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The Role of PET-CT in the Clinical Management of Oesophageal Cancer

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1. Introduction

Oesophageal cancer, once a relatively rare form of cancer, with a non-uniform geographical distribution, is the sixth most common cause of cancer related death in UK for 2005 (1-3). By the time of presentation, only 24-31% of patients are suitable for curative surgical resection and the overall 5-year survival is 20-30% (2, 4). PET-CT, a new staging modality is said to improve patient selection, by the detection of metastatic disease, which is not readily identifiable by other imaging modalities.

Recent published literature demonstrates an ever-evolving role for PET-CT in the management of various cancer types. PET-CT is not only used as a staging tool but can be used to assess early response to chemotherapy and radiotherapy (5). PET-CT can also be employed to identify disease recurrence, often detecting sites of relapse, before any other imaging modality (6). Additionally, metabolic parameters determined from the PET-CT study can provide prognostic information for individual patients (7).

The aim of this chapter is to provide the reader with an introduction to PET-CT, covering cellular metabolism, imaging of glucose metabolism, imaging protocols and the utility of standard uptake value. Following this, we will provide a pertinent review of the current published literature on the prognostic potential of standard uptake value of PET-CT in the management of oesophageal cancer and its ability to supplement the TNM classification. Finally, we will include future applications of PET-CT, including its role as a measure of tumour response following neo-adjuvant chemotherapy, and other de novo techniques currently being considered in the field of PET-CT.

2. Positron emission tomography and computed tomography

Positron Emission Tomography or PET involves an intravenous injection of a radioactive tracer, attached to a biological substance, which then distributes within the body in a recognised pattern. The radiation emitted from this injected substance can then be imaged to reveal the pattern of distribution within the body and abnormal areas of tracer accumulation, can therefore be identified. This creates a functional image. There are many radioactive tracers used, but in the context of this chapter, we will only consider fluourodeoxyglucose, FDG. FDG is a glucose analogue, which has a distribution, similar to simple glucose molecules within the body.

A CT scan uses X-rays to provide an anatomical image of the patient and a PET scan gives an image revealing the distribution of glucose like, metabolic function. Each on its own is a powerful tool but when combined they start to revolutionise cancer imaging. A PET-CT scanner is a single device that combines both modalities to produce an image that contains the metabolic functional information from the PET image and the anatomical information from the CT scan, displaying the resultant data as a fused PET-CT image.

2.1 Cellular metabolism

Cancer cells share similar traits to normal cells, in that they divide and multiply, but do so at a faster rate. Cancer cells also have an inherent tendency to metastasise, once they have overcome the body immunological defence. In order to achieve this objective the cancer cells must have an energy source capable of fuelling this division and growth. Otto Warburg, a German biochemist, noted over 80 years ago that many cancers use glucose as their primary energy substrate for this process (8). As the cancer cells grow, they often become starved of oxygen and therefore anaerobic metabolism of glucose becomes easier to sustain than aerobic metabolism, within the tricarboxylic acid cycle. The result of this is an increase in utilization of glucose within cancer cells, relative to most normal cells. Thus, a cancer cell will tend to have a much greater metabolic rate than the average normal cell.

Some cells within the body can use several different energy sources to fulfill their metabolic needs. Cardiac muscle, for example, preferentially uses free fatty acids as an energy source, but can also use glucose, lipids or amino acids if required. As a result the glucose uptake within the heart varies between people and can change considerably within an individual over a short period, in relation to the blood glucose at the time. Brain cells do not have the ability to use any fuel other than glucose and consequently the glucose activity within the normal brain is always high. In a fasting state, most body tissues, with the exception of the brain, actually use free fatty acids as their preferred energy source. After a glucose-rich meal, these cells may temporarily switch from free fatty acid to glucose metabolism, under the influence of rising insulin levels.

Transmembrane proteins, called glucose transporters, facilitate glucose uptake into the cell. At least 12 different glucose transporters have been identified and are known as GLUT 1, GLUT 2, and so forth.

When the glucose molecule enters the cell, it usually becomes phosphorylated by the enzyme hexokinase. The resultant compound is glucose-6-phosphate. Under normal circumstances the glucose-6-phosphate will undergo further enzymatic change to be converted into other smaller compounds thereby releasing energy, a process called 'glycolysis'. Alternatively the glucose-6-phosphate may be stored as a future energy reserve in the form of glycogen by the glyconeogenesis pathway, or it can be converted into either lipid or protein by other pathways.

The increased energy demands of a growing cancer cell necessitate a more rapid efficient delivery of glucose. As cellular division and growth proceed, a cancer cell uses some ingenious ways of meeting its energy requirements. First the cell can increase the number of transmembrane GLUT transporters to aid glucose delivery. If this is still not sufficient to meet demand, the cell can then increase the rate of phosphorylation, by up-regulating hexokinase activity. The resultant effect is that many cancer cells demonstrate a marked increase in glucose metabolism when compared to normal cells.

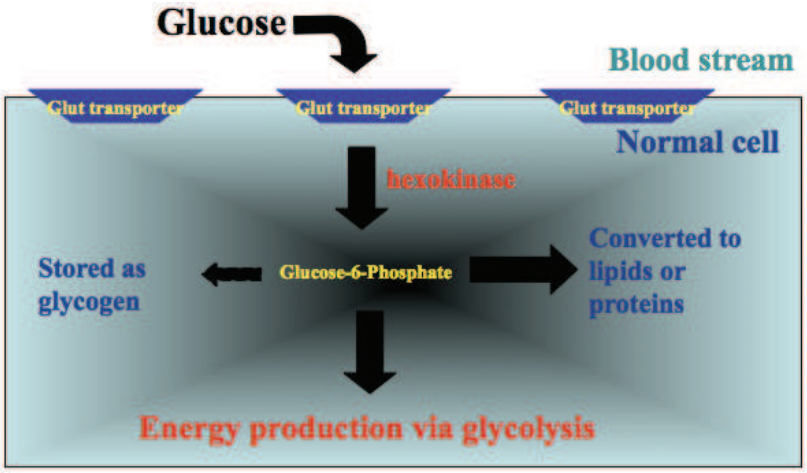

Fig. 1. Uptake and metabolism of glucose in a cell

2.2 Imaging glucose metabolism

FDG is produced in a device called a cyclotron. FDG is a radioactive positron emitter and decays with a half-life of approximately two hours. Due to the relatively long half-life of the FDG, a PET scanner can be located within a 2-hour drive from the cyclotron site. Other positron emitters such as Carbon-11 and Nitrogen-13 have much shorter half-lives and can only be used for PET scanners located in close proximity to a cyclotron.

