Two-step-fusion 18F-fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography (FDG-PET/CT) based radiotherapy in locally advanced oropharyngeal cancer

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ABSTRACT

Aims. To develop two-step-fusion 18F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG-PET/CT) based radiotherapy in locally advanced oropharyngeal cancer at the Beatson West of Scotland Cancer Centre and evaluate the technical and clinical aspect of this multi-modality imaging methodology.

Methods. I conducted a radiotherapy service development project at the Beatson. Contrast enhanced radiotherapy simulation CT (CTsim) and FDG-PET/CT were acquired separately with the same set-up and fused using an automatic rigid fusion algorithm (Eclipse, Varian). The fusion accuracy was assessed with the spatial reproducibility index (R=intersection/union ratio) of bony structures. Radiotherapy target volumes for both primary (T) and nodal disease (N) were defined separately on CTsim and FDG-PET/CT using visual assessment (PET/CT-vis) and segmentation with 50% SUVmax (PET/CT-50%). Volumes (cc) and spatial reproducibility (R) were calculated for the various volumes. Changes in TNM staging definition due to FDG-PET/CT were evaluated and compared with the staging based on morphological imaging (CT±MRI) and clinical information (endoscopy). SUVmax was calculated for T and N and correlated with the HPV-status and the oropharyngeal prognostic groups (low risk: HPV+, ≤10 pack years smoking history; intermediate risk: HPV+, >10 pack years smoking history; high risk: HPV-). Patients were treated using the target volumes defined with PET/CT-vis. Volumetric Modulated Arc Therapy (VMAT) was used with 65Gy and 54Gy in 30 fractions to high and low risk volumes respectively. Tumour outcome and late toxicity were recorded and compared with an internal non-PET/CT-based oropharyngeal series. Data were analysed using Stata v14.2 (StataCorp LLC, Texas). Data were summarised using medians (with range or inter-quartile range IQR). P-values were calculated to test for differences. All tests were 2-sided and a p-value <0.05 was considered statistically significant.

Results. A total of 30 patients were enrolled. The fusion accuracy of FDG-PET/CT and CTsim was calculated in 14 patients and resulted 0.89 (0.83-0.92). SUVmax was recorded for both primary and nodal disease in 27 patients. Among these patients median SUVmax was significantly higher in the primary tumour compared to the nodal disease (19.0 versus 14.0 g/ml, p=0.0001). Median SUVmax was higher in HPV- compared to HPV+ patients for both primary tumour (21.0 vs 16.9 g/ml) and nodal disease (17.0 vs 10.0 g/ml), however these differences were not statistically significant. Nodal SUVmax was higher in the high risk (i.e. HPV-) compared to the intermediate and low risk (i.e. HPV+) group (17.0 vs 8.8 vs

15.o g/ml) although again these differences were not statistically significant. FDG-PET/CT down-staged and up-staged T and N in 6/30 (20%) and 17/30 (57%) patients. Unsuspected distant metastases were not detected in any of the patients at baseline. The median volume of T and N defined with PET/CTvis and CTsim was 11.5cc vs 16.5cc (p=0.31) and 13.8cc vs 11.1cc (p=0.42), with reproducibility index R=0.49 and R=0.47 respectively. PET/CT50% identified hyper-metabolic sub-volumes inside PET/CTvis for both T and N: 4.6cc vs 11.5cc (p=0.001) and 3.5cc vs 13.8cc (p=0.04), DICE index 1. At median follow-up time of 16 (1-44) months, 74% of the patients had complete response, whilst 22% had progressive disease with median time to progression of 6.1 (3.1-15.9) months. The estimated overall survival (OS) at 2 years was 74% (95%CI, 49%-88%). In the sub-group analysis, the estimated OS at 2 years was 83% (95%CI 27-97%), 87% (39-98%) and 67% (19-90%) in the low, intermediate and high risk category respectively. Grade≥2 late xerostomia, dysphagia, dysgeusia and fatigue were recorded in 36%, 35%, 0% and 14% of the patients. Grade≥2 dysphagia was recorded in 38% of the patients who presented with bilateral and unilateral neck nodes (p=1.0).

Conclusions. I developed a 2-step-fusion methodology between FDG-PET/CT and CTsim. PET/CT fusion has been introduced in the routine radiotherapy planning at the Beatson for selected oropharyngeal cancer patients. My data suggest that HPV- are more metabolically active than HPV+ oropharyngeal cancers. My results support the hypothesis of treatment intensification in the high-risk group because more biologically aggressive. Dose intensification to hypermetabolic tumour sub-volumes may improve the outcome especially in the high-risk sub-group. FDG-PET/CT modified tumour staging and radiotherapy target volumes. My outcome and late toxicity results are similar to an internal non-PET-based series and other published studies. A prospective randomised study stratified by risk group would clarify if a true difference exists in outcome and late toxicity between PET-based and non-PET-based radiotherapy.

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Audentes fortuna iuvat (Publius Vergilius Maro, 70-19 a.C.n.)

AUTHOR'S DECLARATION

I declare that this thesis has been written by me and has not been previously submitted for a higher degree. All chapters were written by me. This thesis has been reviewed by my supervisors (Anthony Chalmers, Gerry Gillen) and my reviewer (John Foster). Philip McLoone reviewed the statistics.

ABBREVIATIONS

CE-CT	Contrast Enhanced Computed Tomography
CI	Confidence Interval
CR	Complete Response
CRT	Chemo-Radiotherapy
CTsim	Simulation Computed Tomography
CTV	Clinical Target Volume
D50	Dose(Gy) to 50% of the volume
DICE	Similarity coefficient index
DICOM	Digital Imaging and Communications in Medicine
Dmax	Maximum dose
Dmean	Mean dose
DNA	Deoxyribonucleic Acid
Dx%	Dose to x% of the volume
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
FDG-PET/CT	18F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography
FNA	Fine Needle Aspiration
Gy	Gray
GTV	Gross Tumour Volume
H&N	Head&Neck
HNC	Head&Neck Cancer
HPV	Human Papilloma Virus
IMRT	Intensity Modulated Arc Therapy
ISH	In Situ Hybridization
M	Metastatic disease
MDT	Multi-disciplinary team
MRI	Magnetic Resonance
N	Nodal disease
NPV	Negative Predictive Value
OAR	Organs at risk
OPC	Oropharyngeal Cancer

OS	Overall Survival
PC	Partially cropped
PACS	Picture Archiving and Communication System
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PET/CTvis	Positron Emission Tomography/Computed Tomography with visual assessment
PET/CT50%	Positron Emission Tomography/Computed Tomography with 50% of maximum Standard Uptake Value
PPV	Positive Predictive Value
PRV	Planning Risk Volume
PS	Performance Status
PTV	Planning Target Volume
QA	Quality Assurance
QoL	Quality of Life
R	Spatial reproducibility index (=intersection/union ratio)
RMG	Radiotherapy Management Group
ROI	Region of Interest
RTP	Radiotherapy Planning
SCC	Squamous Cell Carcinoma
SUVmax	Maximum Standard Uptake Value
SUVmean	Mean Standard Uptake Value
T	Primary tumour
TTP	Time to progression
UPC	Cancer of unknown primary
US	Ultrasound
VMAT	Volumetric Modulated Arc Therapy

CHAPTER 1
INTRODUCTION

1.1 Oropharyngeal cancer epidemiology

Oropharyngeal cancer (OPC) is a disease in which malignant cells form in the mucosa of the oropharynx. The oropharynx is the middle part of the throat which includes base of tongue, tonsils, soft palate, and walls of the throat (Figure 1.1.1).

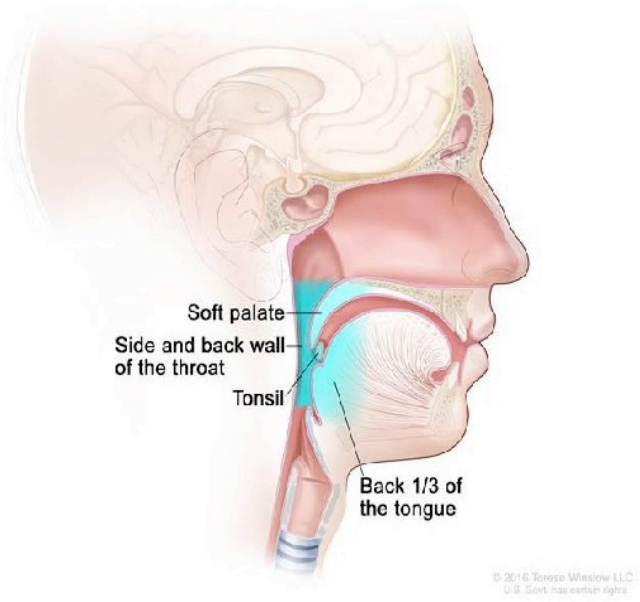


Figure 1.1.1. Anatomy of the oropharynx

The incidence of OPC has increased dramatically, especially in the Western World [1]. In England, the incidence of OPC has more than doubled between 1995 to 2006. Recent figures show that incidence has almost doubled again between 2006 and 2010. There were 1768 new OPC cases a year in UK in 2010 compared to 610 in 1995 [2]. In Scotland, OPC is the fastest rising of all cancers [3]. In the U.S., it is estimated that in 2020 OPC will be more common than cervical cancer [4]. This rapid rise is largely due to the Human Papillomavirus (HPV) infection. In a meta-analysis the proportion of OPC caused by HPV has more than doubled over the past decade to 70% [5].

It is recognised that there are three main risk groups of OPC according to the Ang Classification [6]:

- Patients with low-risk OPC whose cancers are caused by the HPV (HPV+ OPC) and who do not smoke or smoke very little (<10 pack-years) or those HPV+ OPC patients who smoke >10 pack years but have a small nodal disease (N0-N2A). These groups of patients appear to respond very well to standard chemo-radiotherapy and have a much better prognosis.
- Patients with intermediate-risk OPC whose cancers are caused by HPV (HPV+ OPC), have large neck nodes (N2b, N2c and N3) and greater than 10 pack-year smoking history. Also includes HPV- OPC patients who are non-smokers with small tumours (T1-T3).
- Patients with high-risk OPC whose cancers are not associated with HPV (HPV- OPC) and are caused mainly by heavy tobacco smoking or alcohol intake.

The 3-year Overall Survival (OS) is reported as 93%, 70.8% and 46% in the low, intermediate and high risk group respectively.

1.2 Role of smoking, alcohol and HPV

The primary risk factors associated with OPC include tobacco use, alcohol consumption and HPV infection [7]. In heavy smokers, there is an approximately 5-fold increased risk of OPC compared to non-smokers. Starting smoking below 18 years of age and duration of smoking (over 35 years) are high-risk factors, whilst cessation of smoking reduces the risk [8]. Alcohol consumption also increases the risk of cancer in the upper aerodigestive tract. It has been reported that alcohol intake greater than 50g/day (approx. 4 drinks), increases the risk for OPC by 5-6 fold compared to less than 10g of alcohol per day [9]. Changes in sexual behaviour appear to underlie the increase in OPC attributable to oncogenic HPV genotypes, principally HPV16 and HPV18 [10]. HPV is currently tested routinely in all OPC patients: normally p16 is first evaluated as indirect biomarker, followed by HPV DNA analysis with ISH or PCR. The correlation between p16 positivity and HPV DNA detection is around 98%. Over the past decade, there has been a shift in the primary site distribution, with steady increase of OPC and decline in cancers of the larynx and hypopharynx. This change has been observed in parallel with decrease in cigarette smoking and the identification of exposure to high-risk oncogenic HPV as risk factor for OPC [11]. Increase in the incidence of HPV+ OPC have been reported in numerous studies. Rietbergen et al [12] used a validated algorithm to determine the presence of oncogenic HPV infection in OPC in patients diagnosed in the Netherlands between 1990 and 2010. They reported a significant increase in HPV+ OPC from 5.9% in 1990 to 29% in 2010. Tinhofer et al [13] reported an increase in OPC HPV prevalence in a population with a high number of smokers from 27% in the period 2004-2006 to 59% in the period 2012-2013. Abogunrin et al [14] reported a meta-analysis of HPV in European populations giving the prevalence in OPC as 41.3%.

Prevalence varied by anatomical site from 66.4% in tonsillar cancer to 15.3% in pharyngeal cancer. Despite the fact that in many regions recent reports confirm that the incidence of HPV+ OPC is rising compared to HPV- disease, recent studies determined the HPV status using three validated commercial tests (p16 IHC, high-risk HPV DNA ISH, and HPV DNA PCR) from archival tumour tissue block samples from 2002-2011 with the aim of determining the proportion of HPV+ and HPV- OPC within the United Kingdom (UK). Despite the UK incidence of OPC is nearly doubling, the proportion of HPV+ cases remains static at ~50%. This suggests that rapidly increasing incidence of OPC in the UK cannot be solely attributable to the influences of HPV, indicating a parallel increase in HPV+ and HPV- cases. The absence of change in the proportion of HPV associated disease, despite a sustained increase in the incidence of OPC, implies that HPV- OPC, traditionally associated primarily with smoking and other environmental factors, is also increasing in incidence [15].

1.3 Treatment modalities (surgery, chemotherapy, radiotherapy)

Surgery

OPC may be treated with primary surgery (transoral or open resection of the primary, with or without neck dissection). Adjuvant (chemo)radiotherapy is recommended for patients with locally advanced (T3-4a, N0-1 or any T, N2-3) or early stage disease (T1-2, N0-1) with adverse surgical pathological features including extracapsular nodal spread and/or positive mucosal margins (<1mm) [16]. Classic open surgery or minimally invasive procedures such as transoral robotic surgery or laser surgery are used depending on site and tumour characteristics [17]. Where an organ-sparing approach (i.e. chemo-radiotherapy) has been taken in an otherwise resectable patient, if the non-surgical approach taken fails, salvage surgery may still be an option, however this can lead to considerable morbidity (e.g. loss of swallowing, speech and breathing problems) and QoL issues related to the loss of organ function due to the cumulative toxicity effect with the non-surgical treatment [18].

Radiotherapy

For loco-regionally advanced lesions, radiotherapy (RT) is used as post-operative treatment or in combination with chemotherapy as a definitive organ function-preserving approach [19]. However, RT alone is not sufficient to successfully treat most head&neck cancers (HNC) at intermediate or advanced stages, particularly in HPV- OPC. The majority of patients treated with curative intent receive a dose of 65-70 Gy in 30-35 fractions. In addition to anti-tumour effect, ionizing radiation causes damage in normal tissue located in the field

of radiation, particularly in the salivary gland, pharyngeal constrictor muscles and thyroid glands with possible long term complications. Technical advances in conformal RT have revolutionized the treatment of head&neck cancer. The distribution of RT beams can be conformed to the tumour size and shape, thus reducing the dose of radiation to normal tissues. Intensity-modulated radiation therapy (IMRT) is an improved mode of high-precision RT that utilizes computer controlled linear accelerators to deliver precise radiation doses to the tumour. This technique is delivered using linear accelerators with static or multi-leaf collimators or volumetric arc modulated therapy (VMAT). The equipment can be rotated around the patient and the beam moves multiple times, allowing 3D sculpted radiation to the tumour and decreased dose to surrounding normal critical structures. The advantage of IMRT is that it spares important vital structures such as the salivary glands, thus reducing xerostomia and improving Quality of Life (QoL). In a randomised study, G≥2 xerostomia at 24 months was recorded in 29% and 83% of the patients treated with IMRT and conventional conformal radiotherapy respectively [20]. However, dose reduction to the pharyngeal constrictor muscles is difficult to achieve without compromising the target volume, and the risk of aspiration, dysphagia and percutaneous endoscopic gastrostomy tube dependence are still present [21]. Studies are currently ongoing investigating de-escalation of radiation doses in low-risk HPV+ OPC patients, with the hope of improving the therapeutic ratio and long-term QoL for these patients whilst maintaining outcome [22].

Chemo-radiotherapy

To improve cure rates and functional outcomes, chemotherapy has been integrated into various multimodality approaches. These approaches have been applied for both patients with unresectable cancers and those with resectable disease, when the anticipated functional outcome and/or the prognosis is so poor that mutilating surgery is not justified. High-dose cisplatin-based chemo-radiotherapy (CRT) has been considered the standard of care for the past decade, with the most widely used standard regimen 100 mg/m2 cisplatin every 3 weeks, combined with ~70 Gy radiation delivered in 1.8–2.0 Gy daily fractions [23]. This combined treatment is highly effective in the low-risk OPC subpopulation with 3-year Overall Survival (OS) of 93% [6]. However the outcome is worse in the intermediate and high risk group (3-year OS 70.8% and 46% respectively). A number of other medicinal products are approved in the EEA for use in HNC either as a single or in combination with other agents or RT, including carboplatin, cetuximab, bleomycin, docetaxel, fluorouracil (5-FU) and methotrexate.

Epidermal growth factor receptor (EGFR) is highly overexpressed in head and neck squamous cell carcinoma and is associated with poor prognosis. Cetuximab is a monoclonal

antibody that binds to and inhibits the EGFR receptor. In locoregionally advanced disease cetuximab has been shown to increase overall survival when combined with RT [24,25] but not with platinum-based CRT [26]. Cetuximab can also be used as a single agent or in combination with platinum-based CRT in recurrent or metastatic disease [27].

Since patients with locally advanced HPV+ OPC may live longer, late toxicity and QoL are concerns for these patients, hence less-intensive treatments (i.e. deintensification) are being investigated in ongoing clinical trials. Strategies under active investigation include reducing or using response-stratified RT dose, using RT alone versus CRT, using less invasive surgical procedures such as transoral robotic surgery, using sequential systemic therapy/RT, using immunotherapy and targeted therapy agents [27].

Other systemic treatments

Treatments targeting specific cell membrane growth factor receptors (e.g. HER2, HER3, MET) or downstream signalling pathways (e.g. NOTCH1, MET-PIK3CA-MTOR, EGFR-RAS-RAF1-MEK and WNT/β-catenin) in patients with HNC are currently under investigation [21]. To date, there has been no breakthrough targeted therapy in H&N cancer, with single agent response rates in the range of 10-15% [28]. The growing understanding of the role of the immune system in tumour suppression has led to the development of immunotherapy for HNC. The interaction between programmed cell death 1 (PD-1) and its ligand programmed cell death ligand 1 (PD-L1), has been a recent target in immunotherapy efforts. Two clinical trials have shown that the PD-1/PD-L1-targeted drugs, nivolumab and pembrolizumab, improved survival in recurrent/metastatic HNC patients [29]. This led to the approval of these immune checkpoint inhibitor drugs for recurrent/metastatic HNC. Clinical trials combining PD-1/PD-L1-targeted drugs with chemotherapy, RT, CRT and other immunotherapies are all ongoing, and have the potential to revolutionise the treatment of HNC. Despite the predicted benefits of immunotherapy, numerous studies have indicated that HPV+ tumours may respond better to immunotherapy than HPV- tumours [30] suggesting that, even in the age of immunotherapy, there still may be a significant unmet clinical need for novel effective treatments for HPV- HNC.

1.4 Imaging in head&neck cancer

1.4.1 Imaging overview

Squamous cell carcinoma (SCC) is the most common malignant tumour of the head&neck region [31]. RT has a well-established role both in the radical and in the adjuvant setting, as

described above [32,33]. Initial diagnosis and staging are based on physical examination, endoscopy and multimodal imaging including Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET). Clinical guidelines recommend different imaging approaches for each stage of disease [34]. Moreover, modern imaging modalities have an essential role in the tumour response after treatment and follow-up [35,36]. Each of the currently available imaging techniques present different levels of sensitivity and specificity, and it is essential for the radiation oncologist to select the most appropriate one depending on the clinical scenario.

PET with fluorine-18 fluoro-deoxyglucose integrated with CT (18F-FDG-PET/CT) rapidly gained clinical acceptance and has become an important tool in routine clinical head&neck oncology. According to the National Comprehensive Cancer Network guidelines, PET or PET/CT is suggested for Stage III and IV disease due to the possibility of stage migration [32]. The Ontario guidelines suggest that 18F-FDG-PET/CT is also indicated when the primary site is unknown or for the staging of locally advanced disease [34].

T staging

The correct assessment of the size and extent of a primary lesion at staging is crucial to plan surgery and radiotherapy. Indeed, infiltration of adjacent structures is an important issue in clinical practice. The initial assessment of the local tumour extension is generally performed with clinical examination and endoscopy. Even though 18F-FDG-PET/CT detects the primary tumour with high sensitivity (95%) [37,38], contrast enhanced (CE) CT and MRI have been considered the primary imaging modalities for evaluating T stage due to their superior anatomical resolution and tissue contrast. Since it is not possible to exactly define the size and extent of a primary lesion based on 18F-FDG uptake, PET (alone) images are not suitable to define the T stage. In addition, the main limitation of hybrid PET/CT, if performed with low-dose unenhanced CT, is its inability to accurately assess the extent of tumour spread and its relationship with adjacent structures. PET/CT performed with contrast-enhanced CT provides both anatomical and metabolic details at the same time, however there is no clear recommendation for routine use of PET/CT alone in initial T staging.

Some authors showed the potential value of PET/CT to identify the extent of local tumour extension. In a retrospective study [39] 69 patients with oral cavity cancer and non-removable dental metallic implants at the time of the pre-treatment imaging work-up had CT or MRI plus PET/CT for the initial staging. The aim was to analyse the clinical impact of PET/CT for primary tumour detection and volume estimation. A total of 64 PET/CT, 64 CT and 27 MRI were analysed. PET/CT was more accurate in detecting primary tumours than

CT when dental artefacts were present (95.3% vs 75.0%, respectively, $p<0.05$). Among the 27 subjects who had undergone all the three diagnostic modalities, the diagnostic performance for the detection of primary tumours in the oral cavity was 96.3%, 77.8% and 85.2%, respectively ($p>0.05$).

