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Research Article

The Predictive Value of Interim ^{18}F-FDG-PET/CT in Predicting Pathological Response to Neoadjuvant Therapy in Locoregionally Advanced Oesophageal Cancer Patients

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Introduction

Oesophageal has an increasing prevalence worldwide and is ranked the 8th most common cancer. As there is no population wide screening, oesophageal cancer is often diagnosed at advanced stage, and associated with significant morbidities leading to poor quality-of-life and survival outcome [1]. Treatment of esophageal cancer for locally advanced oesophageal cancer has become more standardized since the CROSS trial over the last decade with oesophatectomy with neoadjuvant therapy. Oesopahgectomy for locally advanced oesophageal cancer however carries significant peri-operative and long-term quality of life risk. Despite introudction of minimally invasive surgical approach, morbidity and mortality remain significant at 60% and 5% respectively [2,3]. This neoadjuvant multimodal therapy with Neoadjuvant Chemoradiation Therapy (NCRT) with subsequent surgical resection appeared to achieve the maximal survival outcome [4,5].

^{18}F-Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG PET) combined with Computed Tomography (CT) has become an integral part of multidisciplinary assessment tool of advanced stage oesophageal cancer. PET assessment has been shown to improve accuracy to initial staging of disease in detecting distal metastatic disease metabolic acitivty over conventional trimodality approach with contrast-enhanced CT and endoscopic ultrasonography with biopsy [6-8]. Utility of FDG PET/CT extends beyond staging of disease and had been widely adapated to assess neoadjuvant treatment response. Studies have investigated the prognostic value of index FDG PET/CT in predicting patient outcomes with FDG PET derived parameters [9-11]. Some studies even investigate the role of using FDG PET/CT to guide duration of neoadjuvant therapy, namely the ad-interim FDG PET/CT. An ad-interim assessment in early stage of NCRT to evaluate response of the disease to guide duration of neoadjuvant therapy and it's utility for ad-interim FDG PET/CT remains controversial, and this practice had slowly became out of date [12].

Decision for oesophagectomy after completion of neoadjuvant therapy must be carefully assessed to avoid unnecessary harm to patients. Surgical intervention is inappropriate for patient who had developed interval metastatic disease [13]. The reliability of interval FDG PET/CT after NCRT had been extensively investigated for this purpose. It had been reported that 8% of interval FDG PET/CT detects true distant metastases [8]. Despite this, significant portion of patients with negative FDG PET/CT who underwent oesphagectomy after a negative interval FDG

PET/CT assessment developed metastatic disease shortly after surgery [14]. This reflected that the imaging had underlying significant false negative rate. This highlighted the need to design further parameters to guide decision for surgical resection after NCRT. Studies had investigated interval FDG PET/CT derived parameters to predict pathological response and prognosticate disease survival. Although some predictive parameters have been reported in several studies, the reliability of these parameters have not been adequate to change practice paradigm [15-18]. In this study, our objective is to evaluate oesophageal cancer metabolic response from interval FDG PET/CT after neoadjuvant therapy and its predictive value to pathological response.

Methods

From October 2018 to April 2024, a retrospective cohort of patients in a high-volume referral centre for patients with oesophageal cancer were recruited. Patients were identified through the state-wide electronic medical record system and prospectively followed up. All patients with biopsied confirmed oesophageal cancer underwent index FDG PET/CT for initial staging of disease. Staging laparoscopy were occasionally performed to determine presence of disseminated abdominal disease. For patients with FDG PET/CT suggesting equivocal for metastatic disease, image guided biopsy would be performed to confirm metastasis. All oesophageal cancer patients were presented at our Multidisciplinary Team (MDT) meeting consisted of radiologist, pathologist, radiation oncologist, medical oncologists and specialist surgeon in oesophagectomy. The MDT determined clinical staging of disease, and treatment. Staging of disease was determined according to American Joint Committee on Cancer 8th Edition (AJCC 8th) [19]. A cohort of 70 patients with AJCC 8th Stage II or above but without distant metastatic disease and were deemed appropriate surgical candidate included in the retrospective cohort from the study period. All the patients received neoadjuvant therapy and definitive surgical resection. Patient with metastatic disease at time of diagnosis or developed distal metastases after neoadjuvant therapy were excluded from the study. Patient who was determined unfit for curative intent chemoradiation therapy and oesophagectomy by the MDT were excluded from the study.

