Prevalence of adenocarcinoma of the oesophagus in two teaching hospitals in Gauteng Province, South Africa.

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Acknowledgements

I would like to thank my supervisors Professor A Mannell and Professor D Bizos. This dissertation has been made possible thanks to their constant support and encouragement.

My immense gratitude to Professor Mannell for her dedication, constant faith and guidance throughout this dissertation.

I am hugely appreciative to Professor Bizos for his help in the proof reading of this dissertation and never ceased to offer support.

Thank you to Professor Martin J Hale and the Department of Anatomical Pathology for the provision of records and use of the database for this retrospective study.

Thank you to my parents for their strength, encouragement and support.

A special thank you to my husband Mr. Nivash Suknunun for his continued support and motivation.

Abstract

Introduction:

Oesophageal carcinoma is the eight most common cancers worldwide and sixth most common cause of cancer related mortality. The incidence varies markedly between race, age, and geographic region, environmental and nutritional factors. In western populations carcinoma of the oesophagus is uncommon whereas endemic areas include China, India, Iran, Russia and South Africa. The incidence of oesophageal adenocarcinoma has rapidly risen over the past decades however squamous cell carcinoma of the oesophagus remains the most common worldwide. The prevalence of oesophageal carcinoma is high in South Africa and contributes significantly to the burden of disease. These carcinomas remain asymptomatic during much of their development and once diagnosed are usually at an advanced stage. Hence identifying carcinogens and reducing the exposure to risk factors such as smoking and alcohol, by education together with early detection methods can significantly reduce this burden. This study is aimed at evaluating the cases of oesophageal carcinoma currently presenting to our institutions.

Aim(s):

-To examine the demography and prevalence of adenocarcinoma of the oesophagus in patients presenting to academic hospitals of the University of Witwatersrand.

-To compare the number of patients with adenocarcinoma (AC) of the oesophagus and squamous cell carcinoma (SCC) of the oesophagus.

-To list the number of patients with adenocarcinoma of the oesophagus who underwent resection.

-To determine how often is concomitant Barrett's metaplasia is present in the resected specimen.

Methods:

This is a retrospective study of all the cases of oesophageal malignancy recorded on the NHLS database at CMJAH and CHBAH from 01/01/2001- 31/12/2013. Demographic variables including age, gender and population group where noted were recorded.

Results:

The prevalence of oesophageal carcinoma in our two teaching hospitals was on a downward trend. There was a significant decrease noted in the SCC subtype. The AC subtype prevalence was on an upward trend. The results we experienced were consistent with worldwide trends.

Conclusion:

The prevalence of oesophageal carcinoma in these two teaching hospitals showed a downward trend. This was due to the significant decrease noted in the SCC subtype, AC was still uncommon but the prevalence of the AC subtype appears to be on an upward trend. The results of this study were consistent with worldwide trends.

Ethics clearance number: M140301

Candidate's declaration

I, Kiyasha Singh, declare that this dissertation is my own work. It is being submitted for the degree of Master in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Dedication

This dissertation is dedicated to my husband Mr. Nivash Suknunun.

Chapter 1

Introduction

Oesophageal carcinoma is the eighth most common cancer worldwide [1] and the sixth most common cause of cancer related mortality [2,3]. The incidence varies between race, age, geographic region, enviromental and nutritional factors. In Western populations carcinoma of the oesophagus is relatively uncommon [3], unlike endemic areas, which include China, India, Iran, Russia and South Africa [1,2]. The incidence of oesophageal adenocarcinoma has rapidly risen over the past decades; however squamous cell carcinoma of the oesophagus remains the most common worldwide [2,4].

The prevalence of oesophageal carcinoma is high in South Africa and contributes significantly to the burden of disease [5,6]. These carcinomas remain asymptomatic during much of their development and once diagnosed are usually at an advanced stage. Hence identification of carcinogens, reducing exposure to risk factors, education and early detection methods may significantly reduce this burden. The prevalence of squamous cell carcinoma (SCC) is greater than that of adenocarcinoma (AC) of the oesophagus globally [2,3]; and the recent data available in Gauteng province has been related to a single publication that showed a decrease in the incidence of oesophageal carcinoma [7].

The aim of this study is to evaluate the prevalence and type of oesophageal cancers presenting to two teaching hospitals associated with The University of the Witwatersrand, Gauteng Province, South Africa.

Over the past 20 years the pattern of oesophageal carcinoma has changed [8]. This disease predominantly affects those in the 60 – 70 year old age group with squamous cell peaking in this time period. Worldwide the highest incidence is in Linxian, China[1]; followed by other countries as specified earlier including South Africa. The incidence of oesophageal adenocarcinoma in the United States and Canada has increased among white males while squamous cell carcinoma has remained the same if not decreased among the Afro-American population [8-10]. However, in the last two decades in the United States the incidence of oesophageal adenocarcinoma in white males has surpassed the incidence of squamous cell carcinoma of the oesophagus in Afro-Americans [2,11].

In the South African population urbanization and changes in socio-economic status, lifestyle and dietary intake predispose the population to obesity and gastroesophageal reflux disease [3,5]. With these factors the question of a change in the histopathology in the South African population arises.

Oesophageal carcinomas are of two main histologic types, squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is more evenly distributed throughout the length of the oesophagus and adenocarcinoma is predominantly a disease of the distal oesophagus and gastroesophageal junction. Adenocarcinoma is rarely found in the cervical oesophagus [3,12,13]. These two subtypes have different aetiologies. Squamous cell oesophageal carcinomas are associated with dietary deficiencies,

alcohol and smoking whereas oesophageal adenocarcinoma is associated with obesity, gastroesophageal reflux disease and Barrett's metaplasia and smoking.

Histologically [12], squamous cell carcinoma of the oesophagus is comprised of 3 morphological patterns: a polypoid exophytic lesion which decreases the luminal diameter, a sclerosing type diffusely infiltrating the wall leading to rigidity and an ulcerative type eroding surrounding structures [12].

Gastric metaplasia with intestinal metaplasia is potentially premalignant. Gastric metaplasia without intestinal metaplasia is less likely to develop malignancy.

Microscopically, adenocarcinoma of the oesophagus is a mucin producing glandular tumour [12], which exhibit intestinal type features including goblet cells. Marked cellular morphological changes that may be present only in the mucosal layer are considered high-grade dysplasia lying adjacent to the tumour [12].

The commonest predisposing factor for AC of the oesophagus is Barrett's oesophagus (BO). In this condition metaplastic columnar epithelium has replaced the squamous epithelium extending upwards from the gastro-oesophageal junction [9].