FDG is injected intravenously and is taken up by normal and cancer cells alike. Cancer cells and normal cells compete with each other for cellular uptake using the GLUT transporters. Within a cell, FDG will be converted into FDG-6-phosphate by the action of hexokinase, just like normal glucose. Beyond this point, the fate of FDG and glucose are different. Due to the isomeric constitution of FDG, it cannot undergo further enzymatic change, unlike the glucose molecule. As a result, their pathways diverge; glucose is converted into either energy or stored as glycogen, whereas FDG undergoes no further metabolism and mostly remains trapped in the cell.

The distribution of radioactivity within the body can be imaged using a specialized camera called a PET scanner. An image gives a picture of the areas of the body that have FDG and therefore glucose uptake. The intense accumulation of FDG within many cancer cells allows those cells to be identified, compared to the less intense uptake in normal cells. Patients are imaged in the fasting state since most normal cells will more likely be using free fatty acids as their energy substrate. Figure 2 is a PET scan showing the normal distribution of glucose as identified by FDG uptake.

This image is called the maximum intensity projection image or MIP and is the two-dimensional representation of the accumulation of FDG uptake in the body as a whole. We can see that the brain has intense uptake, with less marked uptake in the heart, liver and spleen. We also see intense uptake in the renal system. Individuals, under normal circumstances, do not excrete glucose through the urinary system. Although FDG is an analogue of glucose, it behaves differently in this regard and is excreted in large amounts through the renal system. Whereas most normal glucose is freely filtered within the renal glomeruli and rapidly reabsorbed by the nephron, filtered FDG is poorly reabsorbed and a large proportion is excreted in the urine.

Fig. 2. The distribution of FDG within a normal individual

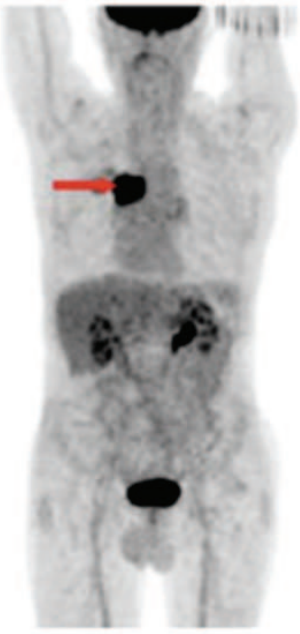

Fig. 3. A FDG +ve right hilar squamous cell carcinoma.

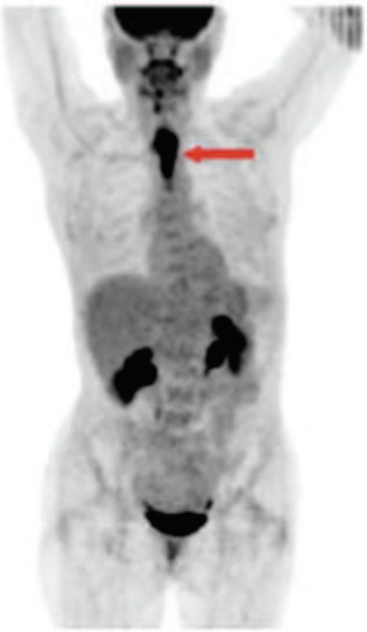

Fig. 4. An upper oesophageal squamous cell carcinoma.

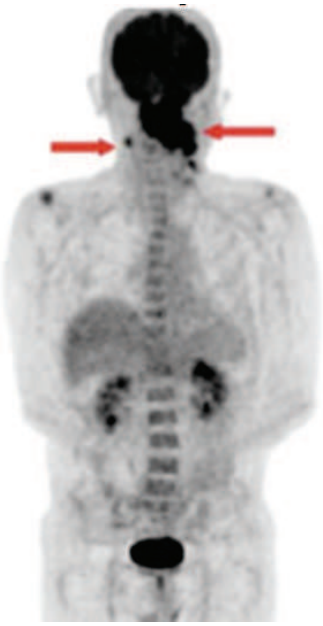

Fig. 5. A naso-pharyngeal lymphoma with bilateral neck node involvement.

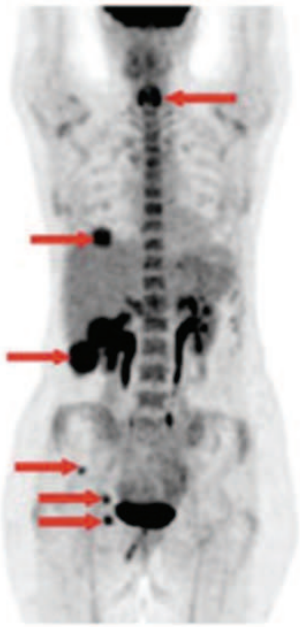

Fig. 6. Recurrent colorectal cancer with metabolically active deposits in the liver and right hemipelvis. The uptake in the neck is due to a coincidental thyroiditis.

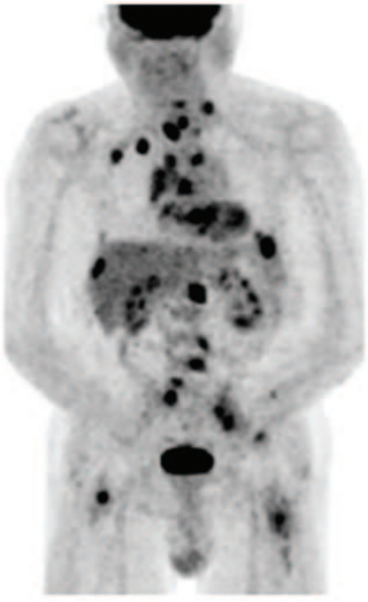

Fig. 7. Multiple bony metastatic deposits.

