Pre and post PET-CT impact on oesophageal cancer management: a retrospective analysis.

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Abstract. Assessment of the retrospective cancer incidence, prevalence and crude survival rates of oesophageal cancer to allow comparison between pre and post PET-CT introduction are part of 4 phase cost effectiveness research. It will provide baseline data for to assess PET or PET-CT cost effective potential for staging. A total of 849 patient’s data received from NWCIS databases with various stages of oesophageal cancer between 2001 and 2008. The fundamental activities are retrospective analysis of patient data. In most cases where appropriate, results are presented with 95 percent confidence intervals (CI). Variances between patient groups and variables are assessed using chi-square test. In cases where it deems vital, multiple logistic regression are used to modify for potential confounder such as age and sex. All p-values are two-sided and any value lower than 0.05 were considered to suggest a statistically significant result. Retrospective analysis were categorised into two categories, patients from 2001-2003 considered as pre PET and post PET for 2004-2008. This categorisation allows better comparison of patients’ survival trend to be made between both groups. Rates are presented in percentages and being grouped by tumour characteristics and other variables associated with demographic profile, diagnosis, staging and treatment. Results allowed comparison of oesophageal cancer trends between the pre and post PET-CT introduction such as changes in incidence rate or changes in survival. These data were used to normalise the decision tree model so that cost- effectiveness analysis can be performed across the whole population.

1. Introduction

Oesophageal cancer, although a malignancy with a relatively low incidence, has a very high mortality, related among other factors, to delayed diagnosis and inaccurate pre-therapy assessment on the extent of the disease (1, 2). Evolution of times brings together a continuous rapid advancement in diagnosis and treatment of oesophageal cancer that not only can improve chances of survival but also make early diagnosis for its late symptom diseases (3, 4). Despite of this advancement, oesophageal cancer continues to be a major health problem worldwide.
As the treatment for oesophageal cancer remains in evolution, the fundamental principle of cancer management is patient’s evaluation for surgical treatment. The domain prognostic factor for survival is whether the patient can be completely resected. As oesophageal cancer comes with significant morbidity, mortality and cost associated with the surgical treatment, it is important to identify and to exclude patient who will not benefit from the surgical treatment. Improved staging techniques may decrease the number of surgically treated patients and result in improving the survival figures for the more selected group. It is a common practice to evaluate patients with potentially operable disease and ensure that all detectable metastases are included.

Oesophageal cancer has high fluorodeoxyglucose (FDG) avidity (5-7). 18-FDG PET is increasingly used for the staging of oesophageal cancer, but provides limited anatomic information. Hybrid PET-CT imaging improve characterisation of FDG activity in the vicinity of highly tracer-avid primary tumours before surgery, in close proximity to organs with high physiological uptake and in the presence of postsurgical distorted anatomy. Integrated PET-CT enables optimal anatomic delineation of PET findings and identification of FDG-negative lesions on computed tomography (CT) images and results in patient management improvement.

In recent study of patients with oesophageal cancer (initial staging, evaluation of neo-adjuvant chemotherapy, or postsurgical follow-up), PET-CT appeared superior to PET or CT alone and had an effect on further management in 22% of patients (8). Management changes were related to better localising PET abnormalities, retrospectively detecting true abnormalities on concurrent contrast CT, guiding endoscopy to the site of suspicious lesions, and eliminating the need for further work-up that would have been necessary with CT or PET findings alone.

This study purpose is to assess the retrospective cancer incidence, prevalence and treatment pathway of oesophageal cancer between pre and post PET-CT. This allowed comparison to be made on oesophageal cancer trends between the pre and post PET-CT introduction such as changes in incidence rate or changes in survival. The prognosis of any patient with disseminated disease is very poor with expected 5 year survival rate less than 5%. For patients with no disseminated disease the survival is also poor but may extend to 10% - 30% (9-12). This is part of a large study on cost effectiveness analysis of PET-CT for oesophageal cancer.