Barrett's oesophagus is secondary to gastroesophageal reflux disease (GERD), exacerbated by obesity and smoking while the risk factors for Squamous Cell Carcinoma also include smoking and alcohol. Dietary deficiencies appear to play a major role [3,10] in the development of SCC of the oesophagus.

Conditions, such as tylosis, achalasia, esophageal diverticula, Plummer-Vinson

syndrome, and human papillomavirus (HPV) infection are known to predispose to SCC [12].

Oesophageal carcinoma commonly presents with progressive dysphagia. Loss of weight, bleeding, hoarseness of voice, cough and epigastric pain, and back pain, anemia and bone pain are symptoms of advanced disease. On physical examination in the early stages there may be no clinical signs. The patient presenting at an advanced stage may reveal signs of metastases such as cervical lymphadenopathy, hepatomegaly, bone tenderness and respiratory complications.

In the diagnosis and staging of oesophageal carcinoma radiological, endoscopic procedures, and minimally invasive surgical techniques are utilised. These include the upper gastrointestinal contrast study (Barium swallow) where the signs are those of shouldering, mucosal irregularity and an "apple –core" deformity which strongly suggest oesophageal carcinoma. Upper endoscopy is mandatory for the diagnosis of oesophageal carcinoma to ascertain the location, and allow for a tissue biopsy for histopathological confirmation. Computed Axial Tomograph is used to stage the disease and allows assessment of surgical resectability of the lesion. Positive emission tomography (PET) [14,15] is also of value to evaluate the primary lesion: This modality may more accurately identify lymph node (LN) metastases including those adjacent to the primary lesion which may be obscured. Magnetic Resonance Imaging (MRI) is useful to define T4 lesions (see appendix 4) as well as liver metastases. Endoscopic ultrasound (EUS) is helpful in determining the length and depth of tumor. These may require dilatation to permit passage of the gastroscope and allow use of through the scope EUS probes. EUS is more valuable for early lesions and to check

for involved LN. Cytological analysis of the fine needle aspirate (FNA) is also possible.

Other investigations include minimal invasive surgical procedures such as endoscopic mucosal resection (EMR)[13] and bronchoscopy, thoracoscopy, mediastinoscopy and laparoscopy may be performed to accurately stage the patient.

Multiple modality treatment approaches are currently being used in tertiary centers. This has been documented in a recent meta-analysis [16]. Surgical resection for cure is often not possible due to advanced disease. Radiation therapy (either brachytherapy or external beam radiation) is an alternative to provide palliation of dysphagia but may be associated with local side effects such as oesophageal strictures and fistulas.

Chemotherapy has been given preoperatively, postoperatively or a combination of both. A cisplatin-based regimen is commonly used as a radio sensitiser [16-18].

Palliation is selected for patients with metastatic disease and for patients who cannot withstand curative treatment. The goal of palliation is twofold: to reestablish swallowing and relieve pain. Methods of palliation include radiation, endoscopic dilation, endoscopic stenting, endoscopic laser therapy and light-based therapy (e.g., photodynamic therapy) [10,13].

In the South African population those affected are predominantly Black South Africans with SCC of the oesophagus being the most common histological type [7]. However, although cases of AC of the oesophagus do occur there is minimal literature available on this pathology in the South Africa context.

The aims of this study therefore are:

1. To compare the demography and prevalence of patients who presented to Witwatersrand Academic Hospitals and were diagnosed with adenocarcinoma of the oesophagus over a thirteen year period .
2. Compare the proportion of adenocarcinoma and squamous cell carcinoma of the oesophagus.
3. How many of the patients with adenocarcinoma of the oesophagus underwent resection.
4. To determine how often is concomitant Barrett's metaplasia is present in resected specimen.

Chapter 2

Methods

Ethical approval to undertake the study was obtained from the Witwatersrand Human Research Ethics Committee, ethics clearance number M140301 (Appendix 1).

Access to the National Health Laboratory System (NHLS) and Laboratory of Data Intensive Systems and Applications (DISA) was obtained from the Department of anatomical pathology with permission from the Head of Department of Anatomical Pathology (Professor M Hale). (Appendix 2)

This is a retrospective study of all the cases of oesophageal malignancy recorded from 01/01/2001-31/12/2013 on the NHLS database at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) was performed. Demographic variables including age, gender and population group were recorded. All patients with a histological diagnosis of oesophageal carcinoma and those with pre- malignant conditions of the oesophagus where included within the study period.

The specimen number and hospital number were then cross checked on the DISA and NHLS pathology system to ascertain whether repeat specimens /duplicated results which where received and then excluded.

Patient's personal details were not recorded on the data sheet and in the study (Appendix 3).

Results obtained where placed onto a standardised Microsoft Excel spreadsheet registration: Microsoft Excel for Mac 2011 Version 14.5.9 (151119) with Excel analysis ToolPak using Chi square analysis was performed to ascertain the prevalence of AC and SCC of the oesophagus.

Other analyses that were performed have been depicted with use of graphs and tables (pages 19-23).

Chapter 3

Results

During this thirteen-year study period (2001-2013) there was a total of one thousand five hundred and fifty patients with oesophageal malignancies (Figure 1) seen at the two teaching hospitals (CMJAH and CHBAH).

The highest incidence occurred in 2002 (Figure 1) with a significant reduction in the 2010 to 2013 period (Figure 1). When the cases of oesophageal malignancies were analysed (Figure 2), regarding the subtypes the majority of cases of 69.74% were squamous cell carcinoma, followed by adenocarcinoma subtype with 8.77 % of cases. Barrett's oesophagus constituted 6.58% of cases, oesophageal dysplasia in 4 % and other types accounting for the final 10.90%.

In all subtypes of malignancy the male population had a higher incidence when compared to the female population (Table 1). Of note is the finding that the adenocarcinoma occurred in 73.33 % of males compared to the male predominance in squamous cell carcinoma of 64.73% with a p value of 0.03. A male predominance was also evident for Barrett's metaplasia of 64.36% (Table 1).

The median age of all patients with oesophageal malignancies in this study was 60 years with median ages for AC subtype of 62 years old and SCC subtype 59 years .

Over the study period there has been a significant decrease in the prevalence of oesophageal carcinoma p <0,0001 (Figure 1). This appears to be a result of the significant decrease in the SCC subtype (Figure 4). However the prevalence of AC during this study period increased significantly (Figure 3). Prevalence of AC was determined using chi square analysis (Figure 5) and showed a strong level of significance with $p<0.01$. Of the patients with adenocarcinoma in the study analysed, concomitant Barrett's metaplasia was evident in 9.56%.