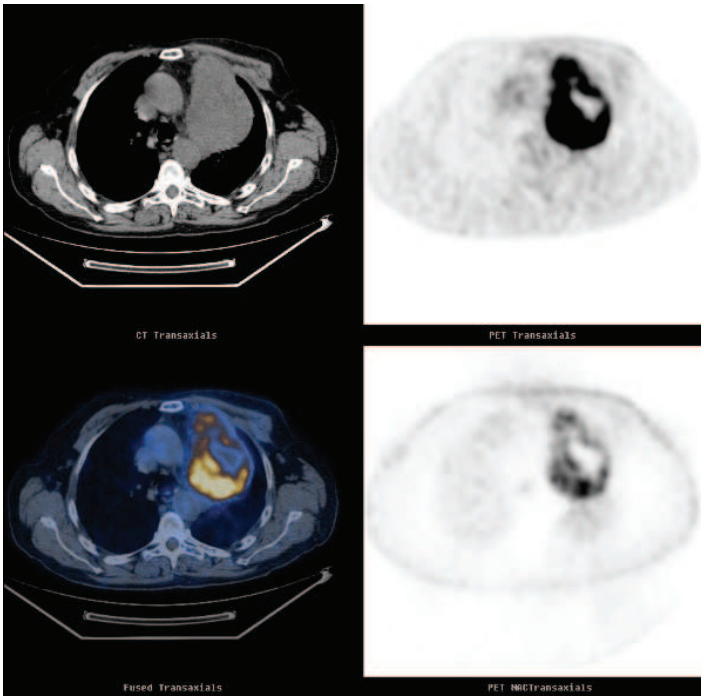

Fig. 8. Fused PET-CT image of a lung cancer.

Figure 3 to 7 is abnormal PET scans with the abnormality highlighted by arrows. Figure 8 is an example of a fused PET-CT image. The CT component is viewed in the top left hand corner and the attenuation-corrected PET in the top right hand corner. This image uses the CT data to correct for the effect of different positron absorption within different density tissues of the patient. The more intense the FDG (or glucose) uptake, the blacker it appears on the PET scan.

The fused PET-CT scan is seen in the bottom left hand corner of the image. This combines the anatomical data from the CT and the metabolic data from the PET, the colour scale chosen, shows the FDG uptake as increasingly orange to yellow, with increasing activity. The bottom right hand image is the non-attenuated PET image, which is effectively the raw PET data.

2.3 Scanning protocol and imaging sequence

Patients should arrive at the nuclear medicine department having fasted for at least four hours. This ensures most tissues are using free fatty acids as their energy source. Diabetic patients are advised to take their normal insulin or medication prior to arriving at the department.

After the staff has made all the necessary patient checks including correct patient identification and a check of blood glucose level, the injection of radioactive FDG can take place. The patient is advised to lie still for approximately 45 minutes to allow the FDG enough time to accumulate in metabolically active cells. Any unnecessary patient movement

during this uptake period can result in muscular uptake than can cause confusion with later scan interpretation. Patients who are tense during this time often show physiological uptake within the muscles of the neck.
Following the uptake period, the patient is taken into the scanning room and lies supine on the table. A picture of a GE Discovery Lightspeed PET-CT scanner is shown in Figure 9.

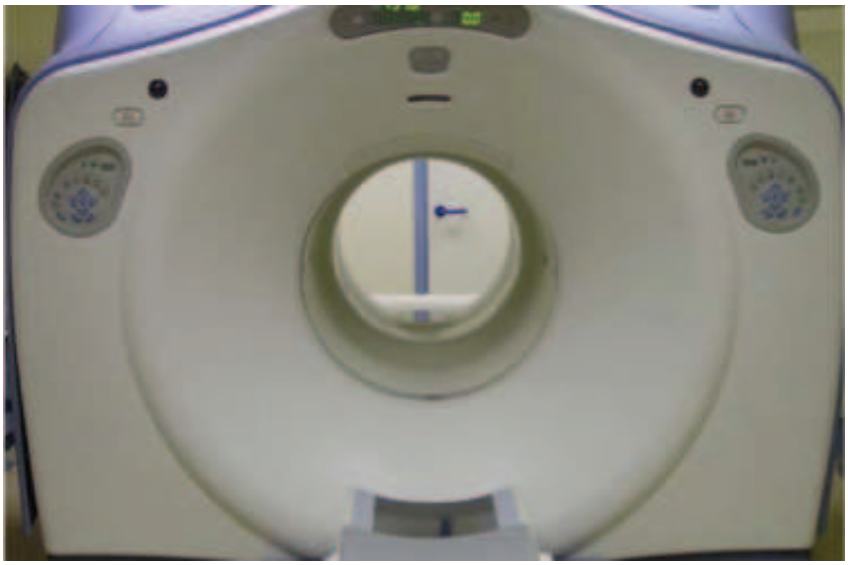

Fig. 9. GE Discovery Lightspeed PET-CT

Many centres now routinely use oral contrast enhancement to help visualise the bowel. Some centres also now recommend the use of intravenous contrast but this is presently not routine practice in the UK.
The CT scan is normally carried out from the base of skull to mid-thigh level. There are a number of reasons for performing this and not a whole body scan:

1. Brain metastases are difficult to detect using FDG as any brain lesion must have an intensity greater than or less than the surrounding brain tissue to be identified.
2. Only a few tumours have metastatic potential to disseminate to the distal lower limbs.
3. There is a decreased radiation burden to the patient from the CT.
4. There is a considerable amount of time saved which can be used to increase the patient throughput.