Neoadjuvant therapy regime was decided by the MDT. Majority of patients received CROSS protocol comprising of 5 cycles of carboplatin and paclitaxel, and concurrent external bean radiotherapy with total dose 41.4 Gy over 4 weeks. All patients underwent an interval FDG PET/CT after completion of neoadjuvant therapy. Ultimately, all patients received two FDG PET/CT for initial staging and interval assessment prior to surgical resection. Index scan was performed after biopsied confirmed diagnosis of oesophageal malignancy and second (interval) imaging was performed 4 weeks after completion of neoadjuvant therapy. FDG PET/CT were acquired on Biograph mCT PET/CT scanner (Siemens Healthineers Medical). FDG PET/CT acquisitions were analysed using Syno.via universal imaging software (Siemens Healthineers Medical). All images would be reviewed by radiologist at our centre at time of the MDT. FDG-avidity variables were recorded, such as SUV_{max}, number of FDG-avid lymph nodes, presence of FDG-avid metastases, mediastinal blood pool SUV, and liver background SUV. All patients deemed appropriate for surgery underwent hybrid Ivor-Lewis oesophagectomy consisting of 2-stages sequentially with abdominal laparoscopy and right thoracotomy or thorascopy depending on surgeon preference.

Radiological treatment response was classified according to European Organisation for Research and Treatment of Cancer (EORTC) PET treatment response criteria [20]. SUV_{max} of primary oesophageal lesion was recorded from index FDG PET/CT, and post-neoadjuvant treatment SUV_{max} was recorded from interval FDG PET/CT. SUV_{max} reduction ratio was calculated using ([Index SUV_{max} - Interval SUV_{max}]/ Index SUV_{max}), and assigned to appropriate EORTC metabolic response group. Pathological treatment response was classified according to the Mandard tumour regression grading system [21]. Pathological TNM staging were assigned according to AJCC 8th Edition. Mandard score was routinely determined by pathologist at our centre. We further classified Mandard score 1-3 as good pathological response and score 4-5 as poor pathological response.

Statistical Analysis

Statistical analyses were performed using Stata Statistical Software: release 18 (Stata Corp., College Station, Texas, USA). Receiver Operating Characteristics (ROC) analyses were performed to evaluate predictive value of SUV_{max} changes to Mandard pathological response. Kaplan-Meier estimators and log-rank test were performed to make comparison between categories of pathological response and metabolic response. Multivariable logistic regression analyses were performed to identified covariables associated with disease recurrence and overall survival. These covariables were carried forward to be included in the adjusted Cox proportional hazard model. Unadjusted and adjusted Cox proportional hazard model was performed for metabolic and pathological response to determine risk of recurrence.

Results

A study cohort of 70 patients with summary of baseline characteristics, initial tumour pathology and index clinical staging were demonstrated. Oesophageal adenocarcinoma accounted for 90%, and squamous cell carcinoma accounted for 10% of the cohort. All patients received neoadjuvant treatment, 61.4% received CROSS, and 38.6% received FLOT. Overall, 57.1%

patient received adjuvant therapy after oesophagectomy. Outcome parameters including FDG PET/CT acquired metabolic response, Mandard pathological response, final tumour histology and post-treatment disease staging. Metabolic response of disease was measured as primary tumour SUV_{max} reduction ratio and further classified according to the EORTC response criteria (Table 2). Majority of patients (n = 38, 54.3%) demonstrated partial metabolic response (PMR). 15 (21.4%) patients had Complete Metabolic Response (CMR). 14 patients (20.0%) had Stable Metabolic Disease (SMD). 3 patients (4.3%) had Progressive Metabolic Disease (PMD) of the primary lesion on interval imaging without developing distal metastases. Patients with stable or progressive metabolic disease were combined in subsequent analysis as the same category.

Mandard pathological response was demonstrated in Table 1. Patients with Mandard score of 1-3 was categorized as good response, and score of 4-5 was categorized as poor response. There were 50 patients (71.4%) with good Mandard response, and 20 patients (28.6%) with poor Mandard response. Association of EORTC metabolic response to Mandard response were demonstrated in Table 3. Patient with poor EORTC metabolic response may be more likely to have poor pathological response with Mandard score of 5. But this observation was statistically insignificant, and no clear distribution pattern were observed in the Madnard score range of 1-4. The predictive value of primary lesion SUV_{max} reduction ratio to pathological response were evaluated with ROC curve analyses (Figure 1). The value of the SUV_{max} reducion ratio to predict good versus poor pathological response was only modest with an AUC of 0.64 (95% CI: 0.46-0.82). We were unable to identify the value of optimal sensitivity and specificity through the ROC analysis given the low power of the finding. Unadjusted and adjusted Cox hazard survival analysis were performed to evaluate correlations between Mandard pathological responses and EORTC metabolic response to recurrence-free survival. In our adjusted analysis, we have not observed any statistically significant difference in disease free survival between the Mandard response and EORTC metabolic response group (Table 4).