Resection specimens were found for only in 1.22 percent of the oesophageal cancers identified. Of these oesophageal resections performed AC accounted for 0.38% and 0.83% for SCC of the total oesophageal malignancies (Table 3). With a more detailed analysis of the AC subtype 4.41% of these patients underwent oesophagectomies compared to 1.19 % of the SCC subtype (Table 3).

The study was divided into two time intervals (Figure 6), 2001-2006 and 2007 to 2013. This is a graphic representation illustrating the decline in SCC prevalence compared to the premalignant conditions and the invasive AC subtypes of the oesophagus.

Race where it was noted and where it was to be inferred by name showed that of the cases of oesophageal malignancies 68.19% was noted in the African population, 11.41% in the white population and the final 20.38% in the Indian and Coloured populations.

The total AC subtype accounted for 8.77% of oesophageal malignancies in this study. However of the total oesophageal malignancies in the white population comprising 198 cases, 50 of these were AC subtype. The incidence in the white subset of patients with AC of the oesophagus (28.25%) was significantly greater than that of the black subset (6.01%) calculated with a p value < 0,000001. This finding is comparable to that of western data.

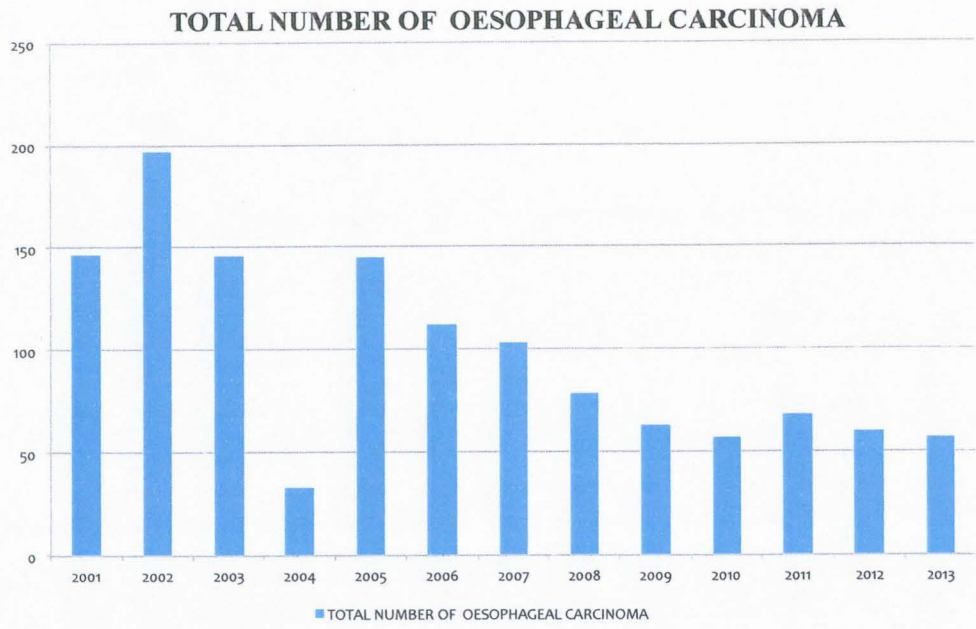


Figure 1:

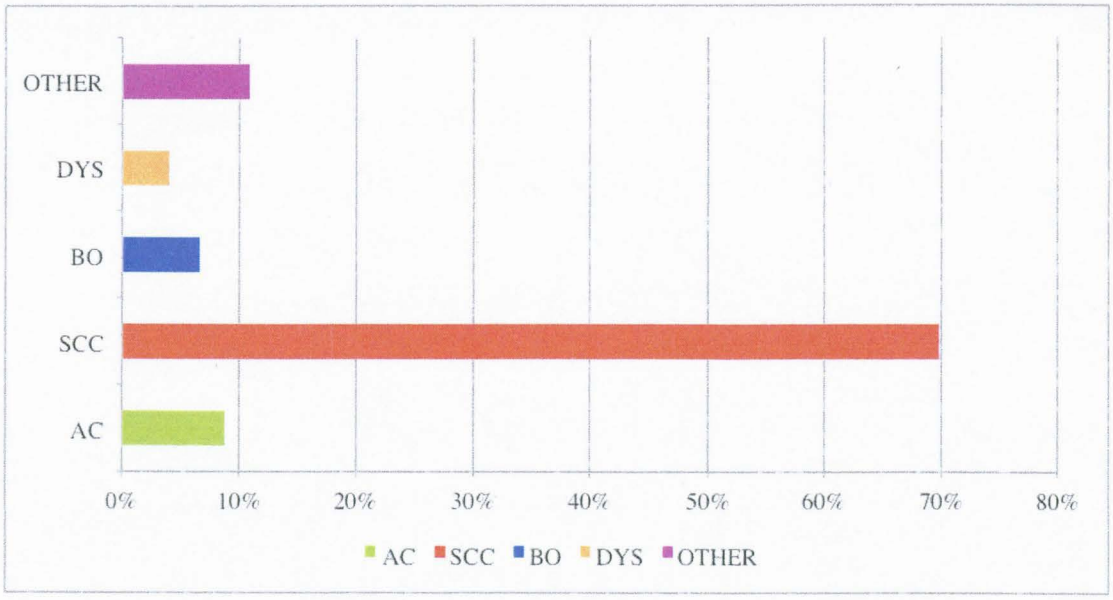


Figure 2: Depicting the percentages of the cases analysed. Adenocarcinoma 8.78 %, Squamous cell 69.79 %, Barrett's oesophagus 6.58 % , Dysplasia 4 % and Other 10.85%.