In another study [40] 44 patients (66% with oropharyngeal carcinoma) who received primary tumour resection and neck dissection were retrospectively reviewed. The authors compared contrast-enhanced CT (CE-CT), PET/CT with contrast-enhanced CT (PET/CE-CT) and standard PET/CT. The primary tumour was correctly identified by CE-CT, PET/CT and PET/CE-CT in 71%, 92% and 95% of cases, respectively. Both PET/CT and PET/CE-CT were superior than CE-CT in identifying the primary site of the tumour. However, there was no statistical difference in the detection of the primary lesion between PET/CT and PET/CE-CT. In this study MRI was not evaluated.

Mandibular invasion is a major determinant of both therapeutic approach and prognosis of HNC [41]. CT and MRI are commonly used to evaluate the status of the mandible. CT has been reported to be the most accurate imaging modality in evaluating discrete cortical bone involvement [42], however MRI is superior to CT for evaluating tumour invasion into the medullary cavity of the mandible [43]. In a study in oral cancer carcinoma, the direct comparison of CT, MRI and PET/CT was evaluated in the detection of mandibular invasion [44]. The sensitivity and specificity was 47.1%, 58.3% and 58.3%, and 100%, 97.1% and 97.1% for CT, MRI and PET/CT respectively. No statistically significant difference in sensitivity and specificity was assessed between the three imaging modalities. A retrospective study compared the diagnostic performance of PET/CT and MRI for the detection of bone marrow invasion of the mandible in patients with oral cancer carcinoma (surgical specimen was used as the standard). PET/CT was found to be more specific than MRI (83% vs 61%, $p<0.05$) but less sensitive (78% vs 97%, $p <0.05$). Given the low positive-predictive value (PPV) of MRI, a positive MRI scan should be confirmed with PET, which shows higher PPV, whereas a negative MRI scan can confidently exclude the presence of bone marrow invasion [43].

The incidence of cervical metastases from unknown primary cancer (UPC) has been estimated to be around 2–9%. The absence of information about the primary tumour strongly influences the therapeutic approach (e.g. bilateral tonsillectomy, additional pharyngeal mucosa field irradiation) [45]. PET/CT can identify approximately 30% [46-52] of primary tumours in patients presenting with cervical lymph node metastases from UPC, in whom the primary tumour was not detected by the comprehensive diagnostic work-up including endoscopy and conventional imaging methods (CT or MRI). PET/CT should be performed before examination under anaesthesia for targeted pan-endoscopy and biopsy, avoiding

potential false positives due to the inflammation that usually follows these procedures [53,54]. Thus, a rigorous physical examination is still essential, considering that small and superficial tumours may not have enough 18F-FDG avidity to be detected by PET/CT [55]. In a meta-analysis reviewing a total of 7 studies (246 patients), the primary tumour detection rate, sensitivity and specificity of PET/CT were 44% (95% CI, 0.31–0.58), 97% (95% CI, 0.63–0.99) and 68% (95% CI, 0.49–0.83) [56]. In the largest prospective study evaluating the diagnostic performance of PET/CT in UPC [54], PET primary tumour detection rate was 30%, with sensitivity and specificity rates of 86% and 69% respectively. This study had some limitations related to the use of different PET (with/without CT) scanners and acquisition protocols, and no comparison was done with other imaging modalities.

In summary, physical examination remains essential for primary tumour assessment, especially for superficial tumour extension in the mucosa. CE-CT and MRI are the reference imaging modalities. PET seems to be an additional staging tool, in particular when morphological examinations suffer from artefacts due to dental implants. PET/CT is recommended to identify primary tumours in patients presenting with cervical lymph node metastases with unknown primary. However, PET/CT should be integrated with other diagnostic procedures to reduce the risk of false positive findings.

N staging

The information about nodal involvement is crucial in HNC, as it strongly influences the treatment and prognosis of the patients. Current non-invasive staging techniques include clinical examination, ultrasonography, CE-CT and MRI. The criteria adopted in the evaluation of the nodal status are the size, CE and radiological aspect of the nodes (presence of necrosis, analysis of the capsule to identify any sign of extracapsular extension) [57]. These techniques can define positive nodes with high specificity, but present limitations in the evaluation of small lymph nodes [58-62]. The overall diagnostic accuracy (using pathology as the reference standard) of CT and MRI for detecting metastases in the clinical node negative neck (cN0) is relatively low. Sensitivity range from 14% to 80% for CT and from 29% to 85% for MRI, and specificity range from 80% to 100% for both CT and MRI. Sensitivity and specificity of the imaging techniques influence the clinical practice of the radiation oncologist. Patients presenting an expected risk of nodal involvement exceeding 20% undergo prophylactic treatment of the neck, including neck dissection or unilateral and/or bilateral neck irradiation [63,64]. Considering these rates of microscopic involvement, it means that there are at least two thirds of the patients who are treated on the

nodal areas without presenting a nodal involvement, only because it is not possible to predict with better accuracy the “real” nodal status.

PET/CT is similar or slightly superior to conventional imaging for the diagnosis of neck metastasis. A meta-analysis on 32 studies (1236 patients) [65] showed that PET sensitivity and specificity were 79% (95% CI, 72–85%) and 86% (95% CI, 83–89%). However, for patients with cN0, sensitivity of PET was only 50% (95% CI, 37–63%), whereas specificity was 87% (95% CI, 76–93%). A prospective study on 134 patients with oral SCC with palpably negative neck compared 18F-FDG-PET, CT and MRI [62]. 18F-FDG-PET was twice more sensitive than CT/MRI for detecting cervical nodal metastasis in patients with palpably negative neck (41.2% vs 21.6%, respectively, p 0.021). Histopathological analysis was used as the gold standard to validate the results obtained with different imaging techniques. The authors concluded that 18F-FDG-PET presented a false negativity rate (of occult neck metastasis) of 15% in T1–3 tumours. However, 18F-FDG-PET, even visually correlated with CT/MRI, was unable to reduce the 20% rate of false negative in patients with T4 tumour (neck treatment being mandatory regardless of PET results). Another study [66] evaluated 32 consecutive patients with oropharyngeal SCC undergoing 18F-FDG-PET and CT/MRI before surgery. All patients underwent curative resection of their primary tumours with also node dissection, with 7 having bilateral dissections, for a total of 39 neck sides. Each imaging modality was interpreted separately to assess primary tumour and cervical node status. Histopathology specimen (in 29 of 39 dissected neck sides and in 47 of 163 dissected cervical levels) showed that 18F-FDG-PET was more accurate than CT/MRI, both in detecting positive neck sides (28/29 vs 22/29, p 0.05) and on a level-by-level basis (45/47 vs 37/47, p0.05). 18F-FDG-PET identified metastatic lesions in approximately two thirds of the CT/MRI uninvolved nodes. A study on 36 patients with HNC clinically and radiologically N0 compared PET/CT and with neck dissection results [67]. PET/CT nodal sensitivity and specificity resulted 84.2% and 76.5% respectively. A prospective study assessed 91 patients with HNC and negative neck palpation findings [68]. PET/CT was more sensitive on a per-level basis than CT/MRI (69% vs 39%, p 0.001), as well as on a per-patient basis (71% vs 50%, p 0.011). PET/CT examination protocols are generally performed without the use of contrast medium, however there is increasing evidence supporting the use of CE-CT as part of routine PET/CT protocols [69,70]. There have been several reports of the possible superiority of PET/CE-CT over standard PET/CT in different clinical settings, including better local and nodal analysis [71,72]. Other studies confirmed the high accuracy of nodal staging by PET/CT, in particular, if CE-CT is used with the PET protocol [73,74].

In summary, 18F-FDG-PET has high diagnostic accuracy in the overall nodal staging of patients with HNC. Studies with pathological confirmation showed that PET/CT is similar

or slightly superior for detecting cervical nodal metastases compared to anatomical imaging (CT, MRI) in patients with clinically evident pathological neck nodes (≥cN1). PET/CT is not as accurate as neck dissection in the identification of occult cervical metastasis in patients without clinically evident neck nodes (cN0). PET/CT should be used to improve the nodal assessment in the context of multimodality imaging in patients with ≥cN1.

M staging

The presence of distant metastases is the most important predictor of patient survival in several cancers. Overall incidence of distant metastasis in HNC is relatively low (2–18%) [75]. Distant metastases frequently occur in the lungs and are routinely detected by chest CT (73% sensitivity and 80% specificity) [76]. Early detection of metastasis has a major impact on patient management avoiding unnecessary radical treatments [77-80]. A meta-analysis evaluated the accuracy of PET and PET-CT in the initial M staging of HNC. A total of 209 out of 1445 (14.4%) patients had distant metastasis or a second primary tumour. PET-CT presented an overall sensibility and specificity of 87.5% (95% CI, 78.7–93.6) and 95% (95% CI, 93.1–96.4) respectively [81].

Regarding the detection of bone metastases, another meta-analysis on 3000 patients showed sensitivity and specificity of 81% and 99% for PET, and 89% and 99% for PET/CT. PET/CT is superior to bone scintigraphy in detecting metastases. Bone scintigraphy relies on the osteoblastic response to bone destruction by cancer cells and the accompanying increase in blood flow. 18F-FDG-PET is more accurate than bone scintigraphy due to their frequent lytic characteristics [82].

PET/CT is superior to conventional imaging in detecting distant metastases. 18F-FDG-PET showed higher accuracy (90–95%) than CT for the detection of distant metastases [83-86]. Given the very high negative-predictive value (NPV), in case of negative PET scan, other imaging techniques are not necessary. Nevertheless, the PPV for detecting secondary primary tumours or distant metastasis is around 60%, suggesting that additional diagnostic methods are still recommended to exclude false-positive results [85].

Senft et al [84] assessed the added value of 18F-FDG-PET to chest CT in the screening of distant metastases in patients with HNC and high-risk factors (more than or equal to three lymph node metastases, bilateral lymph node metastases, lymph node metastases of >6 cm, low jugular lymph node metastases, regional tumour recurrence and secondary primary tumours). 145 consecutive patients with HNC underwent chest CT and 18F-FDG-PET. 18F-FDG-PET improved the pre-treatment screening of distant metastasis compared with chest CT, showing higher sensitivity (53% vs 37%) and PPV (80% vs 75%). Moreover, the authors

showed that the sensitivity of the combination of CT and 18F-FDG-PET was higher (63%) than the sensitivity of each of these techniques alone.

Ng et a[[83] prospectively compared 18F-FDG-PET and extended field contrast-enhanced-CT (from the skull base to the lower abdomen). A total of 160 patients with SCC of the oropharynx or hypopharynx underwent 18F-FDG-PET and extended-field CT to detect distant metastases or secondary primary tumours. In the entire study cohort, a total of 26 patients (16.3%) were found to have distant malignant lesions. Diagnostic yields of 18F-FDG-PET and extended-field contrast-enhanced-CT were 12.5% (20 out of 160 patients) and 8.1% (13 of 160 patients) respectively. The patient-based sensitivity of 18F-FDG-PET for detection of distant malignancies was 1.5 times higher than that of extended-field contrast-enhanced-CT (76.9% vs 50.0%, $p<0.039$), whereas the patient-based specificity of 18F-FDG-PET was not significantly lower than that of extended field contrast-enhanced-CT (94.0% vs 97.8%, $p <0.125$).

In summary, when compared with conventional imaging, PET/CT is a valuable tool to rule out the presence of distant metastases in HNC, especially in case of locally advanced tumours.

Cancer from unknown primary

The incidence of cervical metastases from unknown primary cancer (UPC) has been estimated to be around 2–9%. The absence of information about the primary tumour strongly influences the therapeutic approach (i.e. bilateral tonsillectomy, additional pharyngeal mucosa field irradiation) [87]. PET/ CT can identify approximately 30% of tumours in patients presenting cervical lymph node metastases from UPC, in whom the primary was not detected by the comprehensive diagnostic work-up including endoscopy and conventional imaging methods (CT or MRI) [88-94]. PET/CT should be performed before examination under anaesthesia for targeted pan-endoscopy and biopsy, avoiding potential false positives due to the inflammation that usually follows these kinds of procedures [95]. Thus, a rigorous physical examination is still essential, considering that small and superficial tumours may not have enough 18F-FDG avidity to be detected by PET/CT [55]. Zhu et al [96] performed a meta-analysis of 7 studies (246 patients). The primary tumour detection rate, sensitivity and specificity of PET/CT were 44% (95% CI 0.31–0.58), 97% (95% CI 0.63–0.99) and 68% (95% CI 0.49–0.83).

The largest prospective study evaluating the diagnostic performance of PET/CT in UPC has been published by Johansen et al [95]. The authors reported data about 60 patients presenting primary tumour detection rate of 30%, and sensitivity and specificity rates were 86% and 69%, respectively. However, this study had some limits. It used three different PET

modalities, and among them one was PET/CT, whereas in two cases, it was PET alone. in some cases PET was acquired for the whole body, in other cases for half body. Furthermore, the authors did not perform extensive comparison with other imaging modalities.
In summary, PET/CT is recommended to identify primary tumours in patients presenting with cervical lymph node metastases from UPC. PET/CT should be integrated with other diagnostic procedure to exclude the relatively high risk of false positive findings.

Second primaries

Second Primary Tumours (SPT) are detected in almost 10% of patients with HNC [97,98] particularly in patients with smoking history or negative for human papillomavirus [99]. The identification of synchronous or metachronous SPT can occur more frequently in the head&neck region and/or elsewhere (lungs, oesophagus, colon etc.), and it can influence the therapeutic approach and the prognosis of patients especially if presenting with HNC [84,100,101]. Strobel et al [97] evaluated the role of PET/CT for the initial staging of HNC in 589 consecutive patients for the detection of synchronous primaries. They detected 56 secondary cancers in 44 patients. 46 (82%) were found in the aero-digestive tract as follows: lung (26%), head&neck (15%) and oesophagus (6%). Nine synchronous cancers were detected by endoscopy and missed by PET/CT. The prevalence of synchronous primaries according to the standard of reference (including pan-endoscopy, bronchoscopy, oesophageal or colon endoscopy when necessary) was 9.5%. Of these synchronous primaries, 47 (84%) were detected in 41 patients (93%) by 18F-FDG-PET/CT. Interestingly, in 32 out of 40 patients (80%) with available follow-up, the treatment was modified because of the detection of a synchronous primary. The authors concluded that 18F-FDG-PET/CT detects a considerable number of synchronous primaries (8% prevalence) at the initial staging of patients with HNC. According to Haerle et al [98] synchronous primary tumours were detected in 4.5% of patients by pan-endoscopy compared to 6.1% by PET/CT. Indeed 26% of lesions detected on PET/CT were within the coverage of the panendoscopy.18F-FDG-PET/ CT was superior to pan-endoscopy. The sensitivity, specificity, PPV and NPV for pan-endoscopy and 18F-FDG-PET/CT were 74%, 99.7%, 93%, 98% and 100%, 95.7%, 59%, 100% respectively. According to these studies, with a negative 18F-FDG-PET/CT, the extent of endoscopy can be reduced to the area of the primary tumour.
In summary, PET/CT is an accurate method for detecting second primaries, with a high NPV. Nonetheless, it should be pointed out that due to a low PPV (approximately 60%) in this setting, additional diagnostic methods are necessary to exclude false-positive results (inflammation and hyperplasia in the head&neck region or intestinal polyps in the GI tract). PET/CT should be performed before endoscopy and biopsy to avoid false-positive results.

1.4.2 Principles of PET/CT

The principle of PET is that radiation emitted from a radiopharmaceutical injected intravenously into a patient is registered by external detectors positioned at different orientations. The isotope distributes within different tissues according to the carrier molecule (isotopic labelling) and emits a positron (a positively charged electron). This positron in turn interacts with a free electron and an annihilation reaction occurs, resulting in the production of two 511-KeV photons emitted at almost 180º to each other. The directionality of the annihilation photons (two 511-keV annihilation photons emitted in opposite directions) provides a mechanism for localizing the origin of the photons and hence, the radioactive decay process that resulted in their emission (Figure 1.4.2.1). This permits the distribution of radioactivity to be estimated by filtered back-projection or iterative reconstruction methods.

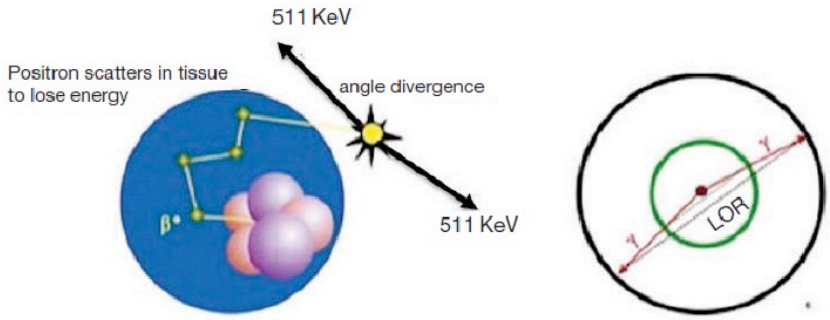


Figure 1.4.2.1. Annihilation coincidence detection (ACD). When a positron is emitted by a nuclear transformation, it scatters through matter losing energy and annihilates with an electron, resulting in two 511-keV photons that are emitted in nearly opposite directions (left). When two interactions are simultaneously detected within a ring of detectors surrounding the patient (right), it is assumed that annihilation occurred on the line connecting the interactions (line of response, LOR). ACD acts as a collimator for the positron emission tomography (PET) scanner (electronic collimation) by determining the path of the detected photons.

A PET scanner consists of several rings of detectors around the patient. The detector crystals are often made of bismuth germanate or lutetium oxyorthosilicate. Electronically coupled opposing detectors simultaneously identify the pair of γ photons by using coincidence detection circuits that measure annihilation events within 10-20 ns. The annihilation reaction is thus known to occur along the line joining the two detectors. Raw PET scan data consist of a number of these coincidence lines, which are recognised as projections. The PET system computer then reconstructs the transverse images from the projection data to form a number of contiguous axial slices. Multi-slice PET scanners permit a simultaneous acquisition of up to 45 slices over an axial distance of 16 cm. The spatial resolution of the PET system is limited to 5 mm. Modern scanners associate a PET and CT imaging system. PET images are corrected and fused with the CT images to facilitate anatomic localization of the radiopharmaceutical [102]. An example of PET/CT scanner and PET/CT acquisition-reconstruction-fusion is presented in Figure 1.4.2.2 and 1.4.2.3.

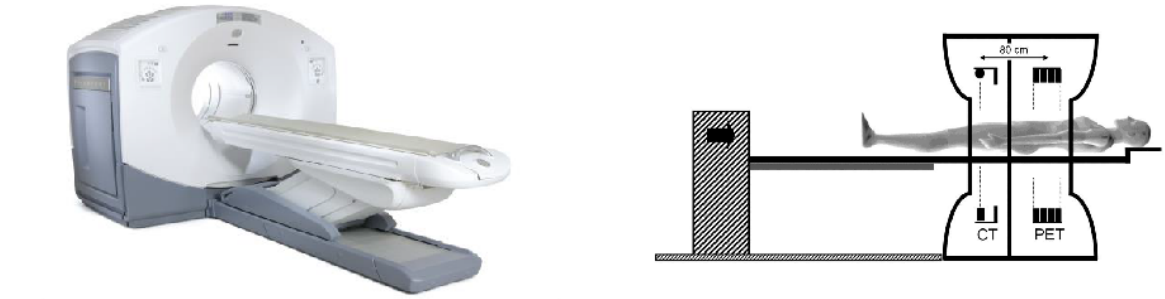


Figure 1.4.2.2. Example of PET/CT scanner from GE Healthcare (a) and schematic view of the equipment (b). Generally CT is acquired first (CT AC and CT Std) followed by the PET scan on the region of interest. PET images are reconstructed, corrected by attenuation and fused with CT.

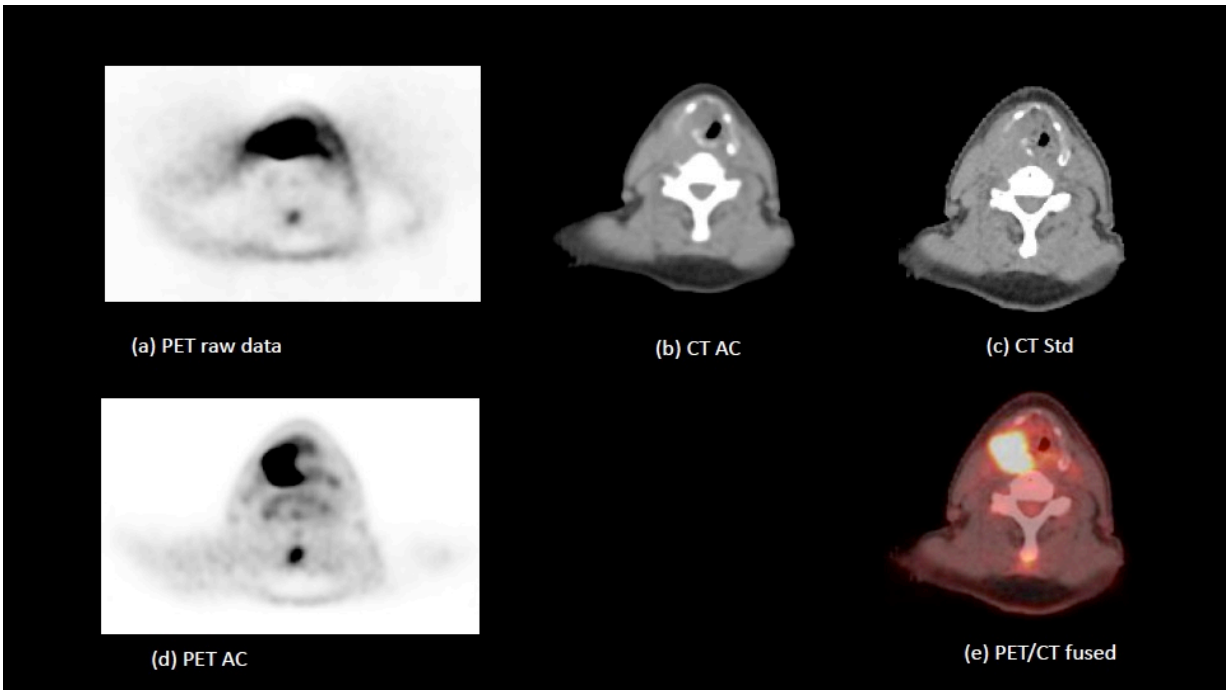


Figure 1.4.2.3. Example of PET/CT acquisition-reconstruction-fusion for a patient with cancer of right pyriform fossa. PET raw data (a) is corrected by the CT Attenuation Correction (b). Attenuated Corrected PET (d) is fused with the Standard CT (c) giving PET/CT fusion (e). Usually CT Std is acquired without contrast. A contrast enhanced CT Std can be used for better anatomical details.