Whole body scans are carried out in some circumstances, for example patients with melanoma due to the widespread and unpredictable lymphatic dissemination that characterises this disease. A similar problem is encountered with the pattern of disease spread in non-Hodgkin's lymphoma, which often requires a larger scanning volume. Patients with head and neck disease often have scans that include the entire skull, and patients with soft tissue sarcomas may also require additional views.
After the CT images are acquired, which only takes a minute or so, when using a modern multislice scanner, the patient is then scanned again using the PET component of the machine. The detectors on the PET scanner can identify radioactive emissions from the FDG within the body. A ring of detectors surrounds the patient. This ring is approximately 15 cm

long and images are therefore acquired in blocks of 15 cm from the base of the skull to mid thigh. In most individuals this area is covered in about five blocks (~75 cm), taller or shorter individuals will take more or less imaging time. The time required for each 15 cm image of the patient is between three and five minutes. This means that the PET component of the study can take at least 15-45 minutes to acquire. Any patient movement during this time will degrade the quality of the images obtained.
After the PET scan has been acquired the patient is free to go but is given warnings about exposure to individuals during the next few hours as the radioactivity decays and is excreted from the body.

2.4 Standard uptake value

A semi quantitative method is available to calculate the intensity of FDG uptake within a range of interest on the PET scan. This value is called the Standardised Uptake Value, SUV, and takes account of factors such as injected activity, patient weight and time from injection. Simply speaking, the SUV assumes that if there's an even distribution of radioactivity throughout the body the SUV would be measured as one. Obviously this is not the case but we can calculate the relative uptake within different parts of the body and relate them to each other. An area with an SUV of five means this area has five times the average uptake. Certain modifications can be made to the SUV calculation to take into account, for example, the patient's body fat, since FDG is not generally taken up into fatty tissue.
The SUV allows comparisons to be made between different parts of the body and between different scans on the same patient over a period of time. It must be emphasised that the SUV is only a semi-quantitative measurement and can vary considerably with changes in the patient's plasma glucose level and are dependent on the uptake time allowed prior to scanning. Therefore, is it important that PET facilities use a standard scanning and imaging protocol for all their patients.
It is the SUVmax that is usually quoted in PET reports and measured in research studies. However there is a growing interest in the measurement of SUVmean, as it is less susceptible to outliers. The maximum SUV represents only one single pixel (the pixel with the maximum SUV within the entire tumour), whereas, the mean SUV in a region of interest, represents the average SUV of the given number of pixels within the ROI. Some clinicians prefer to avoid numbers altogether, and simply use visual interpretation to compare the intensity of one area to another using the background blood pool as a guide to normality. There is evidence to suggest that both methods are equally accurate.

3. The prognostic potential of PET-CT in the clinical management of oesophageal cancer

3.1 Introduction

Oesophageal cancer is staged according to the current American Joint Committee on Cancer guidelines, which incorporate the T, N and M classification (9). The current staging modalities utilize an array of morphological imaging studies, and more recently, minimally invasive surgical techniques, to bridge the gap between clinical and pathological staging. The introduction of PET-CT has provided an incremental yield to the diagnostic accuracy in oesophageal cancer staging (10-11). PET-CT provides an increased sensitivity and specificity of metastatic disease compared to other morphological imaging techniques (PET-CT vs CT: sensitivity 71% vs 52% and specificity 93% vs 91%), changing the operability in up to 20% of patients (12-13).

PET-CT also provides a semi-quantitative value of biological aggressiveness of a malignancy by reporting the standard uptake value, which represents the amount of metabolic activity within the tumour. Like certain biochemical indices, this amount of metabolic activity has been shown to be related to the clinical behaviour for a specific type of tumour for a given patient (7, 14-19). Therefore, it has been suggested that the FDG SUV value, may have a role as a predictive tool for patient outcome in oesophageal cancer (7, 17-19). This has already been demonstrated in other types of malignancies such as lung cancer and head and neck cancer (20-21). However, to our knowledge, there are only limited data available with regards to oesophageal cancer (7, 17-19).

3.2 Methods and materials

3.2.1 Patient population

All patients diagnosed with oesophageal carcinoma that had undergone staging PET-CT imaging between the period of June 2002 and May 2008, were included in this study. The eligibility criteria included only patients diagnosed with adenocarcinoma or squamous carcinoma of the oesophagus, (specifically excluding lesions confined to the upper third of the oesophagus), including those who were suitable for curative surgery, either with or without neo-adjuvant chemotherapy.

Studies were performed at a single institution (Regional Thoracic Surgical Unit, Royal Victoria Hospital, Belfast) with a standardised procedure, a Total Thoracic Oesophagectomy with a cervical anastomosis and two field lymphadenectomy. All patients were discussed at a surgical cancer network multidisciplinary meeting that included a thoracic or upper gastrointestinal surgeon, a nuclear medicine radiologist, an oncologist and a pathologist.

The study protocol was approved by our local research ethics committee (08/NIR03/106). Only electronic patient files including cancer network meetings, pathology reports and nuclear medicine imaging were used to collect the clinical information.

3.2.2 Patient image acquisition of FGD PET-CT data

Patients were scanned after injection of 370MBq 18F-FDG and an uptake period of 45 minutes, on a GE Discovery Light Speed PET-CT scanner, using a standard diagnostic protocol.

3.2.3 Measurement of prognostic variables and clinical outcome

Standardised Uptake Value (SUVmean and SUVmax)

A region of interest (ROI) was created for every individual patient based on the diameter of the FDG avid oesophageal lesion, on the attenuated corrected PET image, with side by side comparison with the CT image. The ROI ranged from 1cm to 3cm in diameter accordingly. This was to prevent overestimation, if a large ROI was used from neighbouring structures especially the heart, or underestimation, if a small predetermined ROI was used. The SUVmean and SUVmax were calculated, with the SUVmean taken at the same corresponding level as the SUVmax for that particular patient.

Clinical Outcome

The outcome evaluated was overall survival, which was from the date of surgery to death, identified from the Hospital Episode Statistics Data. Follow-up was through March 2009, constituting our censoring date for survival.

3.2.4 Surgery and pathological staging

Only patients with middle, lower or OGJ tumours involved were included in this study, with a standard total thoracic oesophagectomy being performed in all patients. This consists of a left thorocolaparotomy incision, resection of all the thoracic and abdominal oesophagus with two field lymphadenectomy, mobilisation of the stomach on the right gastro-epiploic arcade, creating a neo-oesophagus that is then anastomosed in the neck via a left oblique cervical incison. The same experienced surgical team performed all procedures. A single pathologist reported all pathological specimens using the current TNM staging.