2. Materials & Methods
Ethics clearance has been obtained for a retrospective data collection from Merseyside and Cheshire Cancer Registry databases. It provides information on the use of PET and PET-CT in 849 with various stages (0 to 4) of oesophageal cancer from 2001-2008.

All patients were categorised into two categories, in which patients diagnosed from 2001-2003 considered as pre PET and post PET for 2004-2008. This is due to the fact PET only introduced in RLBUHT in 2004 and PET/CT in 2007 (mobile).

Data analysis was done with Microsoft Excel spreadsheet, Version 2007 (Microsoft Corporation, Redmond, Washington, United States) and SPSS PASW Statistics for Windows Version 23 (IBM Company, New York, United States).

3. Results
Demographic profiles on 849 patients evaluated in this phase are as described in Table 1. Rates are presented in percentages and being grouped by tumour characteristics, treatment and other variables associated with demographic profile, diagnosis, staging and treatment information.

In most cases where appropriate, results are presented with 95 percent confidence intervals (CI). Variances between patient groups and variables are assessed using chi-square test. In cases where it deems vital, multiple logistic regression are used to modify for potential confounder such as age and sex. All p-values are two-sided and any value lower than 0.05 were considered to suggest a statistically significant result.
In North West; between 2001-2003 and before the introduction of PET-CT, the proportion of patients diagnosed with oesophageal cancer was 30% higher in comparison to post PET-CT (35%). Mean patient age was 65 years, and most patients were male (63%). Inclusion criteria specified that patients have histologically confirmed cancer.

Over the period of 2001-2008, the number of patients for all grades of cancer has decreased from approximately 407 to 232 during post PET-CT period. This study also reported that post PET-CT has shown decreased in treatment plans from 64% to 36%.

3.1. Pre and post PET-CT comparison on oesophageal cancer grades.

This study provides evidence that post PET-CT introduction leads to changes in the oesophageal cancer grades. Major changes can be seen in moderately differentiated grade (from 151-83) as shown in Figure 1.

This study provides evidence that post PET-CT introduction leads to changes in the treatment plans from 64% to 36% of all patients. The most frequent major change was surgery from 245 to 150 cases. Changes can also be seen for chemotherapy (from 87 to 24) and radiotherapy (92 to 58) as shown in Figure 2.

Table 1. Trend Rate Survey Analysis on demographic and clinical profile

| N = 849 | Pre PET (2001-2003) | Post PET (2004-2008) | Pre Percentage (%) | Post Percentage (%) |
|---------|---------------------|---------------------|--------------------|---------------------|
| **Gender** |                     |                     |                    |                     |
| Male    | 271                 | 142                 | 63.5               | 60.7                |
| Female  | 156                 | 92                  | 36.5               | 39.3                |
| **Age median ( range)** |                     | 65 (25-91 years) |                    |                     |
| Well differentiated | 25                 | 31                  | 5.9                | 13.2                |
| Moderately differentiated | 151               | 83                  | 35.4               | 35.5                |
| Poorly differentiated | 121               | 68                  | 28.3               | 29.1                |
| Undifferentiated | 7                  | 4                   | 1.6                | 1.7                 |
| Not appropriate/not assessable | -               | 1                   | 0                   | 0.4                 |
| Not known | 103                | 45                  | 24.1               | 19.2                |
| **Treatment Plan** |                     |                     |                    |                     |
| Surgery | 245                 | 150                 | 57.4               | 64.1                |
| Palliative treatment | -                 | 1                   | 0                  | 0.4                 |
| Chemotherapy | 87                 | 24                  | 20.4               | 10.3                |
| Radiotherapy | 92                 | 58                  | 21.5               | 24.8                |
| Unknown Drugs | 3                  | 7                   | 0.7                | 0.4                 |
Figure 1. Pre and post PET-CT comparison on oesophageal cancer grades

Figure 2. Pre and post PET-CT comparison on treatment plan

4. Discussion and Conclusion
This study allowed comparison of oesophageal cancer trends between the pre and post PET-CT introduction such as changes in incidence rate or changes in grades and treatment plan. This accumulating data including the current study that was part of cost- effectiveness analysis study, were then used to normalise the decision tree model so that cost- effectiveness analysis can be performed across the whole population.