There are many cyclotron generated positron-emitting radiopharmaceuticals (e.g., 11C, 13N, 15O, 18F, and 68Ga). To date, most clinical applications of PET scans have employed 18F-labeled fluoro-2-deoxyglucose (18F-FDG). 18FFDG is a glucose analogue radiopharmaceutical that has a half-life of 110 min and is commonly used for studying brain and heart glucose metabolism and for detecting cancer. However, the radiopharmaceuticals 11C, 13N, and 15O are primarily used in direct metabolic studies as they have significant physiologic potential because they can replace atoms in molecules that are essential for metabolism. The utility of PET is based not only on its sensitivity but also on the fact that the most commonly used radiopharmaceuticals are isotopes of elements that occur naturally in organic molecules [103].

Standardized uptake value (SUV) is often used in PET imaging for a semi-quantitative analysis. SUV is usually calculated as a ratio of (1) the mean region of interest (ROI) activity in Mega-Becquerels per milliliter and (2) the injected activity in Mega-Becquerels, divided by the body weight in grams.

1.4.3 FDG and alternative tracers in head&neck cancer

Most malignancies show an altered metabolism which can be visualized by PET, a technique commonly used for in vivo molecular imaging. In head&neck oncology, PET has become more and more synonymous to FDG PET. FDG PET is now commonly used in diagnosing high-staged tumours and unknown primaries, and more recently, as a therapy evaluation after (chemo-)radiation and for a better delineation of the tumour before radiotherapy. FDG, 18F-fluoro-2-deoxy-D-glucose, is a sugar derivative, which visualizes glucose metabolism. However, increased glycolysis is just one part of the changed metabolism in malignancies and most malignancies show a much wider alteration of metabolism.
There are alternative PET tracers to FDG for the head and neck region which are presented in the following paragraphs.

Amino acids

Amino acids are building blocks of proteins and precursors for many other bio-molecules. Furthermore, they are crucial in many metabolic cycles. Many of these processes are up-regulated in cancer cells, leading to an increased need for amino acids. Several amino acid-based radiopharmaceuticals have been developed. In vitro and in vivo studies have shown an enhanced uptake of amino acid-based radiopharmaceuticals in malignancies compared to the surrounding tissues. In contrast to FDG, the uptake of amino acid-based radiopharmaceuticals is low in hypoxic inflammatory tissues. Conditions in the early phase after radiotherapy are characterized by hypoxia and inflammation. In theory, amino acid-based radiopharmaceuticals should therefore be better suited to differentiate between post-radiation inflammation and residual cancer. Amino acids have been successfully labelled to 11C and 18F. 11C-labeled amino acids are easier to produce and more stable. Unfortunately, however, the short half-life of 11C-labeled amino acids urges the use of an on-site cyclotron, which has hampered its use on a larger scale. Consequently, whereas in the past, 11C-labeled amino acids were extensively studied, nowadays research is focused on fluorinated analogues with longer half-life.

L-[Methyl-11C]-methionine (MET)

MET has been the most frequently used radiolabelled amino acid. The main reason is the convenient production that allows rapid synthesis with high radiochemical yields without the need for complex purification steps. After injection, MET is rapidly distributed and a high uptake is immediately observed in the liver, kidney, pancreas and salivary glands [104]. There is some MET uptake in inflamed tissue, but the uptake of MET in tumour cells is

significantly higher. Autoradiography shows MET uptake predominantly in viable tumour cells, with low uptake in macrophages and non-viable tumour cells [105]. In addition to the large-scale MET use in visualization of intracranial tumours, lymphoma, melanoma, breast, pelvic, parathyroid and lung cancer have also been visualized with MET. Preclinical studies validating MET in the evaluation of (chemo) therapy, showed a faster decline of MET in the post-radiation phase compared to FDG [106,107]. Minn et al. [108] reported that MET was better correlated with tumour proliferative activity in squamous head and neck carcinoma than FDG, a finding that might be due to the relation of methionine to DNA metabolism. Up to now there have been only a limited number of studies dealing with methionine in HNC. The number of patients included has been small and the results alternating, which make the findings hard to interpret. Eight studies dealt with HNC and MET PET: three feasibility studies, two in which MET and FDG PET were compared and three evaluations of therapy studies [109-115].

The three feasibility studies showed that 68 of the 70 tumours were visualized with MET PET. Unfortunately, only in one study, the population was homogeneous, with only small laryngeal tumors [115]. The other two studies included different head&neck subsites and stages with variable histology. The studies of Lindholm and Geets compared FDG and MET in 37 patients with untreated HNC. Again all subsites, stages and histology were included. FDG and MET visualized the same 36 tumors [111-113]. Cook compared MET and FDG and concluded that FDG showed better anatomical details and MET had a better tumour background ratio. Physiological activity of MET in bone marrow and salivary glands did not interfere with the visualization of the primary site, but it was observed that it could hamper the visualization of lymph node metastases at level I and II [104]. In the study by Lindholm, MET PET was performed before and after radiotherapy. All patients with SUV of more than 3.1 after radiotherapy had residual disease, while three of the ten patients with a post-radiotherapy SUV of less than 3.1 showed residual disease. This resulted in a sensitivity rate of 0.75 and specificity of 0.70 [111]. Nuutinen et al performed PET before RT and 2 weeks after completing RT in 13 patients. In all patients, the SUV dropped, but there was no difference in the SUV values between the patients who were disease free 2 years later and those who developed a recurrence [114]. In contrast, Chesnay et al described that 25% or more decrease in the SUV correlated with a tendency to respond better to chemotherapy. In their study, a MET PET was performed before and 2 weeks after three courses of cisplatin and 5-FU in 14 patients with T3 or T4 hypopharyngeal cancer. After 2 years, 83% of the group with a 25% decline or more in the SUV was alive. The group with a decline of less than 25% showed a survival rate of only 57% [109]. These publications show that the excellent results obtained with MET in vitro are not confirmed in vivo and are more or less

similar to those obtained with FDG, although, especially with regards to therapy evaluation, there is not much data. As mentioned before, the specificity of FDG is low in the early post-radiation phase and MET could be a viable alternative. To answer this question, however, more research would be necessary.

L-1-[11C]-Tyrosine (TYR)

Another essential amino acid is tyrosine. Tyrosine can be labelled with 11C as well as with 18F, in the form of fluormethyl-tyrosine or fluor-ethyl-tyrosine. The few studies (five) concerning TYR and HNC show promising results [116-120], however the laborious production process is a serious limitation to using TYR on a larger scale. Therefore TYR is now largely replaced by either MET or fluorine- labelled analogues.

L-3-[18F]-Fluoro-alpha-methyltyrosine (FMT)

In experimental tumours, FMT shows a higher contrast of tumour to normal tissue and a higher uptake compared to both FDG and C11-MET in preclinical studies [106, 121-123]. Murayama et al. [106] showed in an animal study a much steeper decline of FMT compared to FDG shortly after irradiation of an induced tumour, which is of special interest because results obtained with FDG in humans in the early post-radiation phase have been disappointing. Unfortunately, the results obtained in vivo are less impressive and comparable to those obtained with C11-labeled amino acids. However, most of the FMT studies deal with intracranial tumours, and only a few publications report about extra-cranial tumours. These studies show a sensitivity of FMT, which is comparable to or somewhat lower than that obtained with FDG but with a better specificity. There is only one report dealing with head and neck cancer and FMT. FMT and FDG PET were performed in 36 patients with an untreated maxillofacial malignancy by Miyakubo. FMT and FDG visualized all malignancies, but FMT showed a better contrast between tumour and surrounding tissues [124]. As from one single study, one cannot come to any conclusion, so more studies need to be conducted.

O-(2-[18F] Fluorethyl)-L-tyrosine (FET)

There are four studies dealing with HNC and FET: one feasibility and three studies in which a FET and a FDG PET were performed. A feasibility study by Pauleit et al. [125] showed that all eight HNC, as well as the other two squamous cell carcinomas were visualized by FET, in contrast to adenocarcinoma, of which none of the 28 was visualized. The first study included 21 patients with suspicion of squamous cell carcinoma of the head and neck. All 21 patients received FDG and FET PET before treatment. The sensitivity of FET was 75%

and the specificity 9 %. The sensitivity of FDG was 93% and the specificity 79% [126]. The second study was conducted by Balogova. Twenty-seven patients were included, 15 for initial staging and 12 for therapy evaluation after radiation. The sensitivity of FDG and FET was 95 and 64 %, and the specificity 63 and 100 %, respectively [127]. The third study including 13 patients showed a sensitivity for FDG and FET of respectively 89 and 70% and a specificity of 50 and 90% [128]. All authors came to the same conclusions: although a better specificity compared to FDG was confirmed, FET did not appear to be suited as a first-line PET tracer in head&neck squamous cell carcinoma imaging due to insufficient sensitivity and therefore cannot replace FDG for staging head and neck tumours. However, it was useful in the few selected cases to favour a wait and see attitude after radiation when a FDG positive and FET negative lesion was found. These findings indicate that FET may become a supplement to FDG in case of a positive FDG PET during treatment evaluation.

Nucleosides

Nucleosides are the building stones of DNA and therefore directly linked to cell proliferation. The only nucleoside that has been clinically used is thymidine.

Thymidine (FLT)

The nucleoside thymidine is exclusively linked to DNA. Thymidine is phosphorylated by the enzyme thymidine kinase one (TK1) and phosphorylated thymidine is trapped intracellular. During DNA synthesis, TK1 activity increases almost tenfold and is an accurate reflection of cellular proliferation [129]. 11C and 18F-labeled thymidine are available as tracers. C-11 thymidine has never been used for clinical purposes in the literature. In contrast, much more is known about 18F-labeled thymidine (FLT). Results of FLT studies obtained by visualizing primary breast, oesophageal cancer and melanoma are comparable to the results obtained with FDG. There have been four head&neck studies. Cobben et al and Been et al visualized primary laryngeal cancers. These three small studies (17, 19 and 14 patients, respectively) showed sensitivity rates of. 85% for both FLT and FDG [130,131]. Been's study included post-radiation patients as well. Three of the 14 patients developed recurrent disease after primary radiotherapy, 2 were visualized by FDG and 1 by FLT. Troost et al. [132] demonstrated in 10 stage II or higher head and neck carcinomas an elevated uptake in metastatic as well in non-metastatic lymph nodes. This resulted in sensitivity of 100% and specificity of 16.7%. One could conclude from these studies that the results obtained with FLT in staging head and neck cancer have not been promising.

Far more interesting are the results obtained in therapy evaluation because a decrease in the cellular proliferation rate is one of the earliest events in the response to successful tumour treatment. Murayama et al irradiated mice with inoculated squamous cell carcinoma. The tumour uptake of FLT decreased in the first day after radiation while the uptake of FDG decreased after 7 days and MET after 3 days [106]. FLT declines rapidly during radiation, most likely because the surviving cancer cells will not be in a proliferating phase. Therefore, a sharp decline in the uptake of FLT does not necessarily mean an excellent response to radiotherapy.

Three clinical HNC studies have been conducted. Menda et al showed a steep decline in SUV of FLT in eight patients after 10 Gy [133]. In Troost's study, ten patients with oropharyngeal cancer underwent FLT PET/ CT before and twice during treatment. The SUV FLT declined already after 1 week of radiotherapy, while the gross tumour volume on CT declined after 4 weeks [134]. FLT and FDG PET have been performed shortly before and 10 weeks after radiotherapy in ten patients with laryngeal cancer. The sensitivity for FDG to detect residual tumour was higher when compared with FLT. FDG missed one out of three residual tumours, whereas FLT missed two of the three residual tumours [130]. These results are not promising.

Choline

Choline is a precursor for the biosynthesis of phospholipids, which are essential components of all cell membranes. Biosynthesis of the cell membrane is enhanced in malignancies. In theory, choline could be an excellent radiopharmaceutical to visualize tumour proliferation. Choline has been successfully linked to 11C and, more recently, to methyl 18F. Due to its reduced renal excretion and up-regulation of choline kinase in prostate cancer, 11C-choline is becoming more and more the first choice in molecular imaging of prostate cancer. Most of the publications deal with prostate cancer. There are only a few publications concerning HNC. These studies show that the sensitivity and specificity rates of 11C-choline are similar or slightly worse compared to those obtained with FDG in a heterogeneous head&neck population [135,136]. In theory, 11C-choline could be an alternative to FDG in the early post-radiation phase because 11C-choline differentiates well between radiation induced tissue changes and local tumor recurrence. However, clinical data on HNC have been lacking so far.

Hypoxia-specific tracers

Patients with hypoxic HNC have a higher risk of local recurrences and distant metastases. Moreover, hypoxic tumours are more resistant to radiation and chemotherapy [137,138]. Consequently, visualizing hypoxic areas within tumours may enable application of increased radiation doses to these areas, thus increasing the possibility of successful outcome. Preclinical studies showed that PET can visualize hypoxia in vivo. Several hypoxia tracers have been tested, including 18F-fluoromisonidazole (18F-FMISO), 18F-fluoroazomycin arabinoside (18F-FAZA), 60Cu-labeled methylthiosemicarbazone (60Cu-ATSM), 18F-2-(2-nitro-1H-imidazol-1 yl)-N-(2,2,3,3,3-pentafluoropropyl)-acetamide (18F-EF5) and the single photon (SPECT) tracers 123I iodoazomycin arabinoside (123I-IAZA) and 99Tcm-labeled dioximes (99Tcm-HL91).

18F-FMISO

18F-FMISO has been used most frequently to visualize tumour hypoxia in HNC patients. 18FFMISO is a 2-nitroimidazole molecule. Imidazole derivates are trapped in hypoxic cells. A relatively large study by Rajendran et al [139] found that 18F-FMISO PET scanning was effective in quantifying regional hypoxia in a series of 73 HNC patients. A study by Eschmann et al [140] concluded also that 18F-FMISO PET has the potential to predict response to radiotherapy. Another clinical study by the same research group showed the value of correlated 18F-fluorodeoxyglucose (18F-FDG) and 18FFMISO PET scanning in predicting treatment response in HNC patients [141]. The clinical application of the most frequently applied tracer, 18F-FMISO is, however, hampered due to high lipophilicity and slow clearance from normoxic tissues, which leads to a low target-to-background ratio.

18F-FAZA

18F-FAZA, a relatively new imidazole radiopharmaceutical, shows faster clearance from blood and non-target tissues and is considered to be a better tracer for detection of hypoxia. Although 18F-FAZA PET clinical studies have been pubilshed, there are few clinical studies in HNC research. In a pilot study, Souvatzoglou et al evaluated the feasibility of 18F-FAZA PET in 11 untreated HNC patients. The other purpose of the study was to determine the proper time of clinical imaging. This study acquired good quality 18F-FAZA PET images, suitable for clinical purposes. The authors suggested further studies for analysing intratumoral differences in 18F-FAZA kinetics [142]. In a phase I/II study Postema et al showed clear 18F-FAZA uptake in the primary tumour in five of nine HNC patients; in two of those patients additional uptake in cervical metastases, and in one patient uptake in a neck

metastasis but not at the primary site was detected. Based on their data, the authors concluded that, based on the good imaging properties, 18F FAZA is a very promising tracer for assessing tumour hypoxia [143]. In summary, theoretically hypoxia markers have great potential for targeted therapy of hypoxic tumours either by applying hypoxia sensitizers or by increasing radiation dose using specific intensity modulated radiotherapy techniques. However, clinical data are limited especially for HNC.

Monoclonal antibodies

Advances in molecular and cellular biology have facilitated the discovery of novel molecular targets on tumour cells, for example, key molecules involved in proliferation, differentiation, cell death and apoptosis, angiogenesis, invasion, and metastasis. Monoclonal antibodies can be bound to these molecules, and by linking monoclonal antibodies to a positron emitting radionuclide, molecular targets can be visualized by PET. However, the development of radiolabelled monoclonal antibodies (MAbs) has been limited, due to several requirements that need to be fulfilled. The emitter should allow facile, efficient, and stable coupling to the MAb. The physical half-life (t1/2) should be compatible with pharmacokinetics of the monoclonal antibody. In practice, to obtain sufficient binding, the half-life should be several days. Consequently, the half-life of C11 and shorter-lived isotopes are too short to allow labeling of MAbs, even as fragments. The binding time of MAb fragments are shorter. The half-life of 18F could be sufficient in case of Mab fragments. Unfortunately, however, the weakness of the bond between the 18F-labeled MAb fragment and the target hampers their development. No clinical studies have been published showing a stable 18F-labeled MAb. More suitable are long-lived positron emitters like 124I, 64Cu and 89Zr.
The literature only shows seven head&neck studies. Niu et al labeled panitumumab, a Mab against EGFR, with 64Cu, and tested it in nude mice bearing human HNC cell lines. The results were disappointing: tumours with the lowest EGFR protein expression showed the highest 64Cu-DOTA-panitumumab accumulation, whereas SQB20 tumours with the highest EGFR expression showed the lowest 64Cu-DOTApanitumumab accumulation. An explanation could be the poor penetration of the antibody through perivascular tissues resulting in a low accumulation of 64Cu DOTA-panitumumab in SQB20 tumours [144]. Eiblmaier et al labelled cetuximab and showed positive correlation between 64Cu-DOTA-cetuximab and EGFR expression in five head&neck cell lines [145]. Verel et al [146] showed that an injected head&neck tumour cell line could be visualized by 124I-L19-SIP in eight nude mice. L19-SIP is an antibody fragment directed against the ED-B domain of fibronectin an excellent marker for tumour angiogenesis and has been successfully labelled to 124I. The

same group published a study in which nine head&neck tumor cell lines were injected in six nude mice. At the time of imaging, the volume of the tumours was less than 50 mm^3. All tumours could be visualized by 124I-L19-SIP [147]. Perk et al visualized the anti-MET MAbs DN30. The MET oncogene encodes the tyrosine kinase receptor for hepatocyte growth factor (HGF). On his turn, HGF controls genetic programs leading to cell growth, invasion, metastasis, and protection from apoptosis. DN30 was linked to 89Zr. An excellent correlation was found between PET imaged Zr tumor uptake (89) and ex vivo-assessed (89) Zr tumor uptake. A feasibility study with 89Zr-labeled c-mAb U36, a monoclonal antibody against CD44, showed that all primary tumours and 18 of 25 positive neck levels could be visualized by immunoPET [148]. In another study with 89Zrlabeled c-mAb U36, CD44 was found to be homogeneous in 96% of all primary HNC and lymph node metastases. This study showed in 20 HNC patients scheduled for surgery, an increasing uptake in time of 89Zrlabeled antibody-MAb U36 in metastatic lymph nodes. The results were comparable with those obtained with CT and MRI [149]. It is an exciting thought that specific tumour characteristics can be visualized, not only in samples but also in vivo by dynamic imaging of the whole tumour. However, the application of monoclonal antibody tracers on a larger scale is hampered by the hard and labour intensive production of these radiopharmaceuticals. Therefore, the number of publications is still small at this time, and it is difficult to forecast what the actual value of PET imaging of monoclonal antibodies will be in the near future.

In summary tracers other than FDG have only been used on a small scale and have not become part of routine procedures in HNC. The data show that amino acid-based radiopharmaceuticals have no additional value to FDG as part of the dissemination work up, in the search for unknown primaries or in defining the gross tumour volume. However, amino acid-based radiopharmaceuticals may play a role in therapy evaluation after (chemo-)radiation, especially in the early post-radiation period, because FDG has problems in differentiating radiotherapy sequels from residual disease, resulting in high sensitivity, but lower specificity, rates. Amino acid based radiopharmaceuticals may present better specificity rates in this situation, although this is only documented on a very small scale and only for FET and TYR in vivo. The C-11 amino acid tracers, like methionine, show both excellent sensitivity and specificity. However, the relative short half-life of the carbon isotope hampers further introduction as it requires an on-site cyclotron. Therefore, 18F-labeled amino acid analogues will undoubtedly be further developed and investigated. There is no additional value for using FLT and choline in the head&neck area. Hypoxia tracers and labelled monoclonal antibodies can visualize specific characteristics of a tumour. Tumour hypoxia can be assessed in vivo with a number of available radiopharmaceuticals. Its role

will be to optimize (chemo-) radiation strategies in the future. However, more research is necessary to warrant a clinical introduction. The tracking and quantification of monoclonal antibodies with long-lived PET-isotopes are an exciting novel option to improve diagnostic imaging and to guide MAb-based therapy. Here again further research will be needed, before a wider introduction into clinical practice can be warranted.