3.2.5 Statistical analysis

The associations between the SUVmax and SUVmean with clinical staging (T and N categories) were assessed using analysis of variance or t-test. Pearson's correlation was used to assess the association between the different prognostic variables. Log-Rank and Cox regression tests were performed for disease free survival analysis. A $p < 0.05$ was considered significant. All statistical analysis was performed using the SPSS Version 18 (SPSS, Chicago, IL).

3.3 Results

There were a total of 96 patients during this study period that underwent staging FDG PET-CT scans. Fifty-three patients proceeded to receive neo-adjuvant chemotherapy followed by surgery. A response scan was performed 3 weeks after completion of neo-adjuvant treatment. The remaining 43 patients proceeded directly to surgery following their staging PET-CT.

From the 96 patients, 68.7% had adenocarcinoma and 31.3% had squamous carcinoma. Tumours were located predominantly in the lower oesophagus, 59.4%, followed by OGJ and middle oesophageal lesions, with 25% and 15.6% respectively (Figure 10)

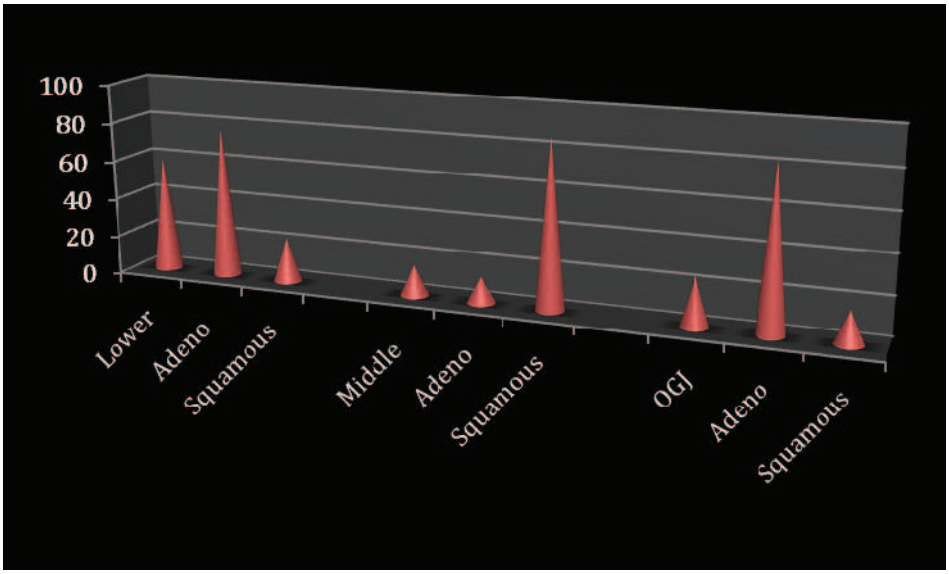

Fig. 10. Distribution of tissue type according to location.

The mean and median Staging SUV values were 10.3 and 9.3 for SUVmax, and, 6 and 5.8 for SUVmean, with a fairly normal distribution for SUVmean within the population studied (Figure 11 and 12).

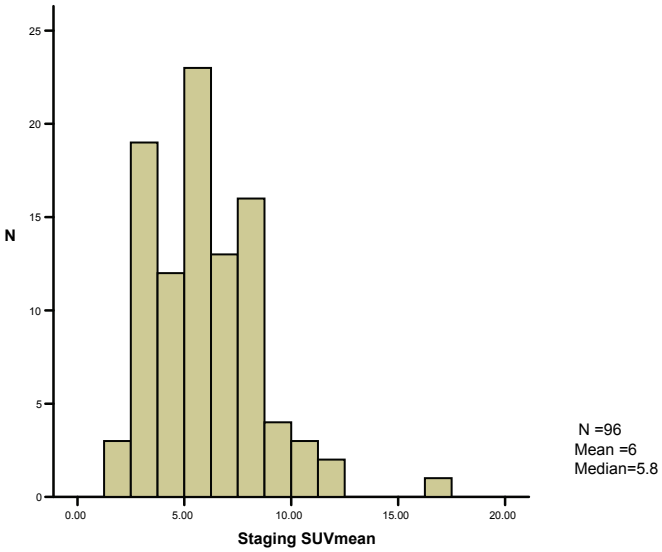

Fig. 11. Distribution of Staging SUVmean amongst study population.

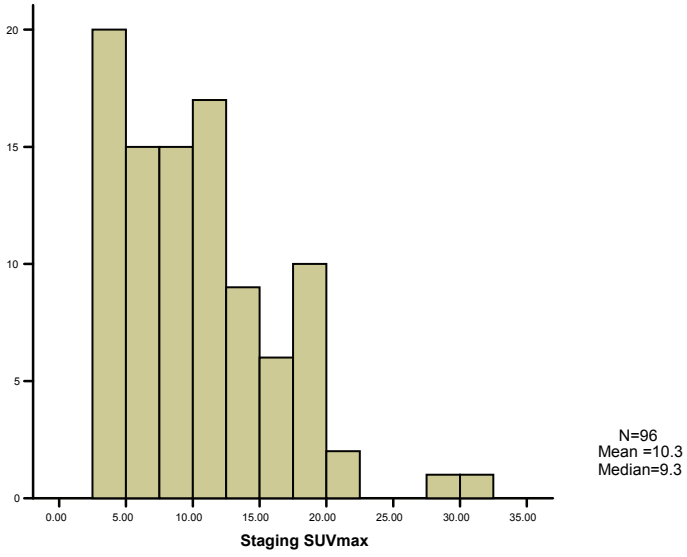

Fig. 12. Distribution of Staging SUVmax amongst the study population.

Both the Staging SUVmax and SUVmean correlated well, with a Pearson's correlation coefficient of 0.91 ($p<0.01$), Figure 13.