Retrospective comparison between pre and post PET-CT introduction shows that the cancer incidence and prevalence of oesophageal cancer in North West have decreased by almost half (46%) post PET-CT introduction.

The main role of PET-CT for pre-treatment staging of primary oesophageal cancer patients is to identify other disease that would preclude definitive curable treatment options. Introduction of PET-CT improves pre-treatment staging accuracy and grading, thus improving patient outcomes and results in more appropriate treatment management.

There are some limitations with this current study. The comparative study of definitive versus palliative therapies were not identified. Therefore, a case linked for increasing patient outcomes post PET-CT introduction for these indications cannot be made.
This study suggests a potential evidence that PET-CT introduction in primary oesophageal cancer patients leads to change in grading and treatment plans in substantial portion of patients. PET-CT itself is a costly technology. However, the potential role in diagnosing oesophageal cancer and directing therapeutic strategies to improve patient outcome may outweigh the cost of scanning and lower the financial individual health-care cost. Thus, the results from this study will provide sequential data for larger ongoing cost-effectiveness analysis study to highlight the role of PET-CT in oesophageal cancer management. The complete research will be beneficial to Malaysia cancer research in term of improving the selection of PET/CT to be made widely available in cancer management based on the clinical values and cost effectiveness.

5. References
[1] Dehdashti F, Siegel BA. Neoplasms of the esophagus and stomach. Seminars in Nuclear Medicine. 2004;34(3):198-208.
[2] Dehdashti F, Siegel BA. Neoplasms of the esophagus and stomach. Semin Nucl Med. 2004;34(3):198-208.
[3] Eslick GD. Epidemiology of esophageal cancer. Gastroenterol Clin North Am. 2009;38(1):17-25, vii.
[4] Eslick GD. Esophageal Cancer: A Historical Perspective. Gastroenterology Clinics of North America. 2009;38(1):1-15.
[5] Torrance AD, Almond LM, Fry J, Wadley MS, Lyburn ID. Has integrated 18F FDG PET/CT improved staging, reduced early recurrence or increased survival in oesophageal cancer? Surgeon. 2015;13(1):19-33.
[6] Noble F, Bailey D, Panel SUGT, Tung K, Byrne JP. Impact of integrated PET/CT in the staging of oesophageal cancer: a UK population-based cohort study. Clin Radiol. 2009;64(7):699-705.
[7] Wong WL, Chambers RJ. Role of PET/PET CT in the staging and restaging of thoracic oesophageal cancer and gastro-oesophageal cancer: a literature review. Abdom Imaging. 2008;33(2):183-90.
[8] Bar-Shalom R, Guralnik L, Tsalic M, Leiderman M, Frenkel A, Gaitini D, et al. The additional value of PET/CT over PET in FDG imaging of oesophageal cancer. European journal of nuclear medicine and molecular imaging. 2005;32(8):918-24.
[9] Greene FL, American Joint Committee on C. AJCC cancer staging handbook : TNM classification of malignant tumors. New York; London: Springer; 2002.
[10] Headrick JR, Nichols FC, 3rd, Miller DL, Allen MS, Trastek VF, Deschamps C, et al. High-grade esophageal dysplasia: long-term survival and quality of life after esophagectomy. Ann Thorac Surg. 2002;73(6):1697-702; discussion 702-3.
[11] Pera M, Trastek VF, Carpenter HA, Allen MS, Deschamps C, Pairolero PC. Barrett's esophagus with high-grade dysplasia: an indication for esophagectomy? Ann Thorac Surg. 1992;54(2):199-204.
[12] Reed CE. Surgical Management of Esophageal Carcinoma. 1999. p. 95-105.

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