1.4.4 PET/CT and clinical impact on treatment decisions

Although PET/CT imaging is effective for the staging of HNC, its impact on patient management remains controversial. Indeed, to date, the overall impact of PET/CT on treatment decisions in HNC has been rarely explored compared with the number of studies assessing the impact of PET on staging. However, there are four prospective trials that have specifically analysed the impact of PET/PET-CT on treatment approaches for HNC. These studies addressed at the same time the issue of the impact of PET on the initial staging and management of patients: globally, PET imaging data changed the original treatment plan in approximately 10%-30% of patients [152-155]. The largest trial, published by Lonneux et al [153] included 233 patients (Stages I–IV) and reported a modification in the original treatment plan in 32 patients (13.7%). In 12 patients (5.2%), the modification was classified as medium (the therapeutic modality remained the same, but PET altered the treatment planning). In 20 patients (8.6%), the impact of PET on patient management was classified as high (change in treatment intent and/or treatment modality, e.g. curative to palliative, surgery to chemoradiation and so on). Interestingly, one of the studies [155] assessed together the usefulness of PET/CT for staging and its overall impact on management plans specifically in patients with Stages III and IV HNC where the treatment plan was altered in 22/84 (26%) patients. These results are in agreement with the NCCN and NCI guidelines [32,33].

In summary, PET/CT may be considered in the diagnostic work-up of locally advanced H&N SCC. Data from the literature suggested that PET/CT can modify the treatment decision plan in approximately 30% of the patients.

1.4.5 FDG PET in radiotherapy planning

CT is the primary imaging modality in Radiotherapy Planning (RTP). The CT images are acquired with the patient in supine position, immobilized with a head support and a rigid customized mask to increase set-up accuracy and prevent movement during image acquisition. All other imaging modalities (such as PET or MRI) are considered as

complementary [156]. The secondary images in RTP will have to be registered (fused) to the primary planning CT scan. When the PET and RTP CT images are acquired on separate scanners, often in position that does not correspond exactly to the treatment position, a registration module in the RTP computer system can be used to fuse images. Regardless of the imaging data used (i.e. separate PET or PET/CT) correct co-registration of the PET data with the CT data used for RTP must be verified, since the difference in spatial localization of tumour may lead to false estimation of the gross tumour volume (GTV). Ideally, the fusion process can be executed automatically by a hybrid PET-CT-dedicated RTP scanner using the same immobilization devices and reproducing the radiation delivery conditions [156].

Recognizing the potential of PET/CT-guided treatment planning, some authors investigated the role of PET in RTP, specifically for the correct delineation of lymph nodes. Schinagl et al [157] compared the volume of metastatic lymph nodes between 18F-FDG-PET/CT segmentation (by ten methods) and CT with the volume as determined by pathological examination. They concluded that beyond the detection of lymph node metastasis (staging), PET has no additional value over CT for the delineation of lymph nodes.

Despite the limited role in improving the delineation of nodes, PET-CT seems to have a main role in improving the definition of the primary tumour. PET/CT information is frequently integrated in RTP. Nevertheless, the use of 18F-FDG-PET for target volume delineation in RTP for HNC has been mainly evaluated in single institution studies [158-161].

Different segmentation methods have been proposed. Visual interpretation of the PET signal, considered the most intuitive method for segmentation, has been commonly applied in many studies. The main limit of this approach is that it is a highly operator-dependent process, and it is influenced by window-level settings. This is one of the major weakness in the use of PET-CT in the target volume delineation of HNC. This variability could be reduced by using a more objective methodology: isocontouring based on a fixed standardized uptake value (SUV) such as SUV of 2.5-3 g/l or relative thresholds such as a percentage of the maximum tumour intensity (40% SUVmax, 50% SUVmax). Nevertheless, according to this method, several structures containing high physiological 18F-FDG uptake, such as the tonsillar area or the vocal cords, can be incorrectly included in the segmented area. Therefore, models using a fixed threshold relying on SUV are somehow debatable [162,163].

To overcome this issue, several authors successfully developed advanced adaptive relative threshold segmentation methods based on maximal tumour uptake, background uptake, tumour dimensions and tumour grade [164,165]. Thereafter, other methods including gradient-based detections have been introduced. In brief, this method relies on the watershed transformation and hierarchical cluster analysis, to allow a better estimation of the gradient intensity. This method allows automatic delineation and therefore is operator independent

process. Most studies comparing GTV definitions using 18F-FDG-PET against CT or MRI reported a decrease in the GTV, especially when using more sophisticated segmentation methods [166].

Few groups have validated delineation process using different imaging modalities against surgical resection specimens. In general, all imaging modalities overestimated the tumour extension compared with surgical specimen. None of the image modalities (CT, MRI or PET) completely encompassed the surgical specimen volume because of an underestimation of superficial tumour extension in the mucosa [167-171].

According to Daisne et al [55] the GTV delineated from 18F-FDGPET applying an adaptive signal-to-background method was significantly smaller than GTV delineated by CT or MRI. In addition, GTV-PET was the closest volume to the pathological GTV obtained from surgical specimen. PET delineated smaller volumes than CT or MRI. Nevertheless, GTV contours on PET were not totally encompassed by those delineated with CT or MRI. Geets et al [159] validated a gradient-based method in seven patients with laryngeal carcinoma. The calculated volumes for laryngeal tumours according to this methodology were compared with the macroscopic specimens and, additionally, with the volumes obtained applying the source-to-background ratio developed by Daisne et al [55]. The gradient-based method proved to be more accurate than the source-to-background ratio but neither the threshold-based nor the gradient-based volumes encompassed completely the laryngeal specimens. In a recent multicentric prospective study by Leclerc et al [172] the primary tumour was automatically delineated on the 18F-FDG-PET images using a gradient-based method previously described by this group. They confirmed that the use of 18F-FDG-PET translated into smaller GTV, clinical target volume and planning target volume for the primary tumour volumes compared to CT, lowering the dose to the organs at risk.

There are studies with other tracers such as fluorine-18 fluorothymidine (18F-FLT) evaluating promising PET-segmentation methods for delineation of the proliferative tumour volume (PV). In contrast to 18F-FDG, 18F-FLT does not accumulate in inflammatory tissue which is frequently found in/near primary head&neck tumours or is induced during the course of chemo-radiation [173]. Arends et al [174] evaluated 46 patients who underwent 18F-FLT PET/CT prior to treatment and in the second and fourth week of therapy. The goal of the study was to compare three semiautomatic PET segmentation methods for the definition of the target volume in primary HNC on sequential 18F-FLT PET images before and during chemo-radiation. The following semiautomatic segmentation methods were applied to sequential PET scans: background-subtracted relative-threshold level, a gradient-based method using the watershed transform algorithm and hierarchical clustering analysis and a fuzzy locally adaptive Bayesian algorithm. The authors concluded that fuzzy locally

adaptive Bayesian algorithm (FLAB) was the best performing method for segmentation on repeat 18F-FLT PET/CT scans during chemo-radiation. FLAB is less sensitive to image noise than the other segmentation approaches tested in the study. This finding may have other potential implications for radiotherapy indicating that FLAB is a promising candidate for radiation target volume adaptation based on sequential 18F-FLT PET scanning.

Currently, there is still no consensus (national/international) regarding the best method to use for delineation. Therefore, data from 18F-FDG-PET can complement other diagnostic imaging modalities for management decisions and guidance of radiotherapy, but it cannot replace physical examination or MRI/CT scans to achieve significant details such as assessing invasion of tumour-surrounding tissues [171]. Moreover, defining the primary tumour boundaries with PET is an unresolved task.

In summary, current evidence is based on numerous heterogeneous small studies with multiple methodologies for different research questions. PET-based radiotherapy is a promising modality to improve contouring accuracy. PET is the imaging modality that defines the closest volume to the pathological specimen. The main drawback is the lack of standardized method for functional volume segmentation, which highly influences the size and shape of the resulting GTV. Currently, the most accurate segmentation method seems to be the gradient-based method validated by Geets et al [159]. However, it may not completely encompass the tumour specimen volume. This issue is more relevant when considering superficial mucosal spread. The use of FDG-PET/CT in radiotherapy target delineation for HNC is recommended for locally advanced disease. PET volumes should preferably be delineated using user independent segmentation algorithms [176].

1.4.6 Monitoring response to chemo-radiotherapy

Early detection of residual or recurrent disease following radiotherapy is a diagnostic challenge owing to post-treatment anatomical distortions, mostly related to oedema and fibrosis [176]. The key role of a diagnostic tool evaluating treatment efficacy is to correctly identify patients requiring salvage-tailored treatments. An early detection of the relapse could help in the selection of patients who could be successfully retreated [177]. In this setting, 18F-FDG-PET/CT is an interesting modality to evaluate response to treatment, as it can assess metabolic activity-rendering malignant process. Isles et al [178] performed a meta-analysis reporting that 18F-FDGPET (without CT) is a highly accurate tool for monitoring response and detecting relapse after chemo-radiotherapy (for both the primary site and lymph nodes).

Several studies have demonstrated that 18F-FDG-PET/CT also has a higher accuracy in the detection of recurrent lesions compared with CT and MRI [179-183]. These results obtained with PET/CT are not significantly different from those obtained with PET alone.

The timing of PET/CT after the treatment is crucial [184-188]. It is widely accepted that PET has a high NPV (around 90%) if it is performed at least 8 weeks after chemo-radiotherapy. Therefore, a negative PET scan after treatment appears to be a consistent predictor of the absence of residual tumour [189]. According to other reports, more accurate evaluation is possible when PET/CT is performed 8–12 weeks after treatment [184]. The meta-analysis of Gupta et al showed a weighted mean (95% CI)-pooled sensitivity, specificity, PPV and NPV of post-treatment 18F-FDG-PET (CT) for the primary site of 79.9% (73.7–85.2%), 87.5% (85.2–89.5%), 58.6% (52.6–64.5%) and 95.1% (93.5-96.5%), respectively. Similar estimates for the neck were 72.7% (66.6–78.2%), 87.6% (85.7–89.3%), 52.1% (46.6 57.6%) and 94.5% (93.1–95.7%), respectively. Moreover, two recent studies showed even further increased accuracy with delayed PET/CT performed approximately 4 months after treatment with NPVs reaching 100% [187,188]. Intuitively, delaying a response evaluation tool would surely increase its accuracy. However, there is no homogeneous data for optimal window for salvage treatment; probably, it would be wise not to postpone salvage surgery beyond a clinically reasonable point.

There is debate regarding the need for elective neck dissection after radical chemoradiotherapy. There are two prospective studies [185,186] addressing the status of neck adenopathy of node-positive HNC that had 18F-FDG-PET/CT at least 12 weeks after chemoradiotherapy. Porceddu et al [185] prospectively evaluated 112 patients presenting with radiological nodal complete response. Residual CT nodal abnormalities were present in 50 patients (45%): 41 were PET negative and 9 were PET positive. Patients with residual CT nodal abnormalities and negative PET were observed regardless of residual nodal size. Importantly, 41 of the 50 patients with a residual nodal abnormality were spared a neck dissection on the basis of negative post-therapy PET, with no subsequent nodal failures in this group. Wang et al [186] prospectively evaluated 44 restaging PET/CT between 12 and 17 weeks after radiotherapy completion, and 10 PET/CT performed in the follow-up of 44 patients. Imaging data were compared with clinic-pathological outcomes. For cervical lymph nodes, sensitivity was 100%, specificity was 98%, PPV was 92% and NPV was 100%. Therefore, both these prospective studies concluded that PET-guided management of the neck after chemo-radiotherapy appropriately spares neck dissections in patients with complete response or presenting with negative PET and residual CT lesions [185,186]. Mehanna et al [190] published a prospective, randomized controlled trial assessing the non-inferiority of PET/CT-guided surveillance (evaluation was performed 12 weeks after

definitive chemo-radiation). Neck lymph node dissection was only indicated when PET/CT presented an incomplete or equivocal response in a total of 564 patients with locally advanced HNC (Stage N2 or N3 disease), who underwent chemo-radiation for primary treatment. Patients were considered to have incomplete nodal responses when PET/CT performed 12 weeks after treatment showed high 18F-FDG uptake (with or without enlarged lymph nodes in the neck). In addition, results of PET/CT presenting mild or no 18FFDG uptake in enlarged lymph nodes or mild 18F-FDG uptake in normal-sized nodes were classified as equivocal responses. The rest of the PET/CT scans were classified as complete responses. Patients showing an incomplete or equivocal response in the neck but presenting a complete response in the primary location underwent neck lymph node dissection within 4 weeks after PET/CT. The survival rate was similar (2-year overall survival rate of 84.9% and 81.5% in the surveillance group and in the planned neck dissection group, respectively) between patients who underwent PET/CT-guided surveillance policy and patients undergoing a planned surgery. Indeed, the hazard ratio for death (upper boundary of the 95% CI for the hazard ratio 1.50; $p<0.004$) favoured PET/CT-guided surveillance policy. Moreover, surveillance resulted in considerably fewer operations (approximately 80% of patients were spared neck dissection compared with planned dissection surgery; 54 vs 221), and it was more cost effective. The per-person cost saving was £1492 (approximately 2200 US dollars), with an additional 0.08 quality-adjusted life years per person. However, these authors recommended that patients with an equivocal 18F-FDG uptake should continue to undergo neck dissection. In addition, when extrapolating these results to daily clinical practice, it should be noted that in this study, only a small number of patients [17/564 (3%)] presented N3 disease. Therefore, a direct extrapolation of a PET/CT-guided surveillance policy to patients presenting N3 (Stage IVb) disease should not be indicated owing to the small number of such patients recruited in the study. 18F-FDG-PET/CT could have a potential interesting role in the follow-up of patients with HNC. Despite that, the clinical advantages and economic costs of this issue have not yet been largely addressed.

One of the largest studies has been published by a group from Pittsburg [177]. They evaluated 388 patients retrospectively to assess the recurrence rate after radical chemo-radiotherapy among patients who underwent PET/CT surveillance. Tumour recurrence was detected in 110 patients (73 asymptomatic and 37 symptomatic). Indeed, 95% (95% CI, 87–98%) of asymptomatic recurrences were observed within 2 years of follow-up. The authors proposed to evaluate patients for recurrence with PET/CT at 2, 5, 8 and 14 months post-treatment. The reason for this protocol is because their study demonstrated that PET/CT detected almost all tumour recurrences within 2 years.

In summary:

(1) The overall diagnostic performance of 18F-FDG-PET/CT for response assessment is good, but its PPV is not optimal. By contrast, the NPV is particularly high and negative post-treatment PET/CT is very suggestive of absence of viable disease that can guide daily clinical management decisions. In this context, the timing of PET/CT after the end of the treatments is a crucial issue. Available evidences suggest waiting a minimum of 8 weeks before restaging with PET/CT, and preferably 12 weeks to increase the NPV.

(2) The available evidence suggests that this strategy is safe and can enable avoidance of neck dissection in patients presenting with negative PET/CT after CRT. The safety of this management is also confirmed by the results of the PET-NECK study [190] where PET/CT-guided active surveillance showed similar survival outcomes compared with planned neck dissection, and considerably fewer neck dissections, and it was more cost effective. However, extrapolation of a PET-CT guided surveillance policy to patients with N3 (Stage IVb) disease cannot currently be justified.

1.4.7 Prognostic value of PET

The treatment outcome of HNC remains heterogeneous. Identification of novel pre-treatment factors (other than tumour stage, lymph node involvement, anatomical sub-site or human papillomavirus status) potentially predicting long-term outcome is of great interest. Quantifying the prognostic value of PET is challenging. In general, the results of prognostic value of SUV remain undetermined because of the small sample of most of the studies. Additionally, it should be considered that HNC prognosis also depends on the initial anatomical tumour site. Data regarding the prognostic value of PET/CT depending on different tumour locations is scarce in the literature. Two meta-analyses have been conducted to estimate the effect of SUV on the prognosis of HNC. Zhang et al [191] analysed the potential of SUVmax and SUVmean as prognostic markers. The authors concluded that increased SUVmax and SUVmean of the primary tumour are poor prognostic factors and have a potential value in predicting local control, disease-free survival and overall survival. Xie et al [192] performed another meta-analysis to evaluate the prognostic value of SUV, confirming that low primary tumour SUV was associated with better survival prognosis. It should be stressed that SUV estimates suffer from poor reproducibility between centres because of the lack of standardization of the acquisition and processing protocols.

Globally, studies evaluating the prognostic utility of PET/CT in HNC are quite heterogeneous. Most of them have focused mainly on the SUVmax. Some studies have demonstrated worse clinical outcomes in association with higher pre-treatment SUVmax

[193-195]. Other studies observed the correlation of survival with several PET data such as SUVmean or metabolic tumour volume (MTV) [196-197]. Kitajima et al [198] reported that the pre-treatment SUVmax of nodal disease (rather than the primary tumour) in patients with laryngeal cancer was prognostic for recurrence. However, a prospective trial [36] evaluated this particular question and failed to demonstrate any significant clinical correlation between pre-radiotherapy PET-CT SUV parameters and treatment outcomes.

According to other authors, SUVmean may be a better prognostic marker than SUVmax. Higher pre-treatment SUVmean correlates with inferior disease-free survival. These results could be explained considering that SUVmax reflects the highest intensity of 18F-FDG uptake as measured in the highest pixels within a concrete region of interest, whereas the SUVmean represents the average of the intensity of the uptake providing a more global picture of tumour metabolism than SUVmax. Nevertheless, a potential pitfall of SUVmean is the lesser degree of reproducibility compared to SUVmax [196]. More recently, there has been an increasing interest in the use of volumetric parameters of metabolism such as the metabolic tumour volume (MTV) and total lesion glycolysis (TLG), which weights the volumetric burden and volumetric activity of tumours respectively. Pak et al [199] conducted a meta-analysis (13 studies including 1180 patients) on volumetric parameters addressing the prognostic value of MTV and TLG in patients with HNC. Despite the various methods adopted between studies, the authors concluded that MTV and TLG are accurate prognostic indicators of outcome. Indeed, high MTV and TLG increased the risk of disease progression and death.

In summary, meta-analysis and several studies showed that PET-quantified data such as SUVmax, SUVmean, MTV, TLG are strongly and negatively correlated with survival. However, given that uncertainty still exists on the definition of the most accurate predictive marker, prospective trials are needed to definitively settle this issue.

1.4.8 PET/MRI

Since information provided by PET/CT and MRI is complementary in many clinical situations, it seems to make sense to combine the two modalities. The high soft-tissue contrast and the different functional imaging techniques of MRI might help to ameliorate the informative value of a hybrid imaging study. Consequently, the discussion about potential applications of this new hybrid technology in oncological imaging and especially in the head&neck has been generated [200]. The feasibility and diagnostic performance (sensitivity, specificity and accuracy) of clinical PET/MRI have been demonstrated in a significant number of studies, but technological and logistic challenges, such as errors in

attenuation correction and long scan duration continue to be the major issues of PET/MRI [201]. PET/MRI has many potential advantages over PET/CT including: detection of perineural spread of tumours and the infiltration of important anatomical landmarks, such as the pre-vertebral fascia and great vessel walls; lower radiation exposure; higher soft-tissue contrast and several functional features [202]. Such potentials will likely lead to new radiopharmaceuticals and applications beyond cancer staging [203].

Although PET/MRI is still in the early stages of clinical development, it is clear that the clinical adoption of PET/MRI is slower than PET/CT. This is not only due to technological challenges (e.g. accurate attenuation correction of PET images) but also to complex logistics of combining a whole body PET scan with a whole body or organ-specific MRI. Key applications of PET/MRI providing clinically relevant information still need to be defined [204]. Further studies exploiting the functional MRI and molecular PET capabilities may report substantial contributions of combined PET/MRI for treatment response prediction, radiotherapy planning, tumour phenotyping and treatment monitoring [205,206]. Future research involving larger patient series is needed to assess the true impact of this technique in HNC and will show whether PET/MRI outperforms PET/CT, MRI, diffusion weighted MRI or their combination.

1.4.9 Future applications of PET/CT in radiation oncology

Dose escalation to 18F-FDG-avid sub-volumes of the tumour as well as adapting the radiotherapy plan during treatment depending on the functional tumour changes induced by radiation are two important topics that have been explored [207-209]. Madani et al [210] performed a Phase I trial to establish the maximum tolerated dose to the metabolically active sub-volume within the anatomically (CT/MRI) based GTV. They demonstrated the feasibility of heterogeneous dose delivery with dose escalation up to 77.5 Gy to the 18F-FDG-avid tumour areas. Another approach is the adaptation of the biological target volume during the course of radiotherapy in order to reduce the treated volume as radiotherapy progresses. Duprez et al [208] used adaptive intensity-modulated radiotherapy planning based on dose painting by numbers according to 18F-FDG-PET voxel intensities concluding that re-planning was possible reaching a total dose of 80.9Gy. It is noteworthy that these kinds of approaches require extreme caution, as a slight shift of the anatomy will not only cause a mismatch of the intra-tumoral dose but also a higher dose to the healthy tissue. Finally, an unsolved issue is the monitoring of the changes of high SUV regions during the course of treatment. The possibility of targeting the radiation resistance within the tumour on the basis of dynamic biological information (e.g. intra-tumoral hypoxic and proliferation

state) obtained from functional imaging with tracers other than 18F-FDG is an emergent strategy [211-215].