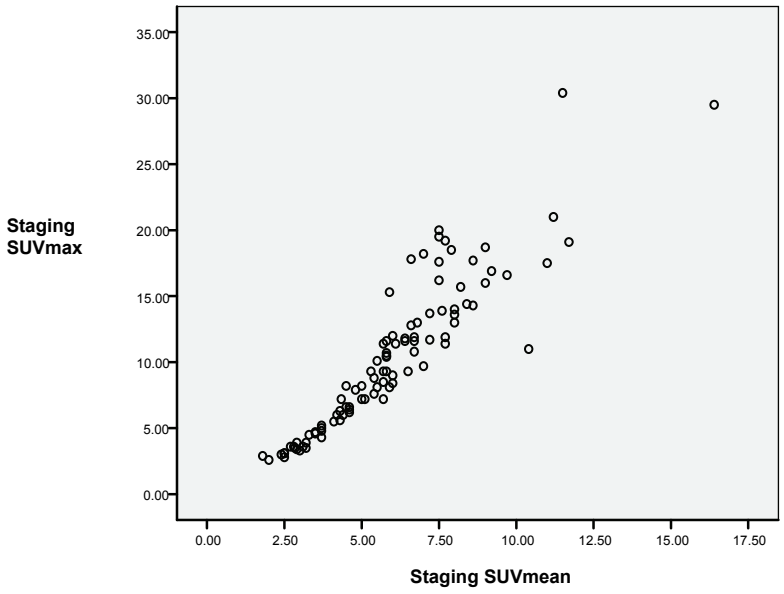

Fig. 13. Pearson's Correlation between SUVmax and SUVmean.

SUV_{max} and SUV_{mean} were both influenced by tissue type, with squamous carcinoma having a significantly higher uptake than adenocarcinoma, SUVmax 13.6 vs 8.8 ($p<0.01$) and SUVmean 7.3 vs 5.3 ($p<0.01$) respectively. SUVmax and SUVmean also varied according to locality, with tumours located in the middle oesophagus having the highest SUV uptake followed by the lower and then OGJ tumours. SUVmax varied from 13.4 to 10.5 to 8.0 ($p=0.02$) and for SUVmean from 6.7 to 6.1 to 5.2 ($p=0.14$) respectively. Logistic regression analysis demonstrated that the SUVmax dropped by 2.6 ($p<0.01$) and SUVmean by 0.8 ($p=0.05$) between tumour locations from proximal to distal oesophagus. However, the effect of tumour location on SUVmax ($p=0.23$) and SUVmean ($p=0.37$) lost its significance when corrected for tissue type.

Prognostically, staging SUVmean had a significant correlation with survival in patients with SUV values of less than 5 having a better survival than those above 5 ($p=0.02$), Figure 14. The risk of death was 2.4 times higher (95% CI 1.1, 5.0, $p=0.02$) in the latter group, after correcting for patients age, tumour type and tumour location. This survival advantage, however, wasn't demonstrated with a SUVmax of 10 and above ($p=0.14$), Figure 15. The effect of chemotherapy did not seem to influence survival in this cohort of patients ($p=0.20$).

Patients with advanced tumours, seemed to demonstrate an increase in metabolic activity, reflected by the increase in SUV uptake. The SUVmax for high-grade dysplasia, Stage I, II and III were 3.5, 5.1, 11.6 and 9.6 ($p=0.02$) and for SUVmean were 2.9, 3.9, 6.5 and 5.3 ($p=0.03$) respectively. Patients with nodal disease also demonstrated an increase in SUV uptake compared to N0 disease, with SUVmax of 11.4 versus 7.4 ($p=0.02$) and SUVmean of 6.1 versus 4.6 ($p=0.03$) respectively.

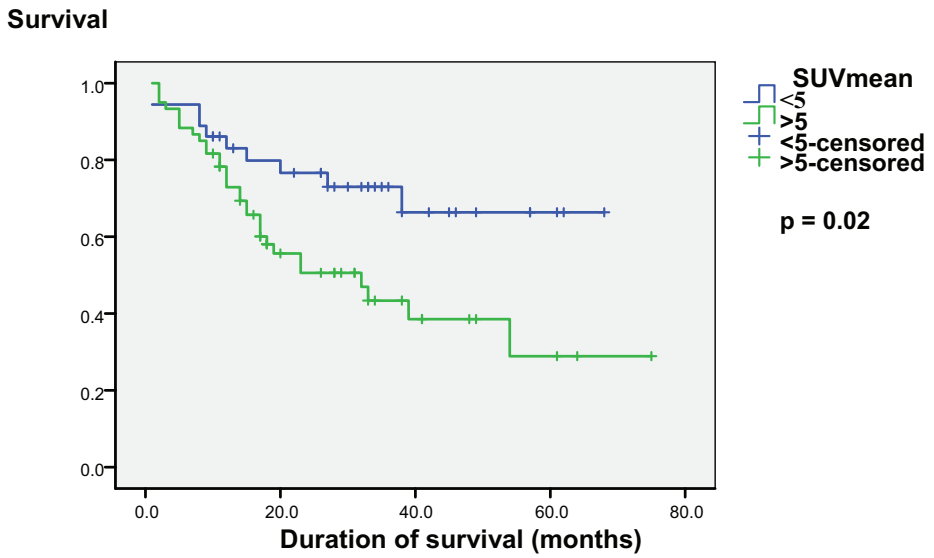

Fig. 14. Survival in operable oesophageal cancer patients around a SUVmean of 5.