Patient demographics and background	Total cohort n = 70 (%)
Age (mean ± SD, years)	62.9 ± 8.8
Sex	
Male	57 (81.4)
Female	13 (18.6)
Tobacco smoking status	
Never smoke	25 (35.7)
Ex-smoker	28 (40)
Current smoker	17 (24.3)
Alcohol misuse	27 (38.6)
Tumour characteristics	
Primary tumour location	
Upper 1/3 oesophagus	2 (2.9)
Middle 1/3 oesophagus	6 (8.6)
Lower 1/3 and gastroesophageal junction	62 (88.8)
Tumour Histology	
Adenocarcinoma	63 (90)
Squamous cell carcinoma	7 (10)
Tumour Grade (Initial biopsy)	
Well differentiated	3 (4.3)
Moderately differentiated	24 (34.3)
Poorly differentiated	24 (34.3)
Not specified	24 (34.3)

Clinical TNM Staging			
Clinical T stage		Clinical N stage	
cT1	1 (1.4)	cN0	40 (57.1)
cT2	2 (2.9)	cN1	22 (31.4)
cT3	59 (84.3)	cN2	7 (10.0)
cT4	8 (11.4)	cN3	1 (1.4)
Neoadjuvant Therapy			
Chemoradiation therapy (CROSS)			43 (61.4)
Chemotherapy (FLOT)			27 (38.6)
Adjuvant Therapy			40 (57.1)
FDG-PET/CT Assessment			**Total cohort n = 70 (%)**
Primary			
SUVmax Pre-treatment (± SD)			13.4 (8.5)
SUVmax Post-treatment (± SD)			5.3 (2.7)
SUVmax Reduction %			49%
Mandard Pathological Response			
Good Response (Score 1-3)			50 (71.4)
1 (No residual cancer)			15 (21.4)
2 (Rare residual cancer cells)			15 (21.4)
3 (Fibrosis outgrow residual cancer)			20 (28.6)
Poor Response (Score 4-5)			20 (28.6)
4 (residual cancer outgrow fibrosis)			14 (20)
5 (Absence of regressive changes)			6 (8.6)
Tumour Histopathology			
Tumour Grade			
Treatment changes (unable define)			18 (25.7)
Well differentiated			5 (7.1)
Moderately differentiated			30 (42.9)
Poorly differentiated			17 (24.3)
Lymphovascular invasion			25 (45.5)
Perineuranal invasion			15 (27.2)
Positive resection margin			7 (10.0)
Pathological TNM staging			
yPath T stage		yPath N stage	
ypT0	16 (22.9)	ypN0	39 (55.7)
ypT1	23 (32.9)	ypN1	16 (22.9)
ypT2	9 (12.9)	ypN2	10 (14.3)
ypT3	22 (31.4)	ypN3	5 (7.1)
ypT4	0 (0)		

yPath Stage Group	
0 (Complete Response)	14 (20)
I	13 (18.6)
II	14 (20.0)
III	25 (35.7)
IV	4 (5.7)

Table 1: Cohort patient demographics and pathology characteristics. Treatment, treatment response, final histopathology and follow up.

Response category	**Definition**	**Primary Lesion Total = 70 n (%)**
Complete Metabolic Response (CMR)	Complete resolution of ^{18}F-FDG uptake, SUV_{max} reduction ratio of > 0.75	15 (21.4)
Partial Metabolic Response (PMR)	Reduction of ^{18}F-FDG with SUV_{max} reduction ratio of ≤ 0.75 after one treatment cycle	38 (54.3)
Stable Metabolic Disease (SMD)	Reduction of ^{18}F-FDG with SUV_{max} reduction ratio of ≤ 0.15, or SUV_{max} increase ratio does not exceed 0.25	14 (20.0)
Progressive Metabolic Disease (PMD)	Increase of ^{18}F-FDG with SUV_{max} increase ratio ≥ 025	3 (4.3)

Table 2: Cohort breakdown of patients with various level of metabolic response.

Mandard Score	Complete Metabolic Response n = 15	Partial Metabolic Response n = 38	Minimal Metabolic Response n = 18
TRG 1	4 (27%)	8 (21%)	3 (17%)
TRG 2	3 (20%)	10 (26%)	1 (6%)
TRG 3	3 (20%)	13 (34%)	5 (28%)
TRG 4	5 (33%)	4 (11%)	6 (33%)
TRG 5	0 (0%)	2 (5%)	3 (17%)
Total	15	38	18
P = 0.053, Pearson Chi-Square Test			

Table 3: Association of EORTC Radiological Response to Mandard Score, n = 70.