1.4.10 UK PET guidelines for head&neck cancer

The latest version of "Evidence-based indications for the use of PET-CT in the United Kingdom" was published in 2016 [150]. Since its introduction into clinical practice in the UK in 1990, PET (and lately PET/CT) has become a key imaging tool in the assessment of cancer and non-cancer medical conditions. This publication is the third edition giving clinical guidelines for the use of PET-CT with fluorodeoxyglucose (FDG) and non-FDG tracers. According to the UK guidelines, the oncology applications of 18F-FDG-PET-CT in HNC are the following:

- Staging of patients where staging is difficult clinically; for example, where there is uncertainty on other imaging or equivocal findings that would preclude radical treatment.
- Staging or restaging of patients with a high risk of disseminated disease such advanced loco-regional disease and primary sites with a high propensity for disseminated disease such as nasopharyngeal cancer.
- To identify the primary site in patients presenting with metastatic squamous cell carcinoma in cervical lymph nodes, with no primary site identified on other imaging.
- Response assessment 3-6 months post chemo-radiotherapy.
- To differentiate relapse from treatment effects in patients suspected to have tumour recurrence where magnetic resonance imaging (MRI) is uncertain or equivocal.

The limitation of "Evidence-based indications for the use of PET-CT in the United Kingdom" (2016) is that this publication reports the guidelines for the diagnostic use of PET/CT but does not give any recommendation for the use of PET/CT in radiotherapy. As an example, PET/CT is recommended in the radiotherapy planning for lung cancer [151], however this is not reported in this publication.

1.5 Thesis overview, development project questions, aims and metrics

This thesis examines the features of 2-step-fusion (FDG)PET/CT-based radiotherapy for patients with locally advanced oropharyngeal cancer with focus on 4 key domains: technical aspects, clinical staging, metabolic aspects and clinical outcome. The thesis overview is shown in Figure 1.5.1.

1.5.1 Development project questions

In relation to the 4 key domains, the development project questions were:

A.1. Is the 2-step-fusion methodology (i.e. fusion of PET/CT with simulation CT) robust and accurate?

A.2. Does PET/CT introduce any changes in definition of the target volumes?

B. Does PET/CT change the TNM classification at baseline?

C. Is there any difference in the metabolic status of T and N at baseline, and is this correlated with prognosis?

D. What is the clinical outcome of PET/CT-based radiotherapy, and is the clinical outcome different from non-PET/CT-based radiotherapy?

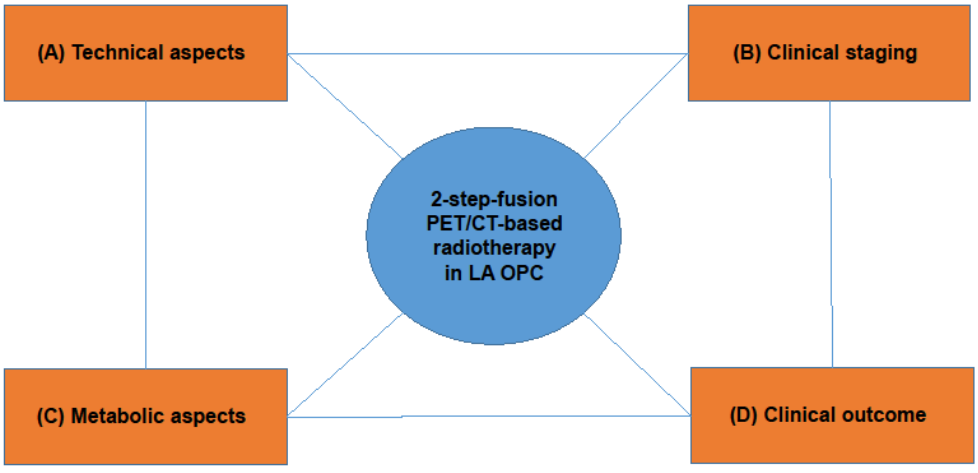


Figure 1.5.1. Thesis overview. LA OPC= Locally Advanced Oropharyngeal Cancer

1.5.2 Aims

I led a single institution service development project of 2-step-(FDG)-PET/CT-based radiotherapy in locally advanced oropharyngeal cancer with the aims to assess:

A.1. The accuracy of the 2-step-fusion methodology (i.e. fusion of PET/CT with simulation CT).

A.2. The changes of the target volumes defined with PET/CT and simulation CT.

B. The staging changes at baseline due to PET/CT.

C. The metabolic status of T and N at baseline, and its correlation with prognosis.

D. The clinical outcome of PET/CT-based radiotherapy, and the differences from non-PET/CT-based radiotherapy.

1.5.3 Metrics

The metrics of the project were:

A.1. Fusion accuracy index for PET/CT and simulation CT.

A.2. Target volume variability of T and N outlined with 3 different approaches: standard simulation CT, PET/CT interpreted with visual assessment and PET/CT segmented with 50% of the SUVmax.

B. T, N and M stage modification due to the introduction of PET/CT in the pre-radiotherapy work-up of the patients.

C. SUVmax of T and N, and correlation with the 3 prognostic risk categories (high, intermediate, low risk) for the patient population enrolled.

D.1 Tumour Response (TR), Time To Progression (TTP) and Overall Survival (OS).

D.2 Late toxicity (LT), i.e. toxicity beyond 3 months after the end of treatment.

D.3 PET/CT-based radiotherapy clinical outcome (TR, TTP, OS, LT) comparison with an internal retrospective series and other published studies of oropharyngeal patients treated with non-PET/CT-based radiotherapy.

CHAPTER 2
SERVICE DEVELOPMENT PROJECT METHODOLOGY

2.1 PET/CT in radiotherapy planning as development project and multidisciplinary internal working group

PET/CT scan is not part of the standard of care in the radiotherapy planning pathway for oropharyngeal cancer at the Beatson as in most of UK Centres. NICE has recommended for PET/CT scan to be used in selected locally advanced head&neck cancers at baseline before treatment. Multi-modality imaging including MRI and PET/CT scan could improve the accuracy and aid target volume definition during radiotherapy planning. In an ideal situation with unlimited resources in the NHS, PET/CT could be part of the radiotherapy standard of care at baseline before treatment, which is already the case in some countries. Therefore, integrating baseline PET/CT into the routine radiotherapy planning pathway could be justified and carried out as service development project at the Beatson. I aimed to undertake this project as service development following approval and review from an internal radiotherapy working group. I established a multi-disciplinary working group including representatives from Clinical Oncology, PET Centre, Radiotherapy Physics and Radiotherapy Radiography. The remit of this group was to develop, peer review and implement the project. The working group agreed that ethical approval was not necessary for the implementation of this development project for the reasons stated above. We discussed the options of using a 1-step or 2-step PET/CT protocol. The 1-step protocol implies the use of the PET/CT scanner for acquiring the CT component of the PET/CT and using it directly for radiotherapy planning. This approach requires the commissioning and Quality Assurance (QA) maintenance of the PET/CT scanner for radiotherapy purpose. Due to lack of resources for completing the commissioning and performing the QA processes, we decided pragmatically to implement a 2-step approach, i.e. acquiring simulation CT and PET/CT separately and fusing them off-line. PET/CT was added in the radiotherapy pathway as additional scan and funded by the NHS as baseline staging scan in selected locally advanced head&neck cancer patients as per UK PET guidelines for head&neck cancer (Paragraph 1.4.10) [150].

2.2 Medical exposure risk assessment for clinical use

The Radiotherapy Physics Department conducted a risk assessment study to evaluate the safety of PET/CT introduction and fusion with contrast enhanced simulation CT in the

radiotherapy planning system (Eclipse, ARIA, Varian). A copy of the risk assessment document is presented in the Appendix (A2.2).

Low dose CT is acquired during PET/CT for the purposes of attenuation correction and anatomical localisation. An automated exposure control (max 240mA) and 120kV are used. Radiation dose depends on coverage and anatomy scanned and is patient dependent due to the use of automated exposure control. DLP (Dose Length Product, mGy-cm) and CTDI (Computed Tomography Dose Index, mGy) are recorded for each patient. For an average 70 kg patient these are 230mGy-cm and 2.35mGy respectively. With respect to effective dose, an average patient undergoing CT from eyes to thighs using the above settings would receive less than 7mSv. Radiotherapy planning CT scan on the head&neck region for an average patient has DLP and CTDI of 252mGy-cm and 6mGy respectively, and an effective dose of less than 3mSv. The multidisciplinary working group agreed that the additional dose exposure due to PET/CT can be justified by the contribution of PET/CT in better staging the patients and in defining more accurately the radiotherapy target volumes.

2.3 Radiotherapy Management Group Approval

My project was approved by the Radiotherapy Management Group (RMG). RMG is multidisciplinary group including clinicians, representatives from Radiography and Physics. The remit of RMG is to discuss and deliberate managerial and research/development strategic decisions within the Radiotherapy Department at the Beatson West of Scotland Cancer Centre. My project was started after RMG approval.

2.4 Project design

A monocentric, service development project for the treatment of locally advanced oropharyngeal cancer with 2-step-fusion (FDG)PET/CT-based Volumetric Modulated Arc Therapy (VMAT). This project was conducted at the Beatson West of Scotland Cancer Centre Radiotherapy Department in collaboration with the PET Centre. A project schematic is shown in Figure 2.4.1.

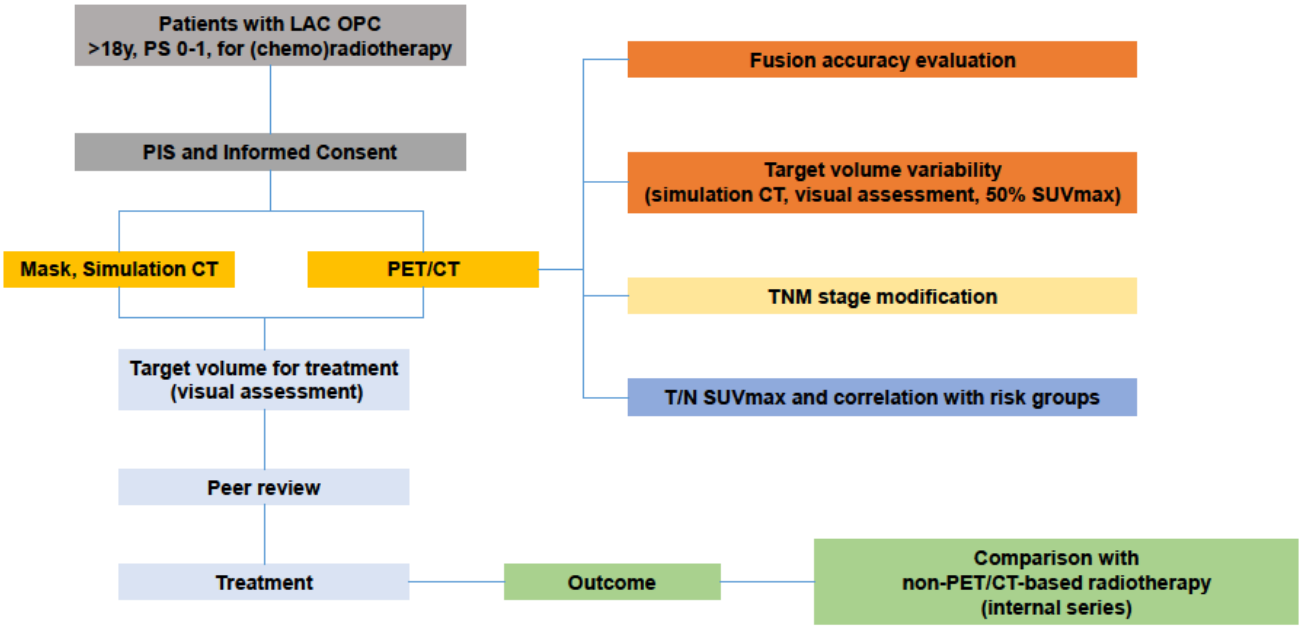


Figure 2.4.1. Project schematic. LA OPC= Locally Advanced Oropharyngeal Cancer, PS= ECOG Performance Status, PIS= Patient Information Sheet.

2.5 Patients selection

I screened the patients at the head&neck MDT (Multi-Disciplinary-Team) meeting. I gave eligible patients the option of radiotherapy planning with standard modality (i.e. contrast enhanced simulation CT only) or with PET/CT in addition to standard contrast enhanced simulation CT. Patients who agreed to receive PET/CT were given a leaflet reporting information for the purpose of this development project. The information leaflet is presented in the Appendix (A2.5). After a cooling off period of at least 24 hours, I asked the patients to sign the standard radiotherapy consent form on which I added that they agreed to have PET/CT with the aim to complete the staging and improve the accuracy of the radiotherapy planning process. Patients were recruited in or excluded from this project according to the criteria reported in Paragraph 2.5.1 and 2.5.2. I agreed with the multidisciplinary working group to enrol initially 10 patients and assess the feasibility of the working plan. After interim review of the first 10 patients, I agreed to recruit a maximum of 30 patients.

2.5.1 Inclusion criteria

1. ≥18 years of age.

2. Histologically confirmed diagnosis of Squamous Cell Carcinoma (SCC) of the oropharynx.

3. Locally advanced disease, i.e. T1-4 N1-3 M0.

4. Indication for (chemo)radiotherapy with curative intent after MDT discussion.

5. ECOG Performance Status 0-2.

2.5.2 Exclusion criteria

1. Post-operative (chemo)radiotherapy

2. Previous malignancy other than basal cell carcinoma of the skin.

3. Metastatic disease.

4. Claustrophobia or other factors compromising the compliance with PET/CT acquired with thermoplastic mask.

5. Uncontrolled diabetes mellitus.

2.6 Booking plan

The booking plan was structured as follows:

- Thermoplastic mask (Monday): standard head&neck thermoplastic mask with 5-point fixation.

- Simulation CT (Tuesday): standard radiotherapy contrast enhanced simulation CT performed in the radiotherapy department.

- PET/CT (1st Thursday): scan with the head&neck radiotherapy protocol performed in the PET Centre.

- Review of PET/CT (Wednesday): I discussed PET/CT results with the PET radiologist and agreed stage and target volumes (primary tumour and nodal disease).

- Contouring and peer review (2nd Thursday): I completed radiotherapy target volumes and organs at risk; I peer reviewed the volumes with the head&neck team in the radiotherapy department.

- Treatment planning (Friday to Wednesday): elaboration of the radiotherapy treatment plan.

- Pre-assessment (3rd Thursday): I reviewed the patients before treatment commencement to check clinical status and fitness.

- Treatment start (Monday).

Overall, the booking plan duration was of 3 weeks (from the time of mask to the time of treatment start). The booking plan is summarised in Figure 2.6.1.

Figure 2.6.1. Booking plan. M= mask, CT= contrast enhanced simulation CT, PET= PET/CT, PETr= PET review with radiologist, Co= target volume contouring, Pr= peer review, Tp= treatment planning, Pa= pre-assessment, Tr= treatment start

2.7 Scanning: thermoplastic mask, simulation CT and PET/CT

2.7.1 Thermoplastic mask

A fixation thermoplastic mask was customised for each patient. The patients laid on the flat table with adequate head rest. The mask is made of thermoplastic material which is softened in hot water. The thermoplastic sheet is placed on the face, neck and shoulders and fixed to the flat table of the scanners and radiotherapy machines. Once solid, the mask prevents the patients from moving during the process of scanning and radiotherapy treatment with an

average set-up error <3mm. An example of thermoplastic mask is presented in Figure 2.7.1. The thermoplastic mask was used for both the simulation CT and PET/CT scanning.

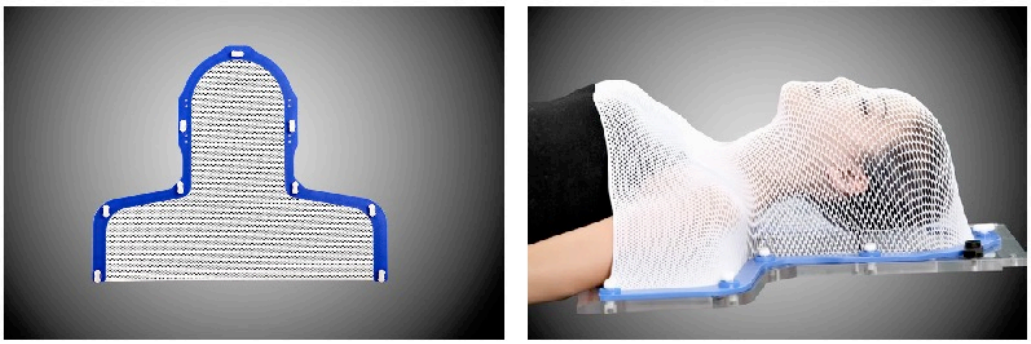


Figure 2.7.1. Thermoplastic mask for scanning and radiotherapy treatment

2.7.2 Simulation CT

A contrast enhanced simulation CT was acquired in the radiotherapy department as per head&neck standard protocol using a 120kV automatic mA modulation range of 15-240mAs with 50cm Dual Field of View. Contrast was given to patients who had adequate renal function. The patients laid on the CT flat couch wearing the thermoplastic mask on adequate head rest. Radio-opaque markers were placed on the mask for laser alignment purposes. After injection of the contrast medium, the CT was acquired from the vertex of the skull to the lung apex with 2.5mm slice thickness. The CT was reconstructed and transferred to the radiotherapy treatment planning system (Eclipse, Varian). An example of contrast enhanced simulation CT is presented in Figure 2.7.2.

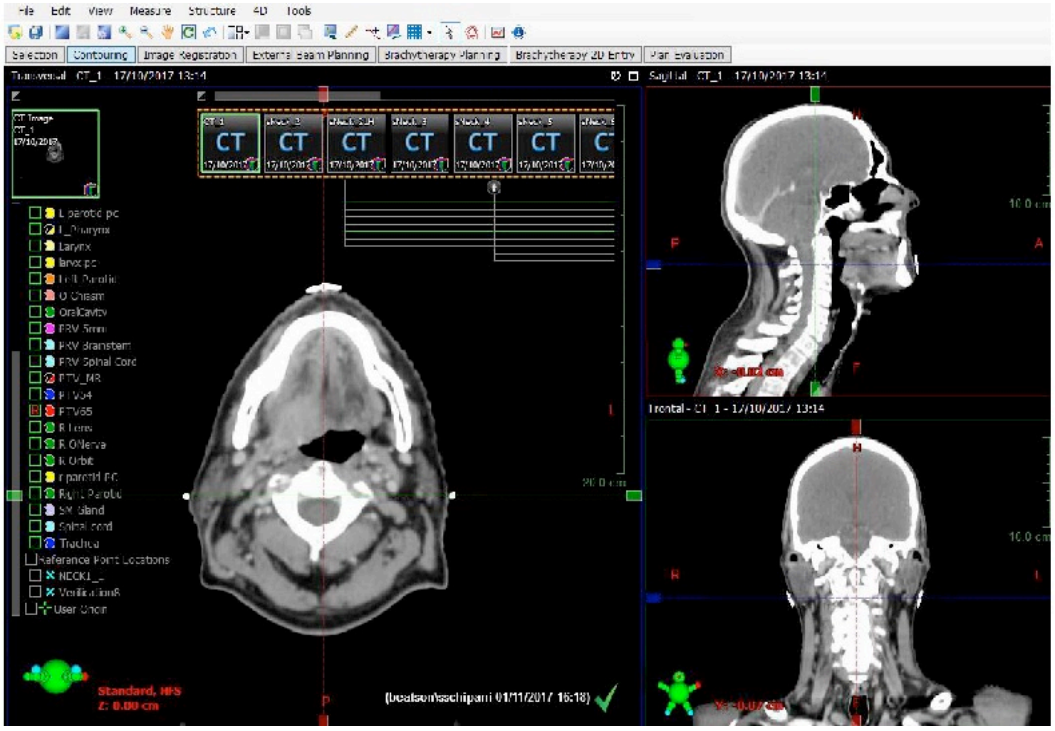


Figure 2.7.2. Contrast enhanced simulation CT of the head&neck region imported in the radiotherapy treatment planning system (Eclipse, Varian)

2.7.3 PET/CT

PET/CT was acquired in the PET Centre. This is a purpose built centre in the Beatson West of Scotland Cancer Centre with facilities for both production and scanning of positron emitting radiopharmaceuticals. The PET Radiopharmaceutical Production Unit houses a cyclotron (GE PET Trace 6) and the associated clean rooms and hot cells required for radiopharmaceutical production. The production unit has two GE Fastlab synthesis units with 18F-FDG being produced on a daily basis. The PET/CT scanning section houses two scanners (GE Discovery 690 and GE Discovery 710), 8 uptake bays, 2 toilets for hot patients, a clinical exam room and dose preparation room. PET/CT scanners have radiotherapy flat bed and fittings to match those used by the radiotherapy department. Prior to undergoing PET/CT imaging, patients were fasting for at least 6 hours. They were injected with the following activity of Fluorine-18-Fluorodeoxyglucose (18F-FDG):

>60 kg = 280MBq

60-70kg = 327MBq

70-80kg = 400MBq

In case of patients with weight >80kg, the administered activity was 400MBq (ARSAC limit) and the PET acquisition time was increased. After resting for 60 minutes, the patients were positioned on the flat bed of the PET/CT scanner without the thermoplastic mask and with their arms by their hips. A first set of images (Body PET/CT) were acquired from the base of the neck to mid thighs. CT images were acquired using a 120kV automatic mA modulation range of 15-240mAs. The encompassed field of view was reconstructed at 2.5mm increments. This was followed by PET acquisition, encompassing the same transverse field of view as the CT. PET attenuation correction was based on the CT data and images were corrected for scatter and iteratively reconstructed using Time of Flight and SharpIR on a 192x192 matrix. All acquired images and SUV data were exported to a dedicated GE workstation (ADW 4.5) for viewing and reporting. The images and SUV data were finally exported to PACS (Picture Archiving and Communication System) for DICOM (Digital Imaging and Communications in Medicine) sharing with the radiotherapy planning system. This scanning process had an average duration of 20 minutes. An example is reported in Figure 2.7.3.