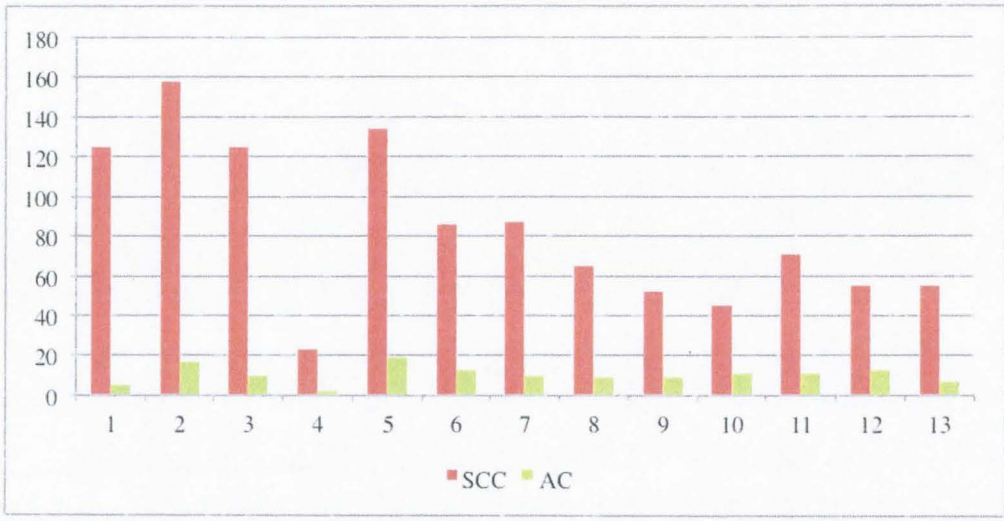
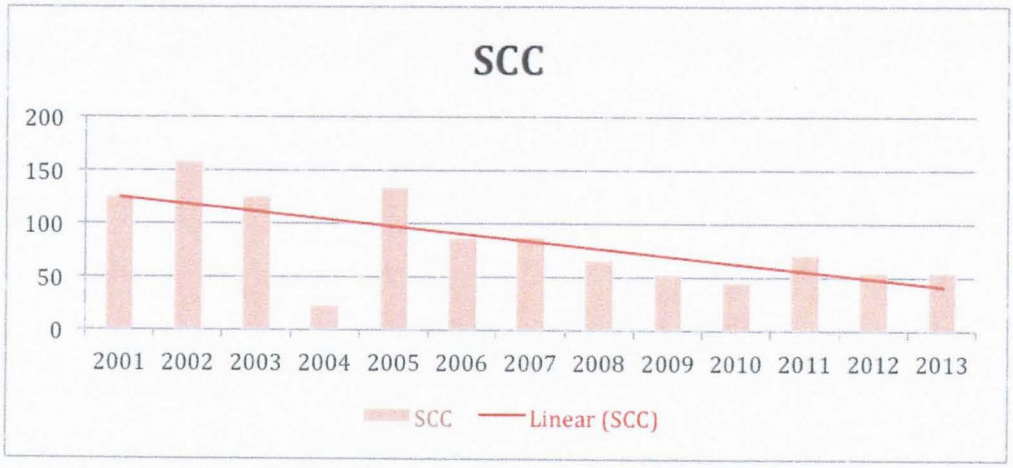
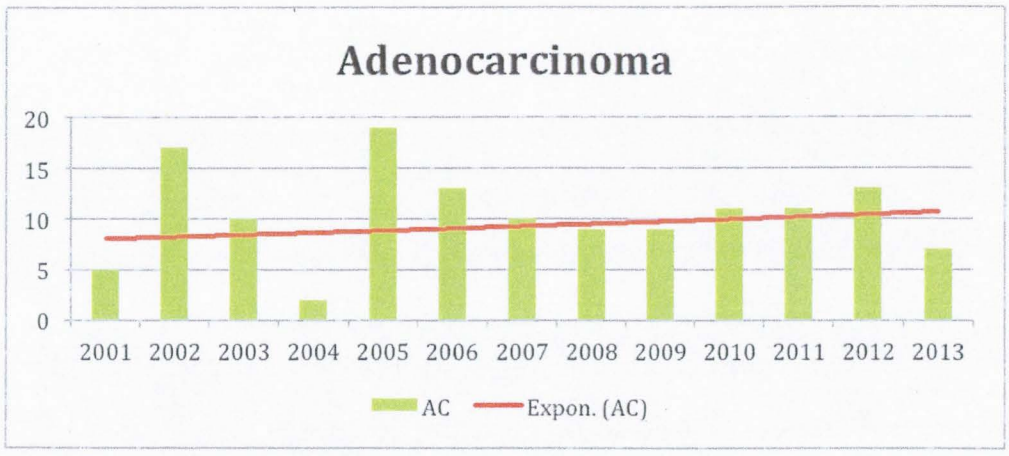


Figure 3: The comparison of SCC: AC over the study period.



Prevalence has decreased, $p<0.01$ (chi square analysis)

Figure 4: Prevalence of SCC



Prevalence has increased exponentially, $p<0.01$ (chi square analysis)

Figure 5: Prevalence of AC

Using the chi square analysis showed statistical significance of the prevalence of adenocarcinoma of the oesophagus.

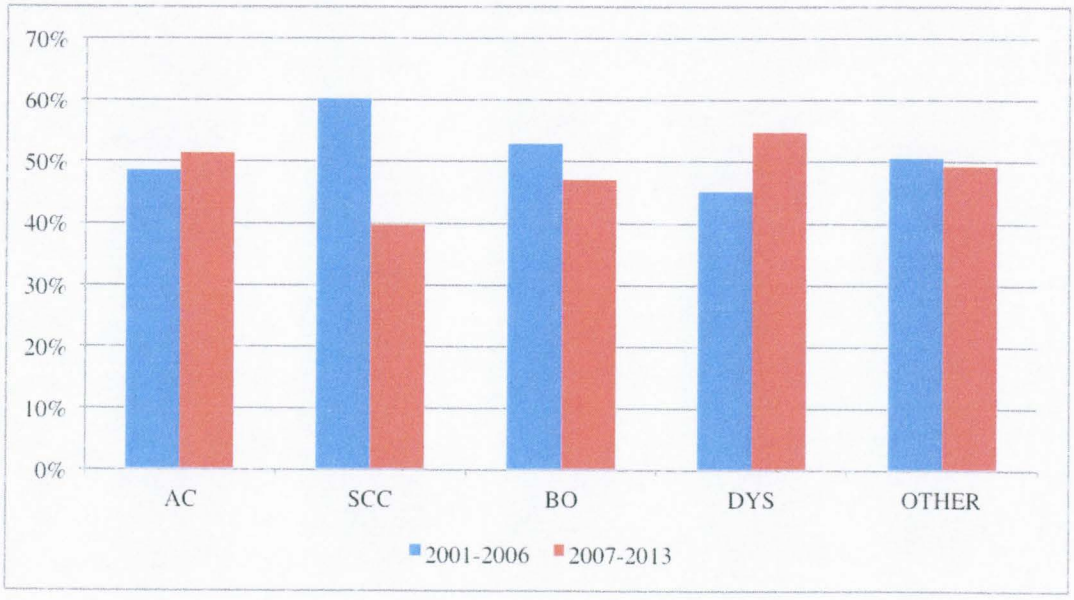


Figure 6: The study divided into two time intervals; 2001-2006 and 2007-2013.

Table 1 depicting the number of cases per subtype of the study and male to female %.

	Number	Male %	Female %
SCC	1081	64.73	35.27
AC	136	**73.33**	26.67
Barrett's	102	64.36	34.64
Dysplasia	62	59.68	40.32
Other	168	64.29	35.71
Total	1550	65.88	34.12

Table 2: Depicts racial % in AC subtype (race was inferred by name).