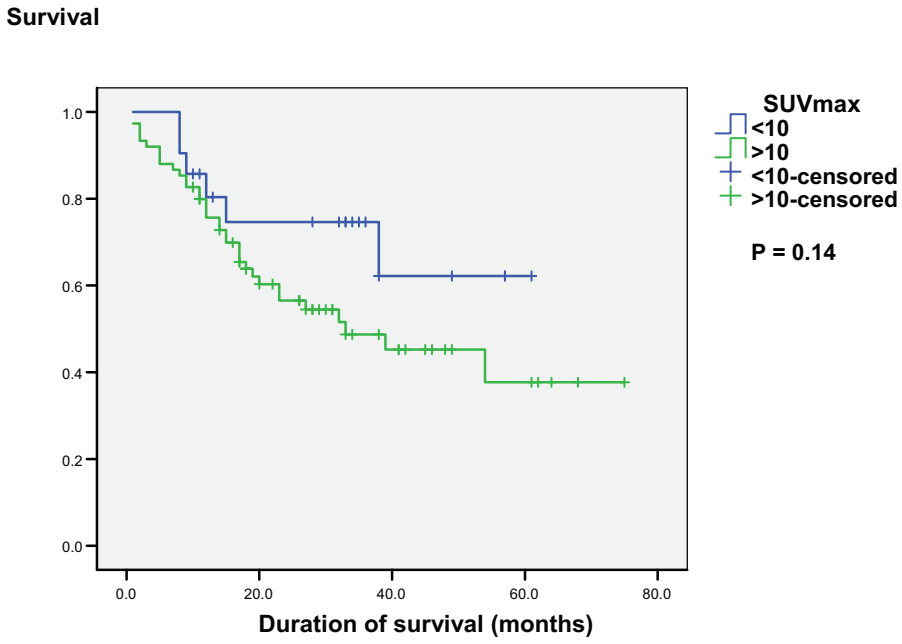

Fig. 15. Survival in operable oesophageal cancer patients around a SUVmax of 10.

3.4 Discussion

The treatment of oesophageal cancer, like any other solid organ tumour, is dependent of the stage of the cancer. However, the current TNM staging system is based only on anatomic and not on any biological factors. Interestingly, there is increasing evidence to suggest that biological factors influence prognosis just as much, if not more than, anatomical factors (22-24). FDG PET may aid in the detection of some of these biological factors that can't be identified with the current morphological imaging techniques. FDG PET has emerged as a useful metabolism-based whole body non-invasive imaging technique for the detection, characterization and staging of oesophageal cancer in recent years (25).

Van Westreenen et al. in a meta-analysis of the staging performance of FDG PET in oesophageal cancer, was able to demonstrate a moderate sensitivity and specificity for the detection of loco-regional metastases, but a reasonable sensitivity and specificity for the detection of distant metastases (26). The limited sensitivity and specificity for loco-regional metastases is due to the reduced spatial and contrast resolutions of PET-CT, and therefore limits visualization of the anatomic extent of the primary tumour as well as the ability to differentiate peri-oesophageal lymph nodes from the primary tumour (27). However, most morphological imaging scans as well as minimally invasive staging methods are able to compensate for this with a high accuracy for T and N staging. PET-CT, however, does have an excellent accuracy for the detection of M staging, accounting for up to 40% change in treatment strategies in patients as described by Chatterton et al. (28).

Recently, there is a growing body of evidence to suggest the prognostic potential of PET-CT in patients with oesophageal cancer, apart from its utility as a tool for radiotherapy planning or measuring tumour response in patients receiving neo-adjuvant treatment (7, 17-19). Its ability to identify metabolic activity within tumours reflects the biological aggressiveness of these cancers. This was first demonstrated by Fukunaga et al., who reported that patients with high SUV value within the primary tumour have a worse prognosis than those patients with a low SUV (29). A recent meta-analysis by Pan et al. demonstrated that patients with high SUV value not only have a worse survival prognosis, HR: 1.86, but also a reduced disease free survival with early recurrence, HR: 2.52 (30). The majority of these studies use SUVmax, to distinguish high from low SUV groups (30). Only one study utilized SUVmean (30).

From our data, we were able to demonstrate the independent predictor of survival using SUVmean and not SUVmax, both with univariate and multivariate analysis. SUVmean is less susceptible to outliers, but bear in mind, this study also showed both SUVmean and SUVmax to correlate well, with a correlation coefficient close to 1, and therefore it would be premature to disregard the prognostic potential of SUVmax. Hence, they should be used hand in hand to complement each other.

The metabolic activity is influenced by the biological properties of the tumour as we know. We demonstrated that squamous carcinomas have a higher SUVmax and SUVmean uptake compared to adenocarcinomas. Unfortunately, due to the small number in our series, we were unable to analyse the prognostic potential of the SUV values within the individual tumour types. Interestingly, both tumour types had a similar range distribution, with squamous carcinomas SUVmax and SUVmean ranging from 3.5 to 30.5 and 3.2 to 11.5 respectively, and, with adenocarcinomas SUVmax and SUVmean ranging from 2.6 to 29.5 and 2 to 16.4 respectively. Also, in the multivariate analysis, SUVmean was shown to be an independent predictor of survival after taking into account of tumour type.

The prognostic potential of SUV is strengthened by its relationship to the T and N staging. We found a linear increase in SUVmax and mean with the T staging apart for stage III, where there was a slight decrease. This could be attributed to the fact that there were more adenocarcinomas than squamous carcinomas (64% vs 36%). Also, the SUVmax and mean

within the primary tumour also related significantly to nodal disease, with a higher incidence of nodal involvement when the SUVmean was greater than 5 (50% vs 23.5%). This relationship between metabolic activity and the current morphological staging has been correlated in only a handful number of papers (7, 17-18).

Finally, how do we translate the wealth of information we obtain from morphological, biological, biochemical and minimally invasive techniques to these patients diagnosed with oesophageal cancer? As we already now, the incidence of oesophageal cancer varies according to geographic location, as well as the treatment practices (31). Apart from the TNM staging which provides prognostic information to the clinician, it allows treatment based algorithms to be compared, with the idea of producing a uniform framework, enabling multi-disciplinary teams to tailor their treatment appropriately according to the disease stage. However, there are subgroups of patients where, surgery alone, even in early cancers (T2N0) will not provide cure, or cases, where surgery itself is prohibitive due to the significant co-morbidities of the patient. Here, the additional biological information provided by PET-CT can better inform the multi-disciplinary team and treat the patient accordingly.

For example patients who are currently staged as T2N0 oesophageal cancers, have no agreed consensus with regards to their optimal therapy. The risk-benefit analysis of proceeding directly to surgery, or being treated initially with neo-adjuvant treatment followed by surgery, fails to reach a clear consensus. When we analysed our data pertaining to this subgroup, it was interesting to find out that patients with a SUVmean < 5 (n=6), only 1 patient died, due to peri-operative complications. However, in patients with a SUVmean > 5 (n=11), 2 patients died due to recurrent disease, both of which were not treated with neo-adjuvant treatment. The remaining patients were alive, taking into account that nearly 90% of these patients had received neo-adjuvant treatment. Though these numbers seem small, the fact that these early tumours with an SUV > 5 demonstrate a greater malignant potential should alert the multi-disciplinary team to adjust their treatment accordingly.