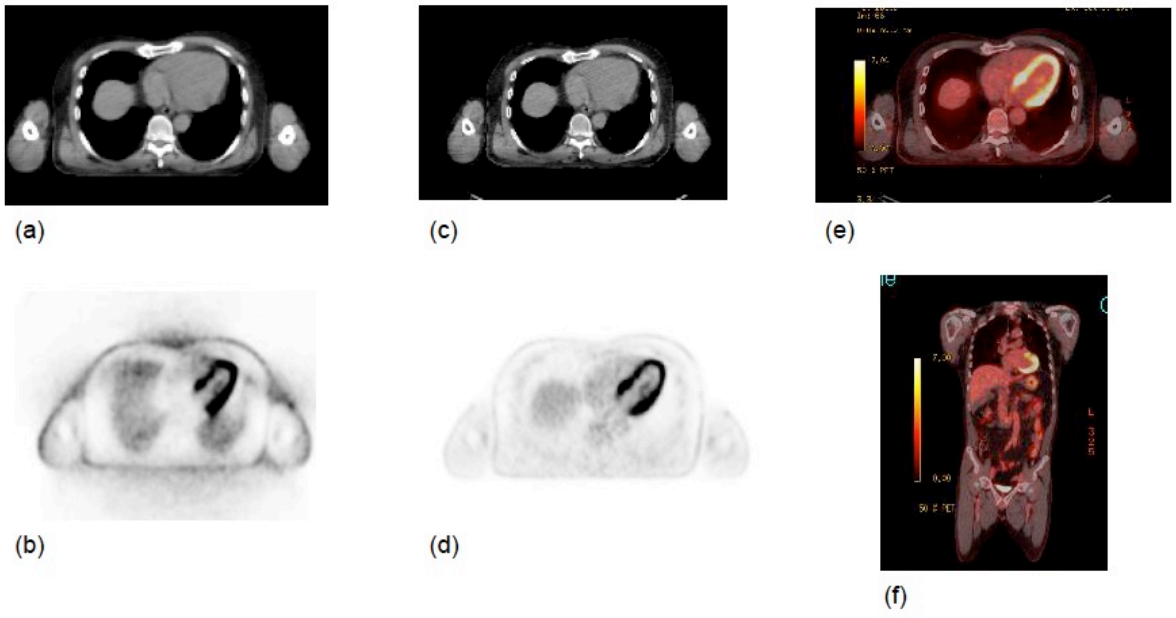


Figure 2.7.3. Body PET/CT from the base of the neck to mid thighs. Raw PET (b) was corrected with CT for attenuation-correction (a). Attenuated-corrected PET (d) was fused with low dose CT (c) for anatomical localization generating fused PET/CT (e and f).

A second set of images (head&neck PET/CT) were acquired and stored in PACS with the same protocol as Body PET/CT but with the patients laying on the flat table of the scanner with the thermoplastic mask and the headrest. Images were scanned from the vertex of the skull to the base of the neck. This scanning process had an average duration of 10 minutes. An example is reported in Figure 2.7.4.

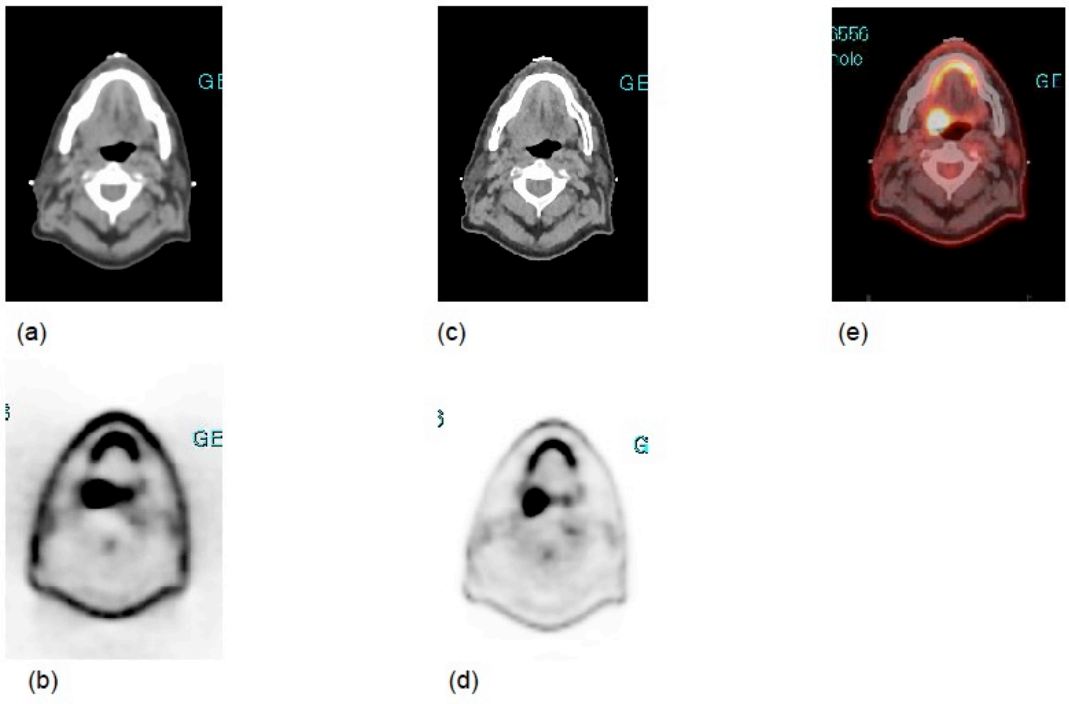
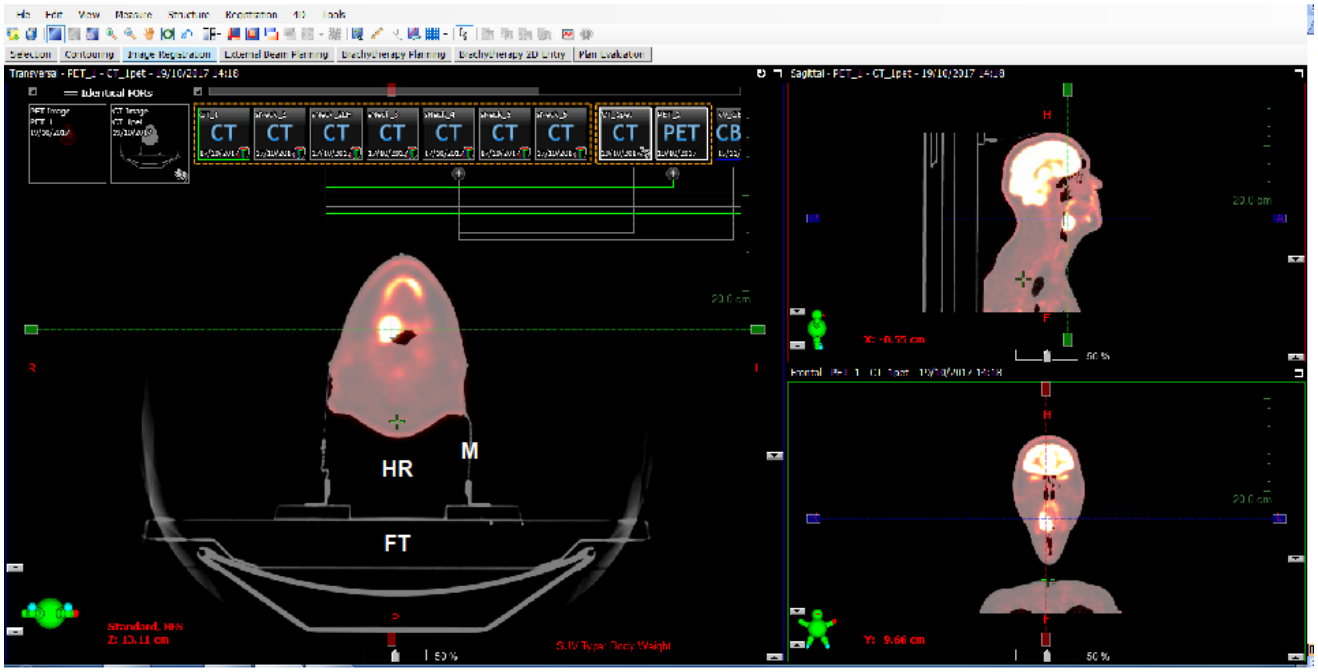


Figure 2.7.4. Head&neck PET/CT from the skull vertex to the neck base. Raw PET (b) was corrected with CT for attenuation-correction (a). Attenuated-corrected PET (d) was fused with low dose CT (c) for anatomical localization generating fused PET/CT (e). In this patient the right base of tongue cancer is clearly visualised.

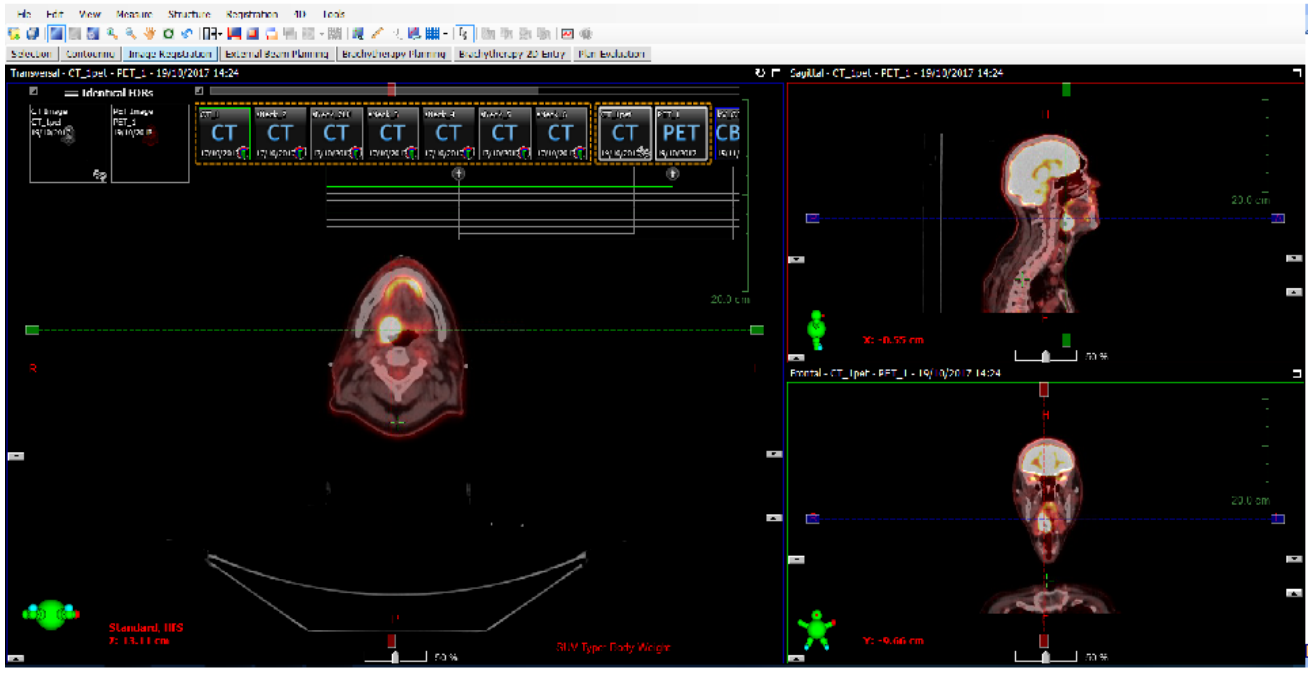
2.8 Image transfer

PET/CT images of the head&neck region (H&N PET/CT) were transferred from PACS to the radiotherapy treatment planning system (Eclipse, Varian) into DICOM format. I indicated the sets of PET and CT images to be transferred on a dedicated Record of Radiotherapy Imaging Form. An example is reported in the Appendix (A2.8). The image

transfer into Eclipse was completed by Radiotherapy Physics staff. An example of H&N PET/CT imported in Eclipse is presented in Figure 2.8.1.



(a)

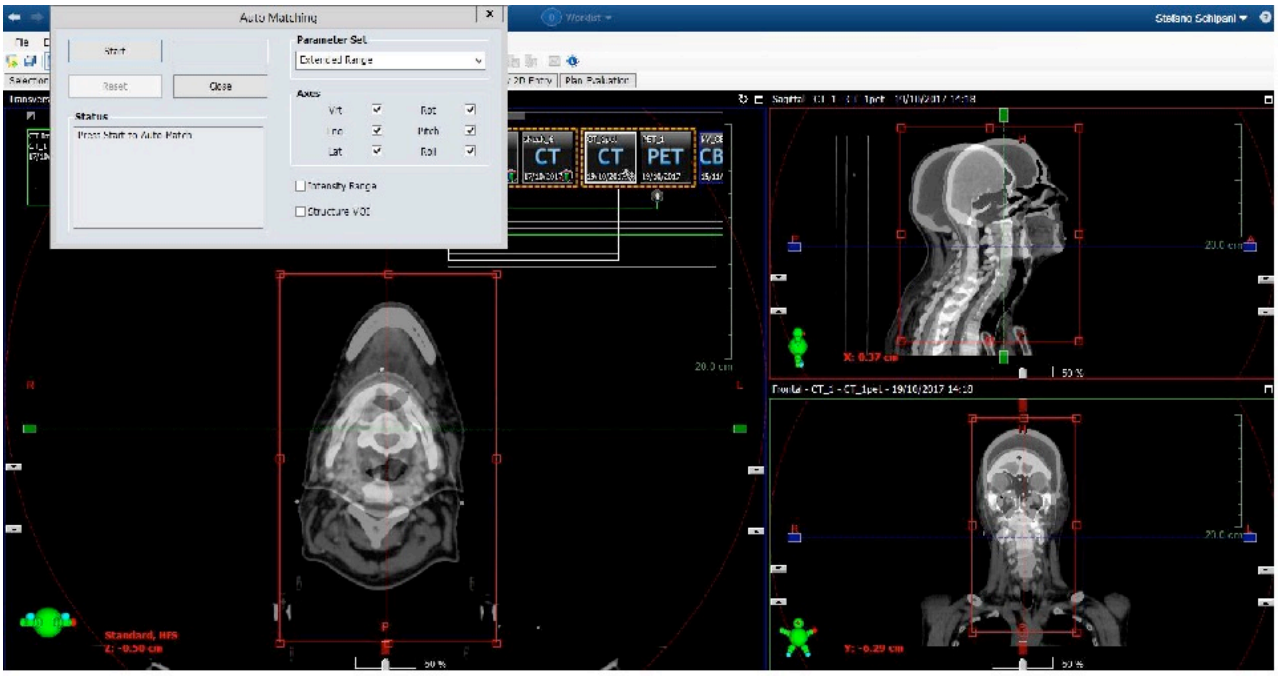


(b)

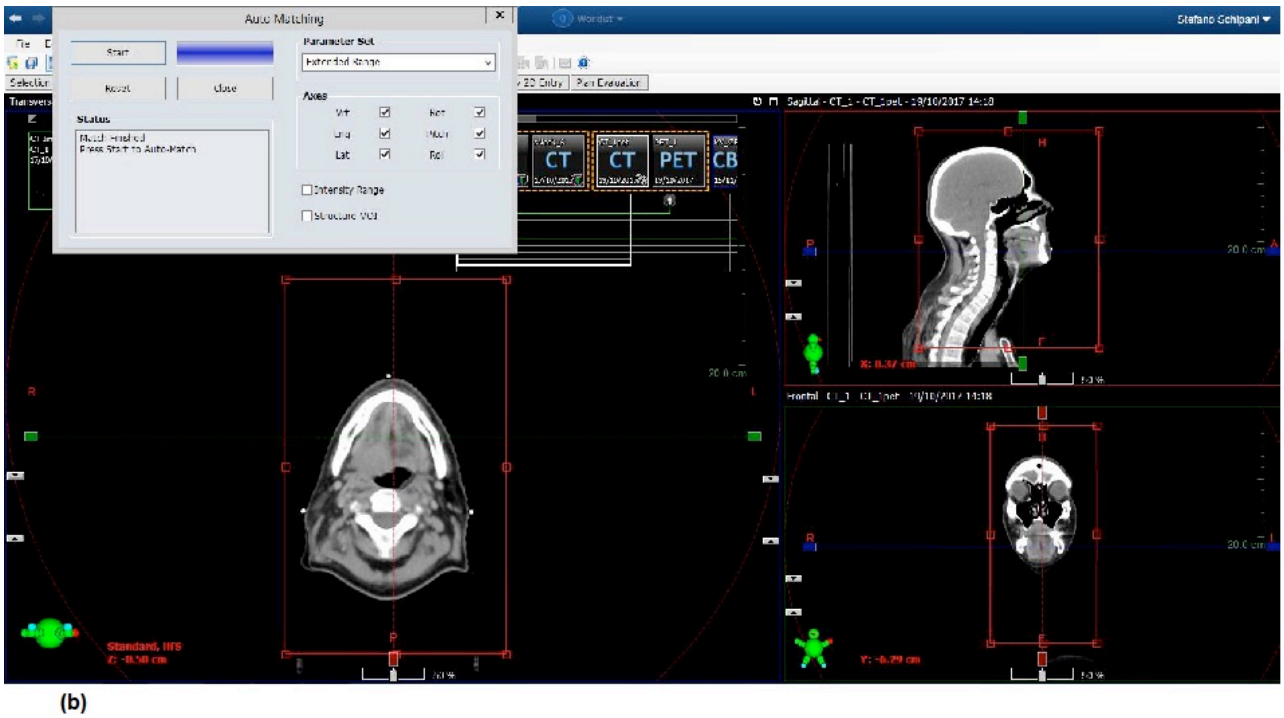
Figure 2.8.1 H&N PET/CT DICOM transfer from PACS into the radiotherapy treatment planning system (Eclipse, Varian). (a) PET/CT was acquired with flat table (FT), head rest (HR) and thermoplastic mask (M). The anatomical details of the CT component are visible in (b). The PET component clearly visualised the right base of tongue cancer in this patient.

2.9 Image fusion

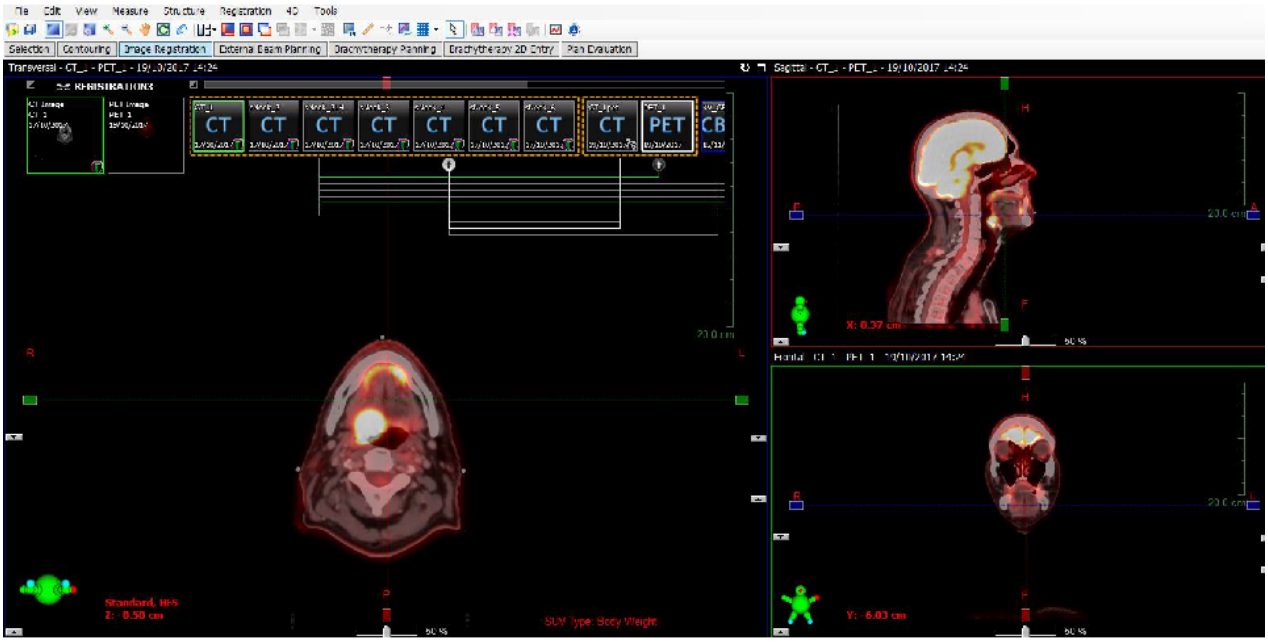
Contrast enhanced simulation CT and H&N PET/CT were fused by Physics staff using the Eclipse (Varian) automatic rigid fusion algorithm. The Region of Interest (ROI) was selected from the vertex of the skull to the sternal notch. Simulation CT and H&N PET/CT were fused using the 6-freedom-degree fusion protocol in order to maximise the accuracy of the fusion. An example of image fusion is presented in Figure 2.9.1.



