probability, but the median figures, and particularly the mean survival figures back up the idea of an increased survival for patients receiving multifactorial treatment. However, the figures shown above need to take account of the fact that the confounding factors, particularly the mean patients' age at presentation and the anatomical site, are not consistently distributed across the four groups of the independent factor. This lack of distribution may be the basis for the rejection of the results seen earlier in respect of both the mean survival figure as well as the survival probability. One fact on the other hand may minimise this negative impact, and this is related with the large number of cases

introduced in the case mix and the length of the follow up period which is large enough to allow for inclusion of the actual survival interval. I wonder though if the particular trends seen in the above graphs are not related to the combination between the distribution within the age groups of these patients and the favourable prognostic in a few, irrespective of the treatment applied.

From a different perspective, there are strong indications from various reports that standardized treatment has a positive influence on survival[43;97]. And not lastly, part of the promising trend in these graphs may be related to other factors, such as the inclusion in the survival probability computation of the gastric lymphoma cases (n = 23) - they are recognized for offering a better prognosis than carcinomas – or the variation in time of the adjuvant therapy regimens – their impact has not been considered as their efficiency is still under review -.

Having said that, these results seem to be encouraging; associating standardized treatment with improvement in the early/advanced cancer detection ratio may bring some answer to the higher incidence and reduced prognostic of these advanced Upper Gastro-Intestinal Cancers. Reducing the number in the first instance of advanced cancers and improving the prognosis of those patients who sadly have the disease may ultimately represent the first step in the battle against this disease.

Chapter IX

CONCLUSIONS

The Upper Gastro-Intestinal Cancers represent a pathological entity with high incidence and prevalence in Britain. It is well known that the diagnosis and treatment of these cancers pose a serious problem for the medical professional and health care organisations alike. Beside the costs associated with the delivery of care for these patients, the reality remains painfully obvious: too many patients are diagnosed in a late stage of their disease, the efficacy of the treatment remains in many circumstances questionable and the survival of these patients is seriously reduced compared to other forms of cancer. There were a number of papers that concluded that the advanced stage of these patients' disease at diagnosis time is related to a certain extent to their wait for diagnosis and treatment. The connotation was that by speeding up their diagnostic and therapeutic management it might be possible to reduce the ratio of advanced stages of the disease at diagnosis time and improve the post-care results, including patients' survival.

In this study I have tried to scrutinize some of the innovative services introduced at the beginning of the 1990's in two neighbouring

NHS Trusts and investigate whether they may bring in any benefit, not only in speeding the patients' throughput and early cancer detection, but also potential gains in their outcome. Since the medical literature does not show clear evidence that these services - originally aimed at speeding gastroenterological patients' diagnosis and treatment - may actually improve their outcome and survival, I have examined a cohort of uncensored 440 patients and assessed the impact Open Access Services may have on the patients' outcome.

One of the first observations I made has implications in the provision of service for cancer. It is related with the model of two neighbouring trusts which have joined forces to a certain extent and provide together for the diagnosis and treatment of Upper Gastro-Intestinal Cancer patients in a sequential manner. There were significant benefits in using a common pathway for both surgical and oncological treatment phases, not least represented by unified standardized approach to the individual cases and better service provisioning for the individual patient. This model does have its major strengths in the fact that it can be replicated throughout the country and can introduce standardization of the patients' management.

Other observations I made are related with the speed of diagnosis, where the strength of the new clinical services shows its major impact. Although there is strong evidence that the advent of open access services is followed in time by a huge increase in the volume of referrals, - per se this is not a bad thing since this is

increasing the probability to detect sinister pathology -, the result of the increase is contrary to that one of a blockage of the service as suggested initially by some authors. In fact it seems that *the Open Access Service can also improve indirectly the waiting times for the conventional referral pathway*, such as the Outpatients Clinic, since some patients with gastroenterological symptoms may not need to be seen in the clinic again. A mean delay of 15.96 days for all cancer patients to receive the first hospital appointment and Upper Gastro-Intestinal Endoscopy at the same time represents an important development in the provision of service. Although this Hospital Delay is slightly above the targeted "two week rule" for cancer, the *median delay of 11 days is within the limits of the imposed standard*, signalling that at least 50% of patients are seen within this interval. Also, it must be noted that the mean *Diagnosis Delay for those patients diagnosed through Open Access Endoscopy is smaller compared to the conventional referral methods*, suggesting that the standardized diagnostic algorithm is more efficient for speedy throughput of patients.