Recurrence Free Survival	**Unadjusted**			**Adjusted**		
Covariate	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Mandard pathological response						
Poor vs good response	1.037	0.497- 2.162	0.924	0.36	0.089-1.444	0.149
EORTC metabolic response						
Complete MR	-	-	-	-	-	-
Partial MR	1.432	0.603- 3.398	0.416	2.012	0.577- 7.018	0.273
Stable MD	1.227	0.443- 3.401	0.694	1.818	0.500- 6.609	0.364

Table 4: Cox Proportion Hazard model for recurrence free survival between Mandard pathological response and EORTC metabolic response

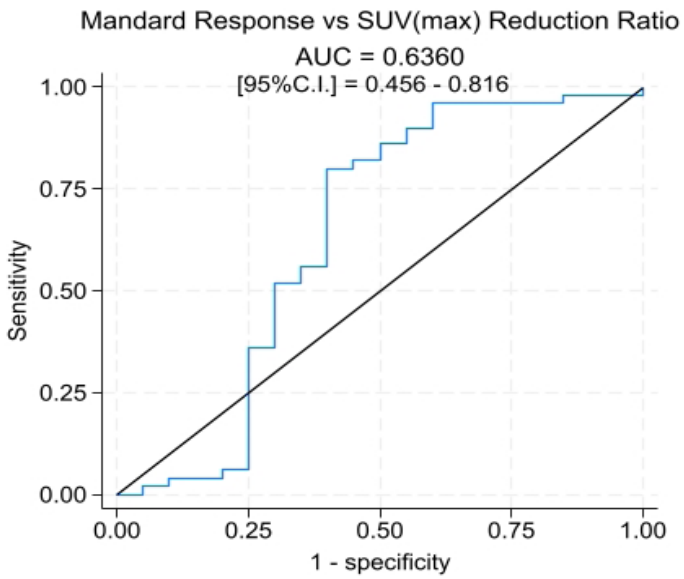

Figure 1: Receiver-Operating Characteristic for the predictive value of SUV_{max} reduction ratio in relation to Mandard pathological response.

Discussion

In this retrospective, we observed that there was no strong association between a patient's FDG-PET/CT metabolic response post neoadjuvant therapy to pathological response on oesophagostomy specimen. In our simple chi-squire analysis between Mandard pathological response and EROTC metabolic response, there were no observable pattern to suggest patient with good metabolic response on FDG-PET/CT were more likely to have good Mandard pathological response. The only observation was that patient with poor metabolic response appeared to be more likely have TRG 5 Mandard score, reflecting failure to any treatment response. Compounding this, one can extrapolate from prior literature to suggest that evaluating disease prognosis can be difficult through FDG-PET/CT measured metabolic response. It had been demonstrated that a poor pathological response with high Mandard score may no necessitate poor response to neoadjuvant therapy, and that patient with poor pathological response does not equate poor survival outcomes [22]. In our study, the link between FDG-PET/CT derived metabolic response and pathological response have not been established. The result demonstrated that an FDG-PET/CT may not necessarily contribute to assessing patient's risk for developing metastatic disease post oesophagostomy. Routine use of this imaging assessment may cause a population of patient unnecessary anxiety, given FDG-PET/CT had been reported to have approximately 5% false positive rate [8]. This could potentially lead to unnecessary further biopsy and delayed of ultimate surgical treatment for this sub-group of patients. Further to this, routine FDG-PET/CT imaging of patient post neoadjuvant therapy could be costly for the health care system. Although there is cost-benefit analysis performed at present, this could be worth while investigating.

This study has several limitations. This study was conducted in a retrospective fashion, and these carries inherent risk of selection bias. Most notably in our cohort, patient with interval FDG-PET/CT demonstrating development of new metastatic disease were not captured, and this could potentially skew results. Further to this, our studies included patient receiving either CROSS (neoadjuvant chemoradiation) or FLOX (neoadjuvant radiation along). Despite adjusting for the difference in our analysis, there may still be treatment effect not accounted for. In addition, this makes comparison to other existing literature difficult as most studies use single neoadjuvant treatment protocol. Lastly, our cohort of 70 patients were relatively small compared to other existing studies.

Conclusion

Our studies demonstrated that interval FDG-PET derived assessment of metabolic response to neoadjuvant therapy for oesophageal cancer did not predict patient's pathological response outcome. Further to this, it appeared that both FDG-PET metabolic response and Mandard pathological response were poor predictor of patient's survival outcomes.

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