	Oesophageal carcinoma total per race	AC total nos per race	% of AC per race
African	1315	79	6
White	198	50	28.25

Table 3: Oesophageal resections performed.

	Number	% of total	% of subtype
AC	6	0.38	4.41
SCC	13	0.83	1.19
Total	19	1.22	

Chapter 4

Discussion

This is a retrospective study over a 13-year period analysing all the cases of oesophageal malignancy through the two Witwatersrand academic hospitals in Gauteng, South Africa. It is important to note that the drainage area of the NHLS included satellite hospitals associated with the University of the Witwatersrand.

The data obtained from the Department of Anatomical Pathology, CMJAH and CHBAH, results showed a significant decline in the incidence of oesophageal carcinoma over the study period in particular the SCC subtype. The prevalence of adenocarcinoma of the oesophagus is low but showed an increasing trend, which was statistically significant.

Oesophageal carcinoma remains the eighth most common carcinoma worldwide and sixth most common cause of mortality [6,20]. Furthermore this disease in Sub-Saharan Africa is associated with significant mortality [5,20-21]. Adenocarcinoma of the oesophagus is a predominant subtype in Europe and North America while the SCC subtype is predominant in Southern Africa [21-23]. In South Africa oesophageal carcinoma contributes to the burden of disease with SCC predominance in the black African population with high male to female ratio that is similar to North America and Europe [8].

In this study the South African prevalence of AC has increased. Rates of obesity are increasing both in black and white African [24,25]. This observation may be correlated to the population at risk for adenocarcinoma of the oesophagus where a raised prevalence found in this study. Since obesity [24-26] increases the risk of GERD [22] which is a risk factor that leads to Barrett's metaplasia and hence AC, it is not surprising that there is an increase in AC of the oesophagus. This follows trends observed in the western population. Smoking is also associated with increased risk to developing Barrett's oesophagus leading to malignant transformation [27].

The number of oesophagectomies done in this study is small. The late presentation of this study group of patients in advanced stages may explain this difference. There is an increase in the number of curative procedures reported in well- resourced centers and management in a multidisciplinary specialist meeting [28]. Contributing to this could be an increase in screening programs for patients at risk i.e. those with reflux and with Barrett's oesophagus [28,29]. These programs are not currently possible in the South African Health Care system.

The decline in the SCC prevalence maybe due to improvement in dietary intake and reduction of ethanol abuse and smoking habits over the past two decades in the black South African population [21,30]. The oesophageal adenocarcinoma cases were predominantly in the white population in this study. The results of this study are similar to those in North America and Europe where AC in white males and SCC in African males predominate [8].

This study shows trends in the prevalence of oesophageal carcinoma in keeping with that of western populations. Further reduction in the incidence of oesophageal carcinoma in South Africa will necessitate education and screening programs similar to those in western populations. Addressing modifiable risk factors such as dietary intake and smoking by means of education are not only feasible but will aid in promotion of general well being and reduction of oesophageal carcinoma.

The limitations of this study were largely due to incomplete data on the specimen form received from doctors requesting histopathology. Thus many of the cases in this study did not identify the patients' race or gender on the formal histopathology reports. This resulted in these variables being inferred from the patients name on the reports hence the data may not accurately reflect the population group involved. However this study is representative of all the South African population groups. The individual patients' risk factors and comorbidities were not obtained from this retrospective study.

Conclusion

The prevalence of oesophageal carcinoma in these two teaching hospitals showed a downward trend. This was due to the significant decrease noted in the SCC subtype, AC was still uncommon but the prevalence of the AC subtype appears to be on an upward trend. The results of this study were consistent with worldwide trends [8,20].

Chapter 5

References

1. Hendricks D and Parker MI. Oesophageal Cancer in Africa. IUBMB life. 2002 Apr 1; 53(4-5): 263-8.
2. Thrift AP. The epidemic of oesophageal carcinoma: Where are we now?. Cancer epidemiology. 2016 Apr 30; 41:88-95.
3. Zhang Y. Epidemiology of esophageal carcinoma. World journal of gastroenterology. 2013;19.
4. Asombang, Akwi W, Kayamba V, Trinkaus K et al. Esophageal Squamous Cell Cancer in a Highly Endemic Region. World Journal of Gastroenterology 22.9 (2016): 2811–2817.
5. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015 Mar 1;65(2):87-108.
6. Jemal A, Bray F, Forman D, et al. Cancer burden in Africa and opportunities for prevention. Cancer. 2012 Sep 15;118(18):4372-84.
7. Gould A, Morgan H, Motha N, et al. Comparison of the incidence of oesophageal cancer in two 6-year periods from selected hospitals in and around Gauteng Province, South Africa. South African Journal of Surgery. 2015 Jul; 53(2):55-8.
8. Castro C, Bosetti C, Malvezzi M, et al. Patterns and trends in esophageal cancer mortality and incidence in Europe (1980–2011) and predictions to 2015. Annals of oncology. 2014 Jan 1;25(1):283-90.
9. Milind R, Attwood SE. Natural history of Barrett's esophagus. World J Gastroenterol. 2012 Jul 21; 18(27):3483-91.
10. Otterstatter MC, Brierley JD, De P, et al. Canadian Cancer Statistics Steering Committee. Esophageal cancer in Canada: trends according to morphology and anatomical location. Canadian Journal of Gastroenterology and Hepatology. 2012;26(10):723-7.

11. Lagergren J. Adenocarcinoma of oesophagus: what exactly is the size of the problem and who is at risk?. Gut. 2005 Mar 1;54(suppl 1): i1-5.
12. International Agency for Research on Cancer (IARC). Chapter 1 Tumours of the oesophagus. Available from https://www.**iarc**.fr/en/publications/pdfs-online/pat-gen/bb2/bb2-chap1.pdf. (30 October 2016, date last accessed).
13. Behrens A, Pech O, Graupe F,et al. Barrett's Adenocarcinoma of the Esophagus. Deutsches Aerzteblatt International. 2011 May 6;108(18).
14. Yang GY, Wagner TD, Jobe BA, Thomas Jr CR. The role of positron emission tomography in esophageal cancer. Gastrointestinal cancer research: GCR. 2008 Jan;2(1):3.
15. Flamen P, Lerut A, Van Cutsem E, De Wever W, Peeters M, Stroobants S, Dupont P, Bormans G, Hiele M, De Leyn P, Van Raemdonck D. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. Journal of Clinical Oncology. 2000 Sep 18;18(18):3202-10.
16. Platz TA, Nurkin SJ, Fong MK, et al. Neoadjuvant chemoradiotherapy for esophageal/gastroesophageal carcinoma. Journal of gastrointestinal oncology. 2013 Apr 17;4(2):137-43.
17. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. Journal of Clinical Oncology. 2008 Mar 1;26(7):1086-92.
18. Heath EI, Burtness BA, Kleinberg L, Salem RR, et al. Phase II, parallel-design study of preoperative combined modality therapy and the matrix metalloprotease (mmp) inhibitor prinomastat in patients with esophageal adenocarcinoma. Investigational new drugs. 2006 Mar 1;24(2):135-40.
19. Wong AT, Shao M, Rineer J, Lee A, Schwartz D, Schreiber D. The Impact of Adjuvant Postoperative Radiation Therapy and Chemotherapy on Survival After Esophagectomy for Esophageal Carcinoma. Annals of surgery. 2016 Jun.
20. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015 Mar 1;136(5):E359-86.