The best by far based on the Hospital Delay and the Diagnosis Delay intervals *fares the Rapid Opinion Clinic, but the end results of clinical TNM stage, operative ratio and outcome are poor*; this may signal a higher ratio of advanced cancers filtered through this method of referral and their identification based on symptomatology which correlates with advanced disease.

It must be mentioned here that the *Treatment Delay is quite long*, adding on average a month and a half to the natural history of these patients; there is evidence of a prolonged Treatment Delay for those patients treated with chemotherapy or surgery associated with chemotherapy; this may signal *a bottleneck at the interface between the diagnostic and oncological interface.*

Although the facts mentioned so far show clearly that these services may have a positive impact on the management of these patients, there are numerous other observations with less positive connotation. Firstly, the statistical figures show that the Admission/Open Access Endoscopy ratio of 33.9% vs. 21.4% remains quite high with *too many patients still referred as Admission but subsequently investigated as Outpatients modality.* This may be related to *the difficulty of a more accurate interpretation of patients' symptoms.* The British Society of Gastroenterology has issued referral guidelines suggesting the prevalence of certain symptoms in Upper Gastro-Intestinal Cancer patients, but these *guidelines do not seem to bring the clarity needed in pointing to the patients with high index of suspicion.* As a consequence, the identification of those patients at risk and potential candidates for urgent and targeted referral to open access services is lacking accuracy. This is followed by an increased number of patients referred to these services, with potential rebound effect on the speed of diagnosis delivery through this method of referral. Based on this cohort of cancerous patients, I *could not make*

any significant correlation between patients' symptoms or association of symptoms and predisposition to be diagnosed with upper gastro-intestinal malignancy. Even when I removed the non-ulcer dyspepsia as a first line symptom from the list, there was no association of symptoms that may give a higher index of suspicion for cancer. The only palpable finding was the dominance of the so-called "sinister symptoms" which were already emphasized in the BSG guidelines.

Another observation with questionable connotation is that a number of *patients are still examined after presentation only by clinical examination or indeed radiologically* by Barium Meal examination. This approach might exclude the diagnostic accuracy in borderline cases and rules out tissue diagnosis at first examination. This contrasts painfully with the reality whereby in most hospital situations the waiting lists are traditionally longer in the Radiology Departments.

There are a few words to be said about the outcome of these patients in conjunction with the measures taken to speed up their throughput. Although the introduction of Open Access Services aimed at diagnosing more early cancers, sadly this was not the case in this cohort. Not only the crude figure of advanced cancers remained as high as ever, but *the ratio early/advanced cancer in this cohort actually deteriorated.* There is direct evidence that the Open Access system has not delivered local expectations in detecting early cancers more often than before. As a matter of fact, no improvement was noted to other general parameters such as clinical TNM stage or operability figures.

However, *the statistical analysis of survival probability indicates that the cases diagnosed through Open Access Services may have a higher probability of longer survival in the long run, but the correlation is quite poor.* A note must be added that, similarly with other studies, the same higher probability of survival in the long run appears to be observed for those cases treated by surgery alone; it may be that under current standardized treatment, these cases are not advanced anyway, i.e. they present with lower T stages and are lymph-node negative; *in the short term it appears that the survival probability is better for those cases receiving combined surgical and adjuvant chemo- ± radio- therapy treatment.*

When planning for the optimisation of these cancer services one may consider introducing several measures to improve the early detection of Upper Gastro-Intestinal Cancers based on the findings shown in this study. The substance of these measures would need further adjustment but in essence might be as follows:

- *there is a need for further prospective research into the early symptomatology of the patients with Upper Gastro-Intestinal Cancer; certain combinations of symptoms must be highlighted and on statistical grounds may trigger the investigation of patients' upper digestive tract;*
- *implementation of some form of supra-selection method based on the initial referral; for fine-tuning of the process for the identification of a potential cancer patient certain measures can be of help, such as the telephone interview with the patient immediately after the referral is received, increased role for the Upper Gastro-Intestinal Specialist Nurse, establishment of priority slots*

on the lists for patients with high index of suspicion that can be examined within a day or two;

- *Open Access Endoscopy service to represent a single pool for all referrals and from all sub-specialties for those patients noted with suspicious symptoms in their initial referral;*
- *protocols to enable cases to by-pass the Outpatients Department for those cases with a hint in the referral letter suggesting Upper Gastro-Intestinal pathology;*
- *further research programme into the ways to organize with minimum funding Japanese-style "walk-in" settings for patients complaining of any symptoms within the list of "alert symptoms".*

It is hoped that such measures may increase the selection process of those patients suitable for urgent referral to Open Access Endoscopy and Rapid Opinion Clinic, increasing at the same time the yield of cancer diagnosis much earlier in the natural history of these patients.