In conclusion, apart from PET-CT serving as a staging modality for oesophageal cancer, it provides important biological information that reflects the metabolic activity of the tumour. This pre-treatment or staging SUV, can provide important prognostic information that can supplement the current TNM staging to improve our decision making process, to ensure patients with oesophageal cancer receive the appropriate treatment care.

4. Future developments of PET-CT

As technology improvements parallel the increase utility of PET-CT, we anticipate further development prospects within the field of metabolic imaging. One such area is the development of new novel tracers that mimic cellular mechanisms, other than glucose uptake. Already tracers exist which can identify regions of hypoxia, examples include, Flourine and Copper labelled compounds, such as, (18F-fluoromisonidazole, 18F-fluoroazomycinarabinofuranoside, 64Cu-ATSM, and 18F-EF5). These tracers can modify chemotherapy and radiotherapy by highlighting areas of hypoxia. These regions can be particularly difficult to treat, and resistant clonal elements can survive, due to the delivery of sub toxic therapies. With this knowledge, dose modification can be carried out, for example using Intensity Modulated Radiotherapy (IMRT). Other potential areas for research include the development of tracers to assess the rate of tumour proliferation and the prospective clinical application of the integrated MRI-PET.

Another growing utility of PET-CT is the ability to predict tumour response to neo-adjuvant treatment by PET-CT (6, 32-35). Metabolic response is suggested when there was a certain relative decrease of the SUV between staging and response PET-CT scans, Figure 16.

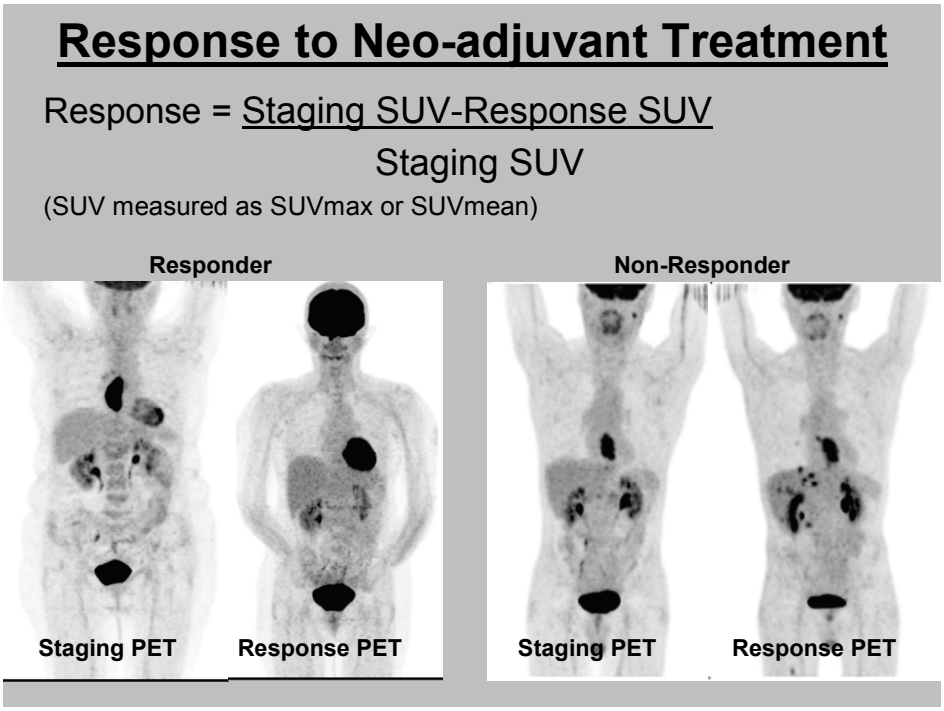

Fig. 16. Response measurement.

Several studies have concluded that FDG-PET is an effective modality for the non-invasive assessment of pathologic tumour response to neo-adjuvant treatment, but other investigations have seen no association between metabolic and histopathologic response (6, 32-35). The reason for these discrepancies between studies could be explained, at least in part, by various confounding factors that have an effect on SUV measurements; such as tissue activity factors, tissue state factors or normalisation factor; but also in part, by the definition of response in these respective studies (36). Simply using a specific cut-off value of SUV, to determine metabolic response from the response PET-CT scan, would be inappropriate, as we have demonstrated a wide distribution of SUV uptake amongst patients with oesophageal cancer, Figures 11 & 12 (34, 37). Additionally, the inflammatory response post neo-adjuvant treatment can complicate the interpretation of metabolic response, increasing the false positive rate of non-responders, as most of these patients have a background diffuse low FDG uptake, with an SUV value as high as 2.6 as demonstrated by Wieder et al (38). More importantly, as we have demonstrated, the biology tissue type influences the SUV uptake, both max and mean, and therefore using a percentage drop of the SUV from the staging to response PET-CT scan would be more judicious.

Recent evidence would suggest an interval PET-CT at 14 days after commencing neo-adjuvant treatment, to judge treatment response and therefore determine further treatment course. Wieder et al was able to demonstrate this, predicting histopathologic response with a sensitivity and specificity of 93% and 88%, respectively, with treatment induced oesophagitis observed in less than 15% of the scans (38). Furthermore, the decrease in metabolic activity at 14 days was significantly associated with overall survival (38). This was also confirmed in the

MUNICON trial, confirming the usefulness of early response evaluation by PET, and therefore tailoring multimodal treatment in accordance with individual tumour biology (39). We anticipate that PET-CT will have a significant impact on patient management by allowing a new means to individualize neo-adjuvant treatment in patients with oesophageal cancer.

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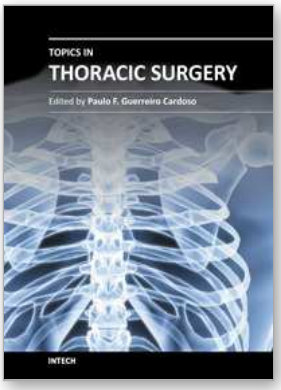

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