21. Kachala R. Systematic review: epidemiology of Oesophageal Cancer in SubSaharan Africa. Malawi Medical Journal. 2010 Sep 1;22(3).
22. Rustgi AK, El-Serag HB. Esophageal Carcinoma. New England Journal of Medicine. 2014 Dec 25;371(26):2499-509.
23. Tettey M, Edwin F, Aniteye E, et al. The changing epidemiology of esophageal cancer in sub-Saharan Africa–the case of Ghana. Pan African Medical Journal. 2013 Feb 23;13(1).
24. Arnold M, Leitzmann M, Freisling H, et al. Obesity and cancer: An update of the global impact. Cancer Epidemiology. 2016 Apr 30;41:8-15.
25. Cois A, Day C. Obesity trends and risk factors in the South African adult population. BMC obesity. 2015 Oct 13;2(1):1.
26. Cook MB, Shaheen NJ, Anderson LA ,et al. Cigarette smoking increases risk of Barrett's esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. Gastroenterology. 2012 Apr 30;142(4):744-53.
27. Sundelöf M, Lagergren J, Ye W. Patient demographics and lifestyle factors influencing long-term survival of oesophageal cancer and gastric cardia cancer in a nationwide study in Sweden. European Journal of Cancer. 2008 Jul 31;44(11):1566-71.
28. Lim HK, Stiven PN, Aly A. Reinterpretation of radiological findings in oesophago-gastric multidisciplinary meetings. ANZ journal of surgery. 2014 Apr 1; 86: 377-380.
29. Katsinelos P, Lazaraki G, Kountouras J, et al. Prevalence of Barrett's esophagus in Northern Greece: a prospective study (Barrett's esophagus). Hippokratia. 2013 Jan;17(1):27-33.
30. Mannell A. Carcinoma of the esophagus. Current problems in surgery. 1982 Oct 31; 19(10):556-647.

Appendix 1: Copy of ethics clearance certificate.

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140301

NAME: (Principal Investigator)	Dr Kiyasha Singh
DEPARTMENT:	Surgery Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Trends in the Incidence and Histololgical Types of oesephageal carcinoma admitted to the Provincial Hospitals in the Gauteng Province
DATE CONSIDERED:	28/03/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof A Mannell

APPROVED BY: _____

Professor PE Cleaton-Jones Chairperson HREC (Medical)

DATE OF APPROVAL: 30/01/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

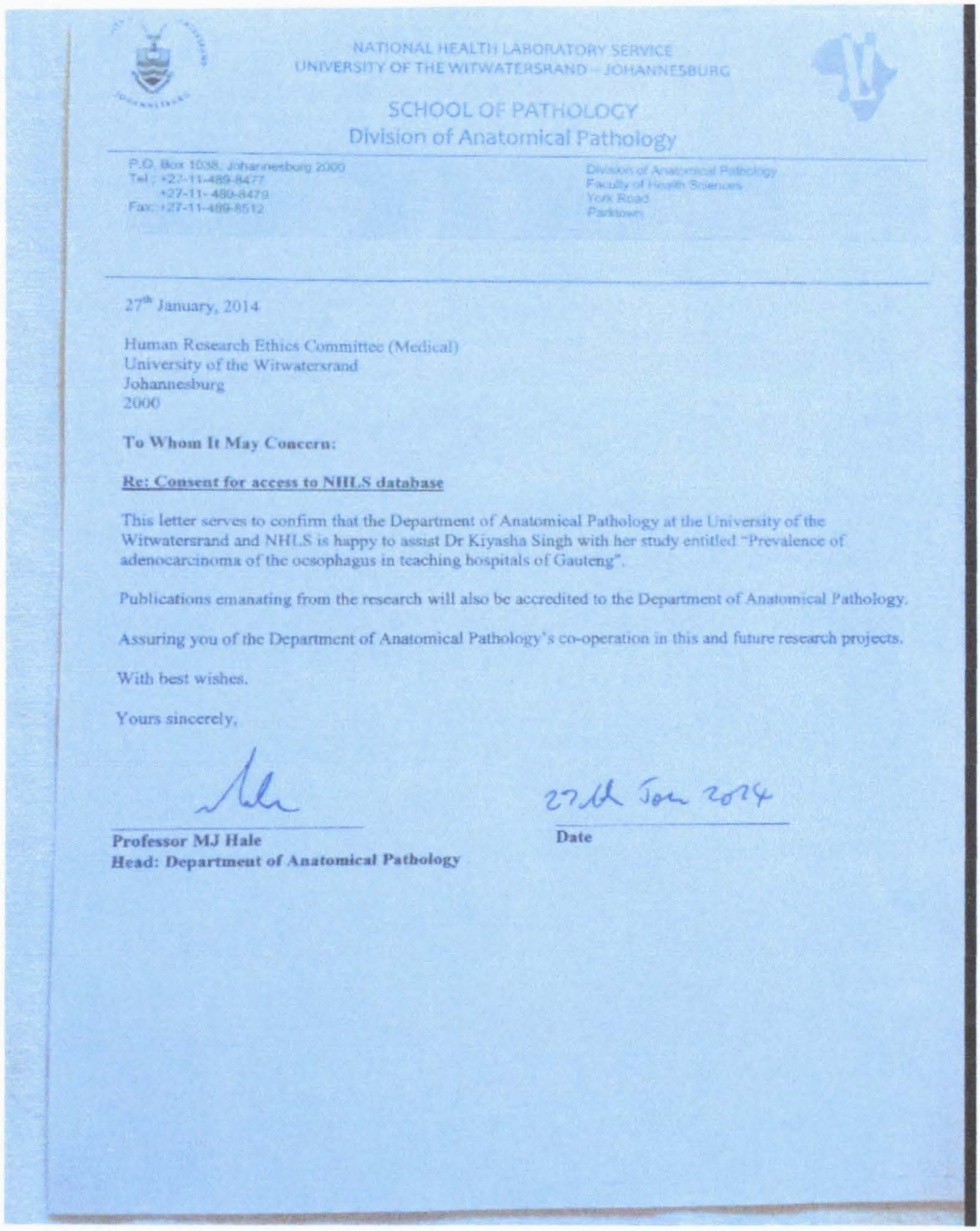
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004 10th floor Senate House University

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved I/we undertake to resubmit the application to the Committee. **I agree to submit a**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2: Consent to access NHLS database.



NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

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27th January, 2014

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
2000

To Whom It May Concern:

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to assist Dr Kiyasha Singh with her study entitled "Prevalence of adenocarcinoma of the oesophagus in teaching hospitals of Gauteng".

Publications emanating from the research will also be accredited to the Department of Anatomical Pathology.

Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Professor MJ Hale
Head: Department of Anatomical Pathology

27th Jan 2014
Date

Appendix 3: Data collection sheet.

Data Collection Sheet:

Prevalence of adenocarcinoma of the oesophagus in two teaching hospitals in Gauteng province, South Africa.

Participant Number: _____

Age: _____

Gender:

M	F

Referral Hospital:

CMJAH	CHBAH	HJH	Other: Specify

Pathology Reference code: _____

Population Group:

African White Coloured Indian

Date of First biopsy:

_____

Date of diagnosis:

_____

The duration of symptoms as per histology report:

_____

Level of biopsy and resected lesion in centimeters as per the histology report:

_____

Histology:

SCC Adenocarcinoma Barrett's

Tumor staging if available:

0 I IIA IIB III IVA IVB

Metastasis:

Yes No

Oesophageal resection:

Yes No

Appendix 4: AJCC staging of oesophageal carcinoma

T	Primary tumour
Tx	Primary tumour cannot be assessed
T1	Primary tumour invading lamina propria or submucosa
T2	Primary tumour invading muscularis propria
T3	Primary tumour invading adventitia
T4	Primary tumour invading adjacent structures
N	Regional lymph nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis (excluding celiac lymph nodes)
N1	Regional lymph nodes metastasis (excluding celiac lymph nodes)
M	Distant metastases
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases
Stages	Grouping
I	T1N0M0
IIA	T2N0M0; T3N0M0
IIB	T1N1M0; T2N1M0
III	T3N1M0; T4N0M0; T4N1M0
1V	Any T, any N, M1

Appendix 5: Research protocol

Study Title:

Prevalence of adenocarcinoma of the oesophagus in two teaching hospitals of Gauteng, South Africa.

Introduction/ Background:

Oesophageal carcinoma is the eight most common cancers worldwide and sixth most common cause of cancer related mortality[6]. The incidence varies markedly between race, age, and geographic region, environmental and nutritional factors. In western populations carcinoma of the oesophagus is uncommon whereas endemic areas include China, India, Iran, Russia and South Africa[2]. The incidence of oesophageal adenocarcinoma has rapidly risen over the past decades however squamous cell carcinoma of the oesophagus remains the most common worldwide[1].

The prevalence of oesophageal carcinoma is high in South Africa and contributes significantly to the burden of disease. These carcinomas remain asymptomatic during much of their development and once diagnosed is usually at an advanced stage. Hence prevention of carcinogens, exposure to risk factors, education and early detection methods can significantly reduce this burden[6]. The prevalence of squamous cell carcinoma is greater than that of adenocarcinoma of the oesophagus however no recent data is available, thus this study is to evaluate what is currently presenting to our institutions.

Over the past 20 years the pattern of oesophageal carcinoma has changed. This disease predominantly affects those in the 60 – 70 year old age group with squamous cell peaking in this time period. Worldwide the highest incidence is in Linxian, China [2] followed by other countries as specified earlier such as South Africa. The incidence of oesophageal adenocarcinoma in the United States has increased among white males while squamous cell carcinoma has remained the same if not decreased among the African American population [10]. However, in the last two decades in the United

States the incidence of oesophageal adenocarcinoma in white males has surpassed the incidence of squamous cell carcinoma of the oesophagus in African Americans.

In the South African population urbanization and changes in socio-economic status makes the black South African vulnerable to Barrett's oesophagus and adenocarcinoma of the oesophagus. Changes in lifestyle and dietary intake predispose the population to obesity and gastro esophageal reflux disease. With these factors are we seeing a change in the histopathology in the South African population?

Adenocarcinoma of the oesophagus is a malignant epithelial tumor that has glandular differentiation. There is increasing recognition of pre -malignant condition Barrett's oesophagus which deters from the past confusion of that of gastric carcinoma's arising from the gastrooesophageal junction[7,11].

The pathogenesis of adenocarcinoma of the oesophagus has multiple steps in its disease progression. The Barrett epithelial cells have higher proliferative activity[11], and dysplastic epithelial cells have lost cell-cycle control[11]. p53 overexpression is present in dysplastic epithelium. This is said to be the result of gastroesophageal relux causing DNA and cell damage. In high grade dysplasia chromosomal 4 abnormalities are present[7]. Other genetic factors *c-ERB-B2,* p 53 mutations and β-catenin are present[7].

Oesophageal carcinomas are of two main histologic types, squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is more evenly distributed throughout the length of the oesophagus and adenocarcinoma is predominantly a disease of the distal oesophagus and gastroesophageal junction, and is rarely found in the cervical oesophagus (references). These two subtypes are of different aetiologies. Squamous cell oesophageal carcinomas are associated with dietary , alcohol and smoking whereas oesophageal is associated with Barrett's metaplasia and gastroesophageal reflux disease.

Histology[4]:

Squamous cell carcinoma: Three morphological patterns: a) protruded a polypoid exophytic lesion that decreases luminal diameter. b) flat diffusely infiltrates the wall leading to rigidity c) excavated that erodes surrounding structures.

Adenocarcinoma: Arise in the setting of Barrett oesophagus. Microscopically these are mucin producing glandular tumors. These exhibit intestinal type features. Dysplastic mucosa are adjacent to the tumor.

Clinical presentation:

Presentation of oesophageal carcinoma commonly presents with progressive dysphagia. Loss of weight, bleeding, hoarseness of voice, cough, abdominal pain (epigastric pain), anemia and bone pain in advanced disease. On physical examination one may find a normal systemic examination unless the patient presents at an advanced stage revealing signs of metastasis such as lymphadenopathy, hepatomegaly, bone pain and coughing or aspiration.