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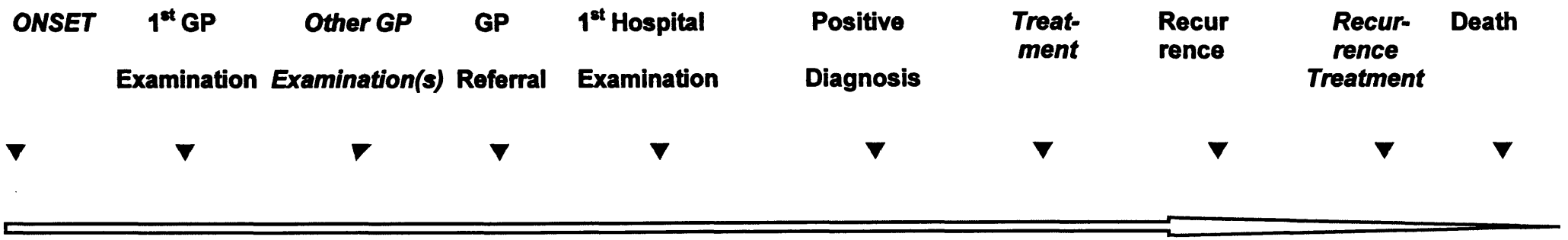
APPENDICES

Appendix 01

Natural History & Defined Intervals



Routine referral to the Department of Gastroenterology, Neath General Hospital, SA11 2LO

Please use this referral form for all **routine** referrals for open access endoscopy. It may also be used for non-urgent outpatients. For all urgent cases please use our urgent referral form.

Tel: 01639 762304
Fax: 01639 641293

1 Patient details:

Name: DOB:

Address: Sex:

Post Code: Tel no:

Hospital No: NHS No:

Preferred service (please tick)

☐ Open Access Gastroscopy (procedure report only)

☐ Open Access Flexible Sigmoidoscopy (procedure report only)

☐ Outpatients (consultation/investigations/management)

2 History, findings, current medication, reason for referral:

3 Other relevant information (for endoscopy referrals - please tick boxes or write free text)

a Current diagnoses:

☐ Diabetes
☐ Ischaemic heart disease/Recent MI/Current CCF
☐ Chronic obstructive airways disease
☐ Family history of stomach or colon cancer
☐ Valvular heart disease
☐ Neutropenia
☐ Other:

b Past procedures:

☐ Gastric surgery
☐ Colonic surgery
☐ Other:

c Family history:

☐ Gastric cancer
☐ Colorectal cancer

d Is the patient taking:

☐ Acid suppressants *(stop before first OGD if possible)*
☐ Anticoagulants
☐ Aspirin/NSAIDs
☐ Insulin/Oral hypoglycaemics

4 Referring doctor details:

Signature:

Name:
(please print)

Date of referral:

Address & tel no for report:

Address:

Tel no:

Day Ward use only: *(Form version 14/2/2001)*

Received date: Booked date: Appointment & information sent date:

DNA/UTA/Performed date: If UTA – rebooked date:

Where Neath ☐ Morriston ☐ Singleton ☐ Other ☐

Date _____ _____ _____ _____

10.) Recurrence Episode Date_____ Follow-Up / Surveillance Yes ☐ No ☐

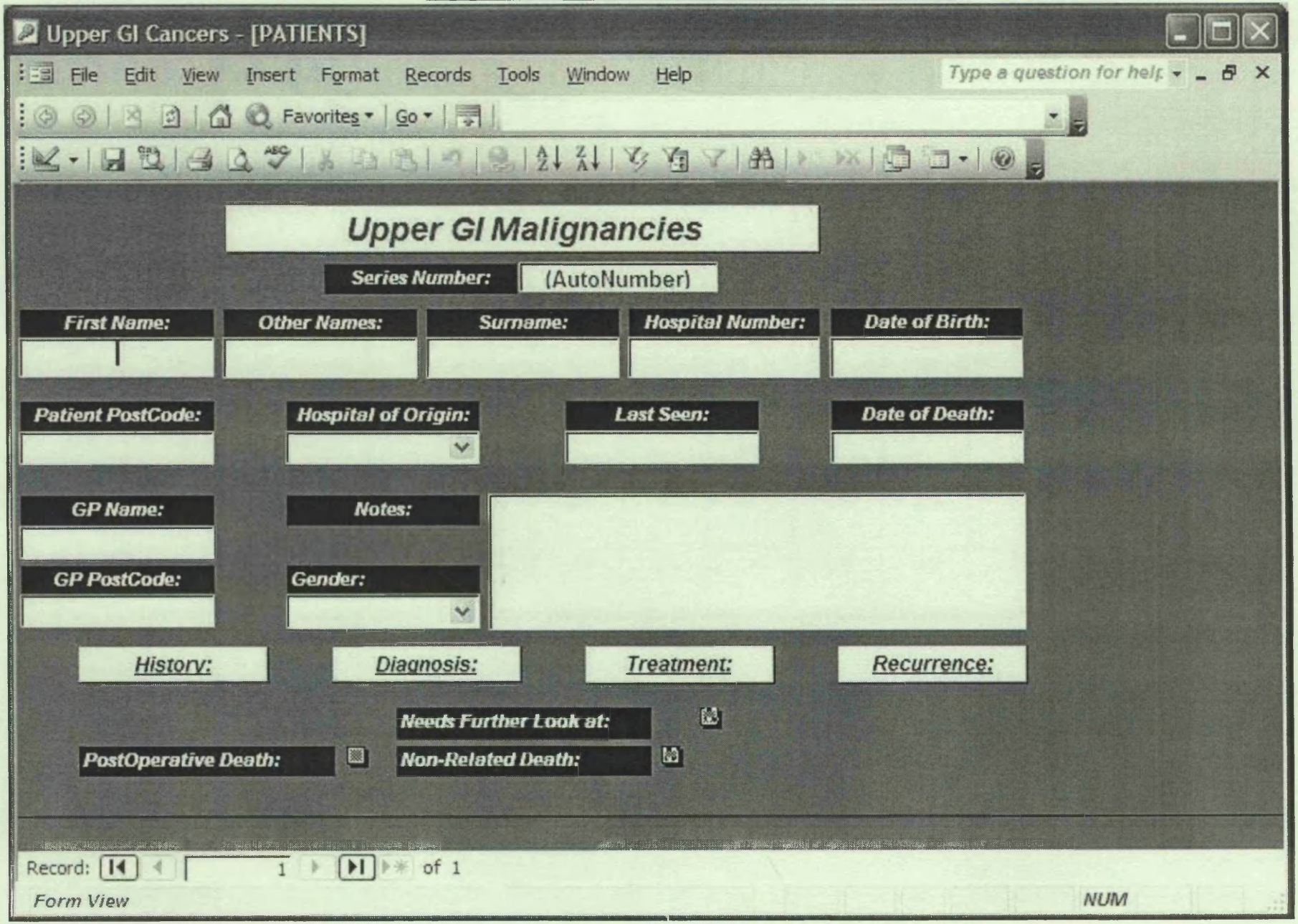
Symptomatic Yes ☐ No ☐ Symptom_____

Clinical ☐ BaMeal ☐ BaEnema ☐ Endoscopy ☐ U/S ☐ Biopsy ☐ Laparotomy ☐ Necropsy ☐

Further Treatment: No ☐ Yes ☐ What: Surgical ☐ Other ☐

11.) Important Notes:

Appendix 06: Database Interface



Appendix A07 - Distribution of cases between hospitals and clinical services used

Department	Morriston Hospital					Neath Gen. Hospital				
	Total	Adm	OPD	OAE	ROC	Adm	OPD	OAE	ROC	Total
Medicine	136	72	60	4		44	33			77
Gastro-enterology	50	5	7	38			10	50	12	72
Surgery	38	16	21	1		10	49			59
TOTAL	224	93	88	43		54	92	50	12	208

Appendix A08 - Distribution of age group for department and referral method

	35=>44	45 => 54	55 => 64	65 => 74	>75
Surgical	3 (3.1%)	5 (5.1%)	11 (11.2%)	34 (34.7%)	45 (45.9%)
Medicine	3 (1.4%)	12 (5.5%)	26 (11.9%)	65 (29.7%)	113 (51.6%)
Gastroenterology	3 (2.4%)	8 (6.5%)	23 (18.7%)	48 (39.0%)	41 (33.3%)
TOTAL	9	25	60	147	199
Admission	1 (0.7%)	9 (6.0%)	10 (6.7%)	41 (27.5%)	88 (59.1%)
Outpatients	6 (3.2%)	8 (4.3%)	28 (15.1%)	66 (35.7%)	77 (41.6%)
O A E	2 (2.1%)	6 (6.4%)	22 (23.4%)	36 (38.3%)	28 (29.8%)
R O C		2 (16.7%)		4 (33.3%)	6 (50.0%)