(a)



(b)



(c)

Figure 2.9.1 Image fusion. Simulation CT and H&N PET/CT were fused using the Eclipse (Varian) automatic 6-freedom-degree rigid fusion algorithm (a,b). The PET component is shown in (c).

2.10 Simulation CT and PET/CT fusion accuracy assessment

I calculated the fusion accuracy of simulation CT and H&N PET/CT as the spatial reproducibility of specific bony structures: maxillary sinuses (MS), first and fourth cervical vertebra (C1 and C4). I contoured MS, C1 and C4 as single bony structure on the simulation CT and the CT component of the H&N PET/CT. The spatial reproducibility index (R) for the fusion accuracy was defined as the intersection/union ratio of the bony structures. The fusion accuracy of 100% (i.e. perfect fusion) and 0% (i.e. no fusion) is represented by R=1 and R=0 respectively as shown in Figure 2.10.1. An example of fusion accuracy evaluation with the specified bony structures is presented in Figure 2.10.2.

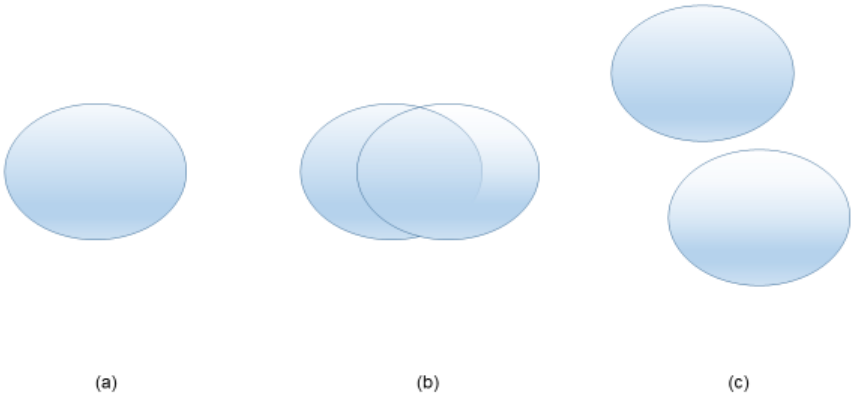


Figure 2.10.1 Schematic representation of the calculation of the fusion accuracy of PET/CT and simulation CT. The reproducibility index (R) was calculated as the intersection/union ratio of maxillary sinuses, C1 and C4 which were contoured as single bony structure on the CT images. The fusion accuracy of 100%, 50% and 0% is represented by R=1 (a), R=0.5 (b) and R=0 (c) respectively.

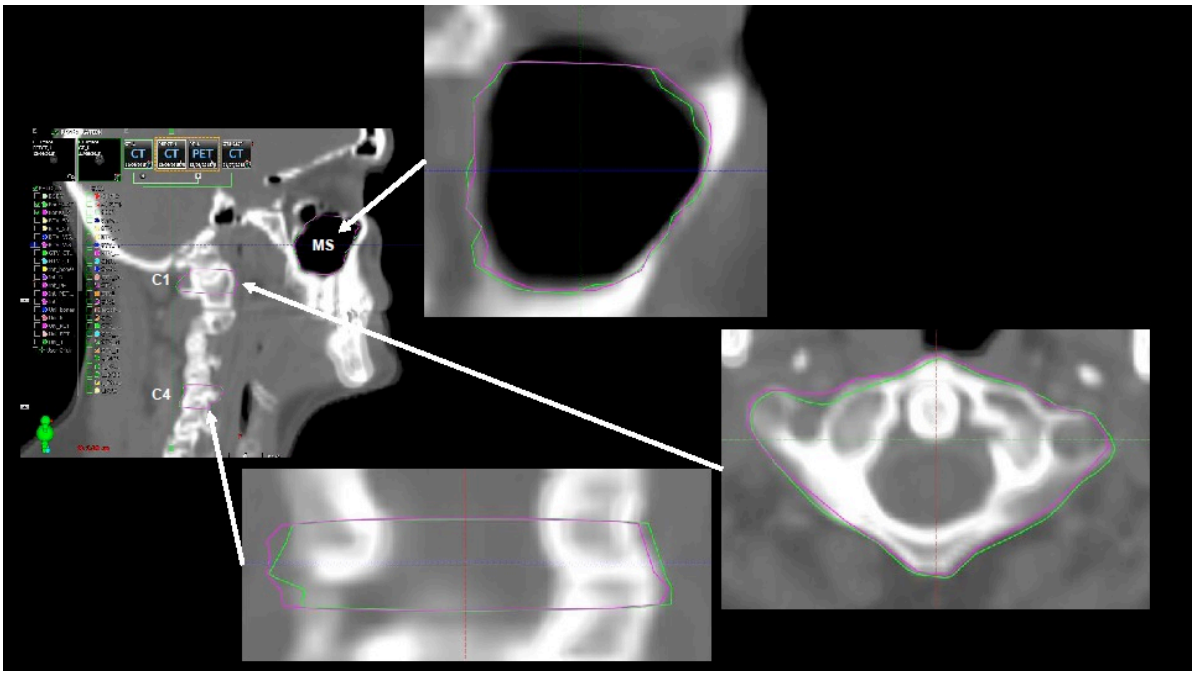


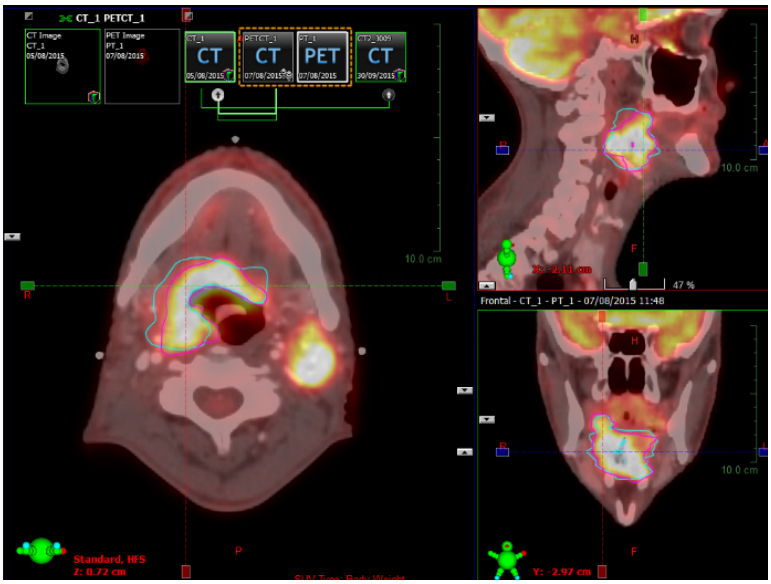
Figure 2.10.2. Fusion accuracy of simulation CT and H&N PET/CT. Maxillary sinuses (MS), C1 and C4 were contoured as single bony structure. The magnified pictures show sagittal, axial and coronal view of MS, C1 and C4 respectively on simulation CT (green) and CT component of PET/CT (magenta). The reproducibility index (R) of the bony structures was calculated as described in the text.

2.11 Target volume definition with different imaging modalities and variability assessment

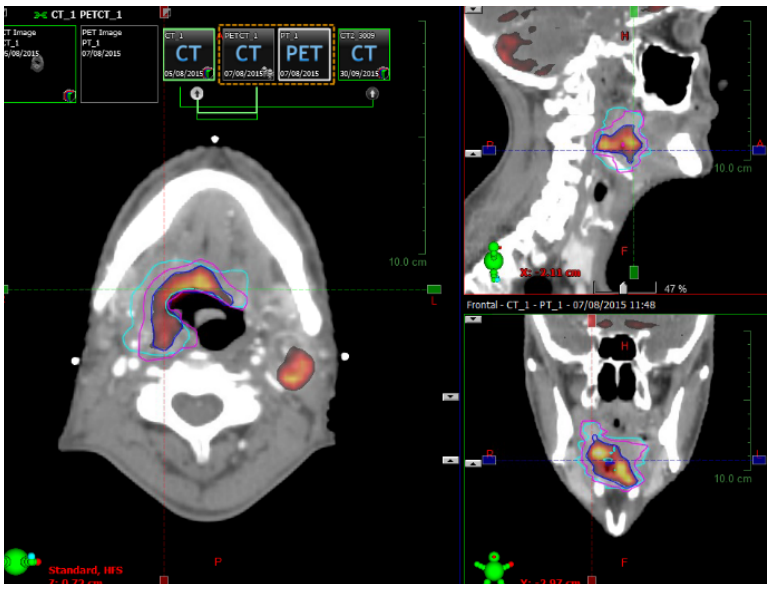
I defined the target volumes separately as primary (T) and nodal tumour (N). As first step, I defined the target volumes on the contrast enhanced simulation CT (CTsim) without the information from the PET/CT. Subsequently, the PET specialist (1 observer) and I defined together the target volumes considering the PET/CT images. T and N were contoured on PET/CT with visual assessment (PET/CT-vis) and segmentation (PET/CT-50%).

For visual assessment purposes, SUVmax was measured in T and N, and the PET intensity scale was fixed from 0 to SUVmax of T and N separately. Volumes were defined visually as per clinical judgement taking into consideration all the clinical information (CT, PET, endoscopy, etc). For segmentation purposes, the PET intensity scale was fixed from 50% to SUVmax of T and N separately. In the literature there is no recommendation on the %SUVmax for segmentation purposes, so the choice of 50% threshold was arbitrary and in accordance with an ongoing clinical trial [216].

I calculated volumes (in cc) and spatial reproducibility index $R=\cap/U$ and compared the different imaging modalities (i.e. CTsim vs PET/CT-vis vs PET/CT-50%). R=0 and R=1 were the lowest and highest grade of spatial reproducibility. The concept of R is the same as shown in Figure 2.10.1. An example of target volume definition with different imaging modalities is presented in Figure 2.11.1 and 2.11.2.

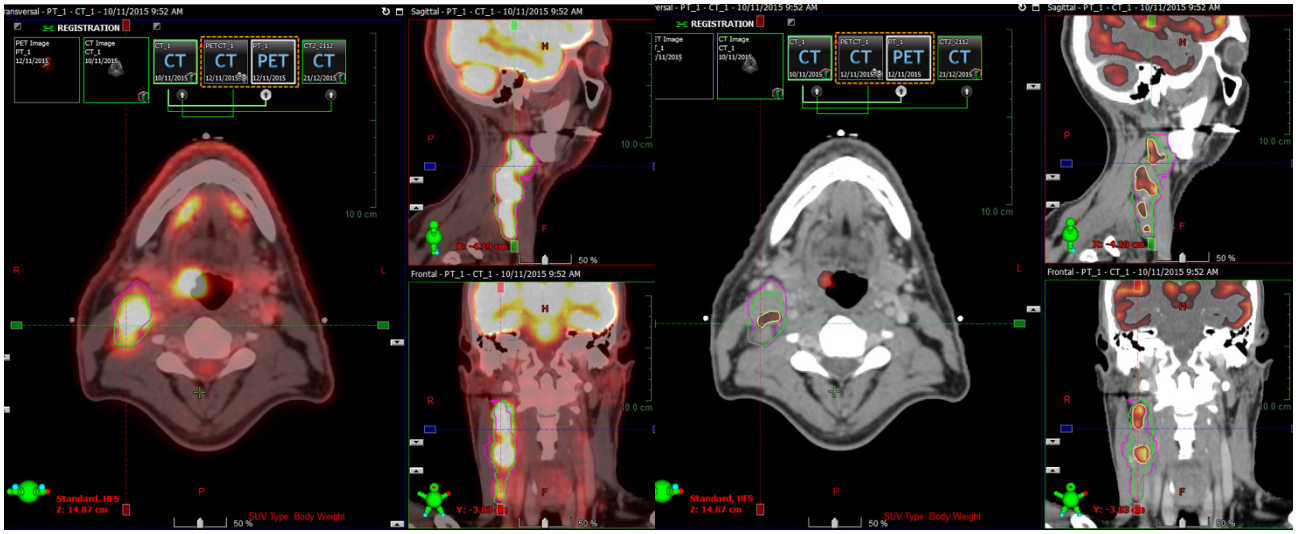


(a)



(b)

Figure 2.11.1 Patient with locally advanced cancer of the right base of tongue. (a) Primary tumour defined on CTsim (cyan), PET/CT with visual assessment (magenta) and (b) 50% threshold of SUVmax (blue) are shown.



(a) (b)

Figure 2.11.2 Patient with bulky N3 disease in the right neck. (a) Nodal tumour defined on CTsim (magenta), PET/CT with visual assessment (green) and (b) 50% threshold of SUVmax (yellow) are shown.

2.12 TNM stage definition with PET/CT

Patients were initially staged at the MDT taking into consideration clinical (endoscopy) and cross sectional anatomical imaging (CT, MRI) information. The TNM stage was agreed according to the 7th Edition definition [217]. Following PET/CT, I agreed any change in the TNM stage with the PET specialist. In case of upstaged nodal disease (ipsi or contra-lateral), I requested Ultrasound (US) and Fine Needle Aspiration (FNA) only in case of equivocal nodes on PET/CT. US and FNA were not requested in case of frankly pathological nodes on PET/CT. This was a pragmatic approach in order to avoid additional examinations for the patients and possible delays of the treatment. The change in nodal staging from unilateral (i.e. N1-2b) to bilateral disease (i.e. N2c) was clinically relevant because of the extended volumes of the neck to be irradiated with high dose of radiotherapy as shown in Figure 2.12.1.

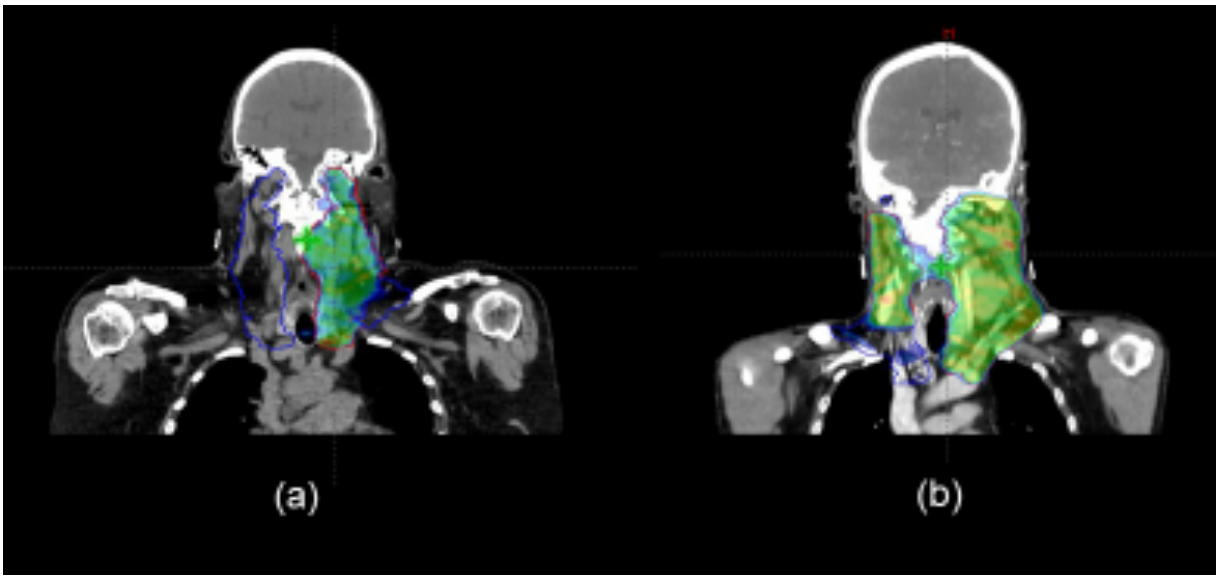


Figure 2.12.1. Example of nodal disease upstaging with PET/CT. In case of ipsilateral nodal disease the contralateral neck received a prophylactic dose of 54Gy (a). Patients with bilateral nodal disease received a full radical dose of 65Gy to the contralateral neck (b) with potential increased risk of radiotherapy related toxicity.

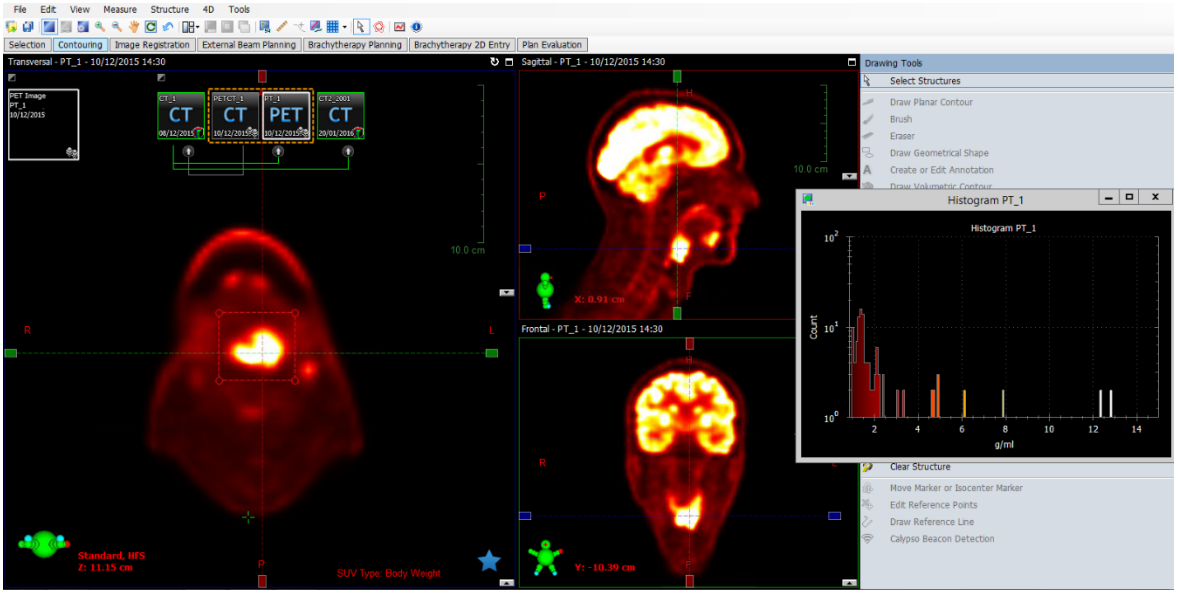
2.13 SUVmax analysis and correlation with risk groups

The use of standardized uptake values (SUVs) is common in clinical FDG-PET/CT oncology imaging and has a role in assessing patient response to cancer therapy. Ideally, the use of SUVs removes variability introduced by differences in patient size and the amount of injected FDG. However, there are several sources of bias and variance that are introduced in the measurement of FDG uptake in tumors and also in the conversion of the image count data to SUVs. The FDG uptake in tumours is related in a complex manner to the proliferative activity of malignant tissue and to the number of viable tumour cells. There are several methods for measuring the rate and/or total amount of FDG accumulation in tumours. PET scanners are designed to measure the in vivo radioactivity concentration [kBq/ml], which is directly linked to the FDG concentration. Typically, it is the relative tissue uptake of FDG that is of interest. The two most significant sources of variation that occur in practice are the amount of injected FDG and the patient size. To compensate for these variations, at least to first order, the standardized uptake value (SUV) is commonly used as a relative measure of FDG uptake. The basic expression for SUV is

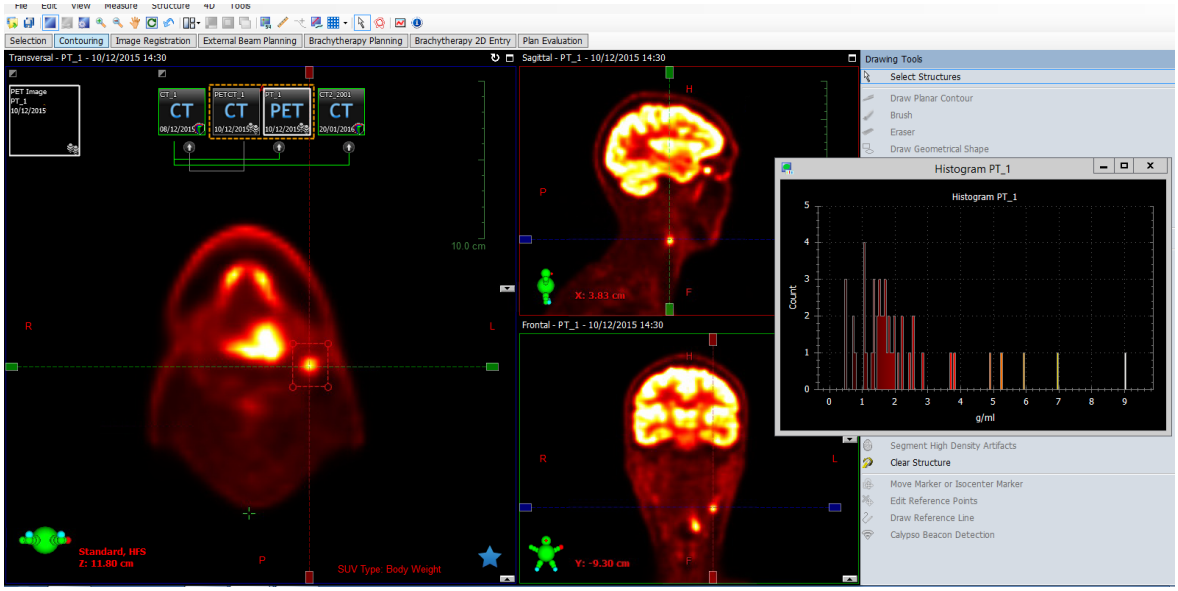
$$\mathrm{SUV} = r / (a\,' / w)$$

where r is the radioactivity activity concentration [kBq/ml] measured by the PET scanner within a region of interest (ROI), a' is the decay-corrected amount of injected radiolabeled FDG [kBq], and w is the weight of the patient [g], which is used a surrogate for a distribution volume of tracer. If all the injected FDG is retained and uniformly distributed throughout the body, the SUV everywhere will be 1 g/ml regardless of the amount of FDG injected or patient size. SUVs are dimensionless under the assumption that 1ml of tissue weights 1 gm. Both approaches are used in practice. The use of lean body mass for w has also been suggested to account for the lower uptake of FDG. The use of SUVs as a measurement of relative tissue/organ uptake facilitates comparisons between patients and has been suggested as a basis for diagnosis. However, the practice of using SUV thresholds for diagnosis is not widely accepted. In an ideal case, where there was no resolution loss or uncertainty in boundary definition, simply computing the average SUV within a region of interest (ROI) would produce a reliable estimate of the mean SUV, which is defined as SUVmean. However, in practice, there are challenges imposed by image noise and the limited resolution of PET imaging. Both of these effects contribute to problems in defining the boundary of the region over which the average is to be computed. Numerous studies have attempted to define methods that are accurate and/or reproducible. The use of the maximum SUV value, defined as SUVmax, is becoming more common. In addition, SUVmax has a significantly improved reproducibility as compared to SUVmean, since the maximum value within an ROI is typically invariant with respect to small spatial shifts of the ROI. A concern with the use of SUVmax is that it is basing a reported value for a lesion on perhaps only one pixel. Thus, SUVmax is potentially biased and more noisy when compared to SUVmean and/or the true SUV. Recent results have indicated both the bias and increased variance are less than might be expected, likely due to the noise correlations introduced during the image reconstruction process. In addition, several patient studies have shown that SUVmax is a robust metric for assessing treatment response.