Diagnostic investigations include:

Diagnosing of oesophageal carcinoma utilise radiological, endoscopic procedures, and minimally invasive surgical procedures. These include upper gastrointestinal contrast study (Barium swallow) whose classic sign is an apple –core lesion.
Upper endoscopy: an extremely useful tool in diagnosing carcinoma as we can ascertain the location, nature of tissue being examined and biopsied.
Computed Tomography Scan: This is used in the staging of the pathology, dimensions of tumor and metastasis and surgical resectability of lesion. Positive emission tomography (PET) used in evaluating the primary lesion and lymph nodes. Magnetic Resonance Imaging (MRI) can determine T4 lesions and metastasis to the liver. Endoscopic ultrasound is used to determine length and depth of tumor. Other investigations such as endoscopic mucosal resection and minimal invasive surgical procedures (bronchoscopy, thoracoscopy, mediastinoscopy and laparoscopy).

Multiple modality treatment approaches are currently being used. Unfortunately due to late presentation and patients with advanced disease adequate surgical resection

will prove to be difficult. Radiation therapy is an alternative to surgical resection however does come with its associated side effects such as toxicity.

Chemotherapy has been given preoperatively, postoperatively, or both. A cisplatin-based regimen is often used [2].

Palliation is used for patients with metastatic disease. The goal of palliation is relieving obstruction and dysphagia. This can be treated with palliative chemotherapy, radiation, endoscopic dilation, endoscopic stenting, endoscopic laser therapy, light-based therapy (e.g., photodynamic therapy).

In the South African population those affected are predominantly Black South Africans with squamous cell carcinoma being the most common histological type. However, cases of adenocarcinoma do occur but there is minimal literature available on this pathology in South Africa. Therefore the researcher would like to investigate the demography of the patient diagnosed with adenocarcinoma of the oesophagus, and if common how often is Barrett's metaplasia reported in the patient diagnosed with adenocarcinoma of the oesophagus and resectability. Furthermore to compare the above findings with patients diagnosed with squamous cell carcinoma of oesophagus.

Abstract

- Aim: To examine the prevalence of adenocarcinoma of the oesophagus in patients in the teaching hospitals of Gauteng.

- Objectives

  1) To compare the demography and prevalence of patients who presented to Witwatersrand Academic Hospitals and were diagnosed with adenocarcinoma of the oesophagus.
  2) Compare the proportion of adenocarcinoma and squamous cell carcinoma of the oesophagus.
  3) How many of the patients with adenocarcinoma of the oesophagus underwent resection of the oesophagus.
  4) To determine how often is concomitant Barrett's metaplasia is present in resected specimen.

- Type of Research

  Epidemiological research.
- Study Design

  Retrospective study review .
- Setting

  Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital, Helen Joseph Hospital.
- Study Population

  Patients referred from the above institutions and those present on the National Health Laboratory System in Gauteng.
- Study Sample :

  Inclusion criteria: All patients diagnosed with oesophageal carcinoma registered on National Health Laboratory System in Gauteng.

  Exclusion criteria: Patients not in the NHLS data system.
- Variables

  Demographic variables include: Age, gender, and population group. Site of lesion and histopathology of the biopsies taken and of the resected specimens.
- Data Collection

  The principle investigator will perform a retrospective data review from the National Health Laboratory System and data will be recorded on standardised data collection sheets and subsequently onto an Excel spreadsheet.
- Statistical Methods

  Data will be summarised and described using measures of central tendency and dispersion. The variables will be categorized and the association tested between the carcinomas described.

- Timeline:

Process	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Project Idea	X											
Literature Review	X	X										
Preparing Protocol			X									
Protocol Deadline				23/10/13								
Protocol Assessment				06/11/13								
Ethics Application						X						
Collecting Data						X	X					
Data Analysis								X	X			
Writing up- Report										X		
Report Submission											X	
Writing up- Paper												X

- Limitations

  Information may be incomplete on some of the reports from the requesting doctor's.

- Ethical considerations

  Ethical approval will be sought from the Human Research Ethics Committee and the relevant hospital managers and heads of department.

- References:

1) Mannel A. et al. Carcinoma of the esophagus. Current problems in Surgery. 1982 Oct;Vol XIX, Nos 10; 557-647.
2) Lagergren J, et al. Adenocarcinoma of oesophagus: what exactly is the size of the problem and who is at risk? Gut. 2005 Mar;54 Suppl 1:i1-5.
3) Platz TA, Nurkin SJ, Fong MK, Groman A, et al. Neoadjuvent chemoradiotherapy for esophageal/ gastroesophageal carcinoma. J Gastrointest Oncol. 2013 Jun; 4(2):137-43.
4) Terada T, et al. A clinicopathologic study of esophageal 860 benign and malignant lesions in 910 cases of consecutive esophageal biopsies. Int J Clin Exp Pathol. 2013; 6(2):191-8.
5) Tettey M, Edwin F, Aniteye E, Sereboe L, et al. The changing epidemiology of esophageal cancer in sub-Saharan Africa- the case of Ghana. Pan Afr Med J. 2012; 13:6.
6) Hendricks D, Parker MI, et al. Oesophageal Cancer in Africa. IUBMB Life. 2002 Apr-May; 53(4-5):263-8.
7) Zhang Y, et al. Epidemiology of esophageal carcinoma. World J Gastroenterol. 2013 Sep 14; 19(34):5598-5606.
8) Verma YP, Chauhan AK, Sen R, et al. Primary adenocarcinoma of the upper oesophagus. Ecancermedicalscience. 2013 May 2; 7:314.
9) Katsinelos P, Lazaraki G, Kountouras J, Chatzimavroudis G, et al. Prevalence of Barrett's esophagus in Northern Greece: A Prospective Study (Barrett's esophagus). Hippokratia. 2013 Jan; 17(1):27-33.
10) Otterstatter MC, Brierley JD, De P, Ellison LF, et al. Esophageal cancer in Canada: Trends according to morphology and anatomical location. Can J Gastroenterol; 26(10): 723-727.
11) Milind R, Attwood SE, et al. Natural history of Barrett's esophagus. World J Gastroenterol. 2012 Jul 21; 18(27):3483-91.
12) Cook MB, Shaheen NJ, Anderson LA, Giffen C, et al. Cigarette smoking Increases Risk of Barrett's esophagus: An analysis of the Barretts and

esophageal Adenocarcinoma Consortium. Gastroenterology. 2012 Apr; 142(4):744-53.

13) Behrens A ,Pech O, Graupe F, Lorenzo D, et al. Barrett's adenocarcinoma of the oesophagus. Dtsch Arztebl Int 2011; 108(18): 313-9

14) Harrison VL, Hunter JG, et al. Revised staging system for Esophageal cancer. AccessMedicine from McGraw-Hill © 2010 the McGraw-Hill Companies.