I calculated SUVmax (g/ml) for both the primary tumour and the nodal disease. In case of multiple pathological nodes, I reported the highest value of nodal SUVmax. An example of calculation of SUVmax is presented in Figure 2.13.1.



(a)



(b)

Figure 2.13.1 Calculation of SUVmax. The Eclipse Treatment Planning System (Varian) was used to calculate the SUVmax in the (a) primary tumour (13 g/ml in the left base of tongue in this example) and (b) nodal disease (9 g/ml in left level II in this example). The Region of Interest (ROI) can be selected (red square) and the system calculates the SUVmax (histogram).

I looked for differences in SUVmax for the primary tumour and the nodal disease in the three risk categories of oropharyngeal cancer according to Ang et al [6]:

- Low risk: HPV+, non-smokers or smoking history of ≤10 pack years; good prognosis (3-year overall survival >90%).

- Intermediate risk: HPV+, smoking history of >10 pack years; intermediate prognosis (3-year overall survival 70%).

- High risk: HPV-; bad prognosis (3-year overall survival 45%).

2.14 Target volumes for treatment and Organs at Risk

The target volumes for treatment were defined considering endoscopic information, anatomical imaging (diagnostic CT and MRI if available, contrast enhanced simulation CT) and PET/CT. The PET radiologist (1 observer) and I defined together the target volumes considering the PET/CT images and the contrast enhanced simulation CT (fused with PET/CT). T and N were contoured on PET/CT with visual assessment. For visual assessment purposes, SUVmax was measured in T and N, and the PET intensity scale was fixed from 0 to SUVmax of T and N separately. The PET radiologist (1 observer) and I defined the volumes visually as per clinical judgement taking into consideration anatomical/functional imaging and clinical information (endoscopy).

There is no available data showing differences in sensitivity and specificity of baseline pre-treatment PET between HPV+ and HPV- patients. Considering that baseline pre-treatment PET has overall sensitivity and specificity of 80% and 85% in detecting nodal metastases [65], if PET was frankly positive or negative, this was considered as true positive or negative result respectively so Ultrasound (US) and Fine Needle Aspiration (FNA) were not performed as confirmation of the PET result. This was a pragmatic approach to avoid additional procedures and a delay of treatment. If PET was equivocal, US+FNA were performed to minimise the risk of false positive (20%) or negative (15%) results of PET. This pragmatic approach reflects the recommendation of the PET-neck study [190] for neck dissection in case of positive, equivocal or negative PET after chemo-radiotherapy.

I contoured the Gross Tumour Volume (GTV) for T (GTV_T) and N (GTV_N). I contoured the "High risk" Clinical Target Volume (CTV65) as GTV_T and GTV_N with a margin for microscopic infiltration of 15mm and 10mm respectively with correction for airways and anatomical barriers (i.e. bone). 15mm and 10mm are the standard margins used at the Beatson for primary and nodal disease respectively in oropharyngeal cancer in accordance with international guidelines at the time patients were treated (updated guidelines in 2018 advise instead the concept of smaller 5+5mm and 5mm margin for primary and nodal disease

respectively [175]). I included the whole nodal levels including GTV_N in CTV65. I contoured the "Low risk" Clinical Target Volume (CTV54) as the nodal levels at low risk of tumour dissemination according to the international guidelines [218]. I generated the "High" and "Low" risk Planning Target Volume (PTV65 and PTV54) with an isotropic set-up safety margin of 3mm from CTV65 and CTV54 respectively. 3mm is the standard set-up margin used for head&neck VMAT at the Beatson which derives from an internal audit on average set-up errors with the use of standard thermoplastic masks. An example of target volumes for treatment is presented in Figure 2.14.1.

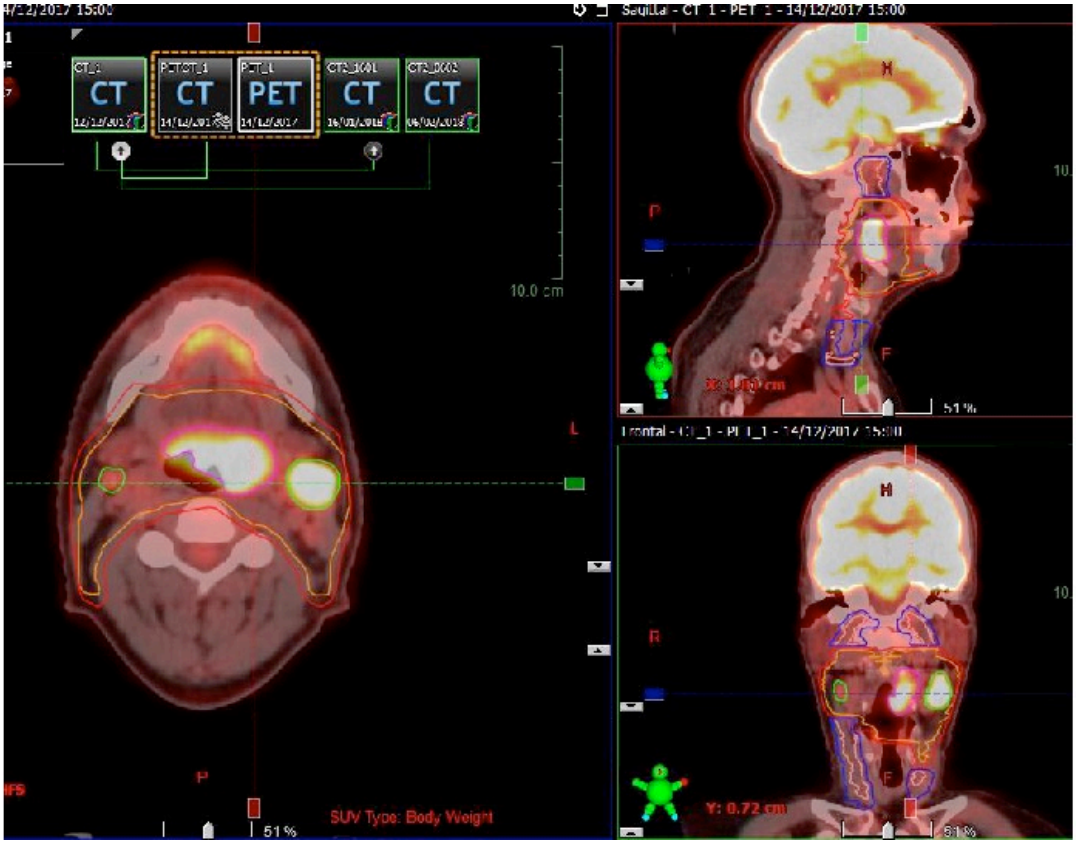


Figure 2.14.1 Definition of target volumes with PET/CT-visual assessment. GTV_T (magenta) and GTV_N (green) with an isotropic margin of 15mm and 10mm respectively, and the corresponding high risk nodal levels were included in CTV65 (orange) with correction for airways and anatomical barriers. CTV65 was expanded with a 3mm margin to generate PTV65 (red). Low risk nodal levels were included in CTV54 (pink) with a margin of 3mm for PTV54 (blue).

I contoured the following Organs at Risk (OARs):

- Eye globes

- Lenses

- Optic nerves

- Optic chiasm

- Cochlea

- Brainstem: the whole brain stem was outlined from the most superior slice of the spinal cord.

- Spinal cord: the spinal cord was outlined from the slice below the level of the foramen magnum to 2cm below the most inferior slice of the PTV.

- Parotids: the parotids were contoured separately. Both superficial and deep lobes were defined as single organ. Where blood vessels were encased by the gland, these were included. Where applicable, the accessory parotid gland extending along the parotid duct and the masseter muscle was included.

- Larynx: the larynx was contoured from the superior border of the hyoid bone to the inferior border of the thyroid cartilage.

- Trachea/oesophagus: trachea and oesophagus were contoured as a single medial organ from the inferior border of the thyroid cartilage to 2cm below the most inferior slice of the PTV.

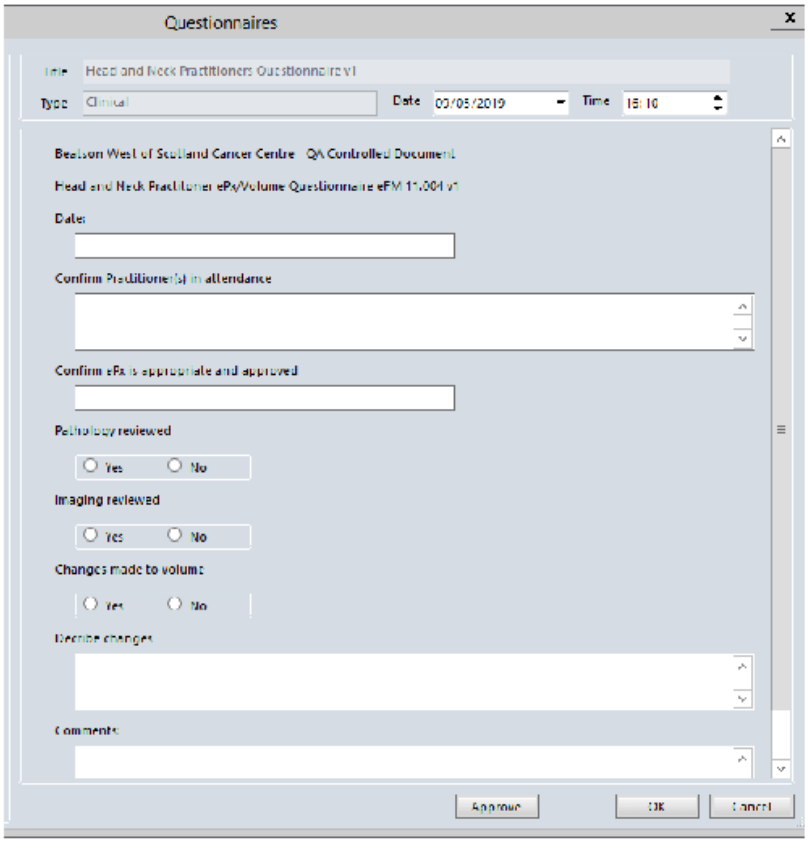
- Oral cavity: the oral cavity included mandible and soft tissue of the mouth with a 5mm margin from PTV.

I expanded spinal cord and brainstem with an isotropic 4mm margin to generate the Planning Risk Volume (PRV_spinal cord and PRV_brainstem respectively). I defined Parotid_PC as parotid cropped 5mm from PTV for dose reporting. An example of OARs is presented in Figure 2.14.2.

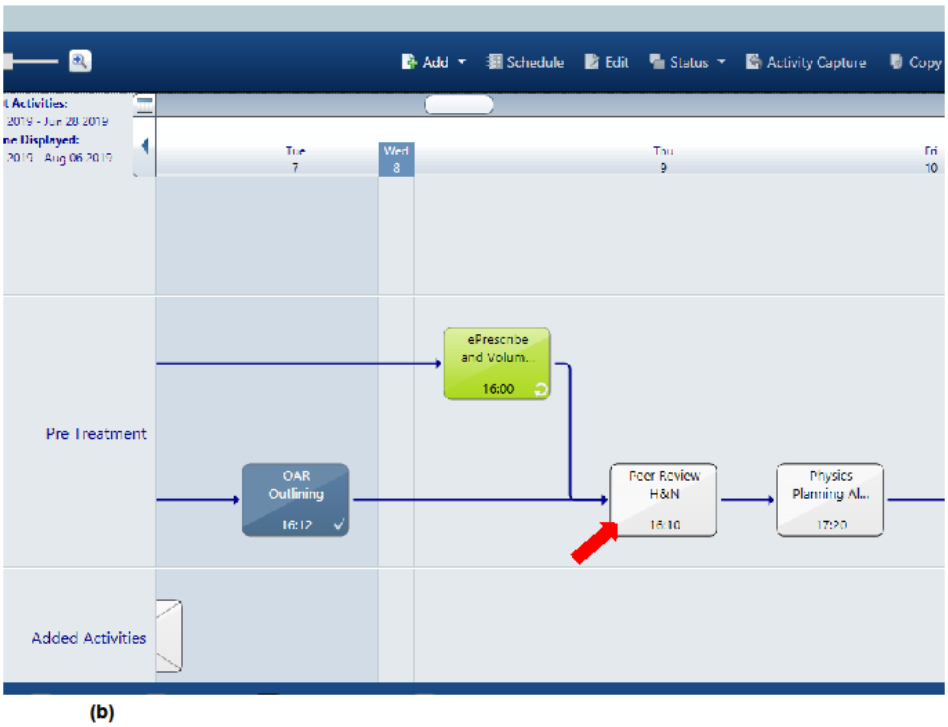
Figure 2.14.2 Organs at Risk

2.15 Peer review for clinical use

I presented the target volumes for clinical use at the "Peer Review Meeting" which is attended by head&neck oncologists, radiographers, physicists, dosimetrists and trainees. The aim of the "Peer Review Meeting" is to discuss the clinical information and the radiotherapy target volumes of the patients undergoing radiotherapy. This multidisciplinary group reviews radiology (CT, MRI, PET), pathology, relevant clinical information including endoscopy and radiotherapy target volumes. The group approves the volumes or advises for any changes to be made. It was my responsibility to make the proposed changes if necessary and approve the final volumes for treatment planning. The final approval is formalised by a "Peer review task" that is completed in the radiotherapy treatment planning system (Eclipse, Aria). An example is shown in Figure 2.15.1.



(a)



(b)

Figure 2.15.1 Peer review for clinical use. After the Peer Review Meeting, the consultant in charge of the patient authorises the radiotherapy target volumes, completes the ePrescribe/Volume task (b, green), the peer review questionnaire (a) and the peer review task (b, red arrow) in the radiotherapy treatment planning system (Eclipse, Varian).

2.16 Treatment planning

I prescribed a dose of 65Gy and 54Gy in 30 fractions to “High” and “Low” risk Planning Target Volume (PTV65 and PTV54) respectively. Treatment planning was optimised by Physics staff with the AAA algorithm for Rapid Arc (Varian). Various constraints were applied to PTV65, PTV54 and the Organs at Risk as summarised in Table 2.16.1.

	Constraint	Dose %
PTV65	D99%	>90
	D95%	>95
	D5%	<105
	D2%	<107
PTV54	D99%	>90
	D95%	>95
	Mean	53-56Gy
	D5%	<117
	D2%	<122
		Dmax (cGy)
PRV Spinal Cord	D1%	4400
PRV Spinal Cord	point max	4800
PRV Brainstem	D1%	4800
Optic Nerve	D1%	5000
Optic Chiasm	D1%	5000
Parotid_PC		2400 (Dmean)
Oral cavity		3500 (Dmean)
Larynx		4000(Dmean)
Cochlea		5000
Lens		800
Eye		800 (Dmean)

Table 2.16.1. Head&neck Rapid Arc dose constraints. PTV= Planning Target Volume, PRV= Planning Risk volume, Parotid_PC= parotid cropped 5mm from PTV

2.17 Plan approval

I reviewed the Rapid Arc (VMAT) plan assuring adequate dose coverage of the PTVs and OAR constraints within the defined limits. I approved the plan in Eclipse electronically.

2.18 Pre-assessment

I reviewed the patients the week before the beginning of treatment for assessing fitness and nutritional status.

2.19 Clinical treatment

Radiotherapy was given once daily, 5 days a week for 6 weeks. If indicated, I prescribed concomitant chemotherapy with Cisplatin 100mg/m2 day 1 and day 21. Patients not fit for Cisplatin and <70 years of age were offered Cetuximab (250mg weekly). Patients ≥70 years of age were given radiotherapy alone since there is no evidence of advantage in the use of concomitant treatment in this group of patients. Patients were reviewed clinically once a week by the head&neck specialist nurses.

2.20 Follow up and outcome data collection

At the time most of the patients were treated within this project, there was no consensus on the systematic use of PET for treatment response after (chemo)radiotherapy in patients with nodal disease. PET-neck study was published in 2016 and showed the advantage of PET for post-treatment assessment [190]. For the purpose of this project patients had CT (before 2016) or PET/CT (from 2016) at 3 months after the end of treatment. In case of residual primary or nodal disease, endoscopy+biopsy or US+FNA were performed respectively with salvage surgery as appropriate. After the 3-months scan, patients were followed-up without imaging unless clinically indicated. I followed up the patients at 3, 6 and 12 months after the end of treatment, then every 12 months up to 60 months. I collected and recorded electronically outcome and late toxicity data.

2.21 Statistics

Data were collected in an Excel database and secured for confidentiality purposes. Data were then analysed using Stata v14.2 (StataCorp LLC, Texas). Continuous data were summarised using medians (with range or inter-quartile range IQR). Kruskal Wallace and Mann-Whitney tests were used to test for differences in median values between 3 or more groups or two groups respectively. Wilcoxon signed rank test was used to test for differences between paired measurements, for example SUVmax for primary and nodal disease. All tests were 2-sided and a p-value <0.05 was considered statistically significant.

CHAPTER 3

RESULTS (A): DEMOGRAPHICS, FUSION ACCURACY, SUVmax

In this Chapter demographics, fusion accuracy between PET/CT and simulation CT, and SUVmax results for both the primary tumour and the nodal disease are reported. The clinical characteristics of the patients enrolled are presented. The accuracy of the fusion between PET/CT and simulation CT was calculated with a reproducibility index (R) of selected bony structures (maxillary sinuses, C1 and C4) to assess the robustness of the fusion methodology. SUVmax (g/ml) was calculated from primary tumour and nodal disease and correlated with the three prognostic groups (low: HPV+, non-smokers or <10 pack years smoking history; intermediate: HPV+, >10 pack years smoking history; high risk: HPV-) to assess the hypothesis that aggressive tumours are more hyper-metabolic (i.e. have higher SUVmax).

3.1 Demographics

Between September 2014 and March 2018 a total of 30 patients with locally advanced oropharyngeal squamous cell carcinoma were enrolled. Patient characteristics are summarised in Table 3.1.1. The majority of the patients had base of tongue (36%) and tonsillar (30%) tumour and stage IV disease (77%) according to TNM7. A smoking history of ≤10 and >10 pack years was recorded in 13/28 (46%) and 15/28 (54%) patients respectively. Nine patients were non-smokers. The smoking history was not known in 2 patients. HPV status was assessed in 24 patients and 18 (75%) were HPV positive as assessed by p16 and DNA PCR, which were concordant in 100% of the cases in accordance with data from the literature (98%) [219]. Twenty-seven (90%) and 3 (10%) patients had ECOG PS≤1 and PS>1 respectively before the beginning of treatment. Chemo-radiotherapy with concomitant Cisplatin (100mg/m2 every 3 weeks) or Cetuximab (250mg weekly) was given to 22 (73%) and 1 patient (3%) respectively and 7 patients (24%) received radiotherapy alone. Patients who were not fit enough for or had contra-indications to Cisplatin (e.g. renal impairment, peripheral neuropathy, etc) received concomitant Cetuximab or radiotherapy alone depending on fitness, age and co-morbidities. Patients with age >70 (n=3) received radiotherapy alone.

		N=30
Gender	Male:Female	24:6
Age	Median age (range)	58 (42-75)
	≤70	27 (90%)
	>70	3 (10%)
Site	Base of tongue	11 (36%)
	Tonsil	9 (30%)
	Soft palate	2 (7%)
	OP other	8 (27%)
Stage (TNM7)	III	7 (23%)
	IVa	19 (63%)
	IVb	4 (14%)
HPV	Positive	18 (60%)
	Negative	6 (20%)
	Unknown	6 (20%)
Smoking - pack years (py)	≤10py	13 (43%)
	>10py	15 (50%)
	Unknown	2 (7%)
Risk category	Low	9 (30%)
	Intermediate	9 (30%)
	High	6 (20%)
	Unknown	6 (20%)
PS (ECOG) at baseline	≤1	27 (90%)
	>1	3 (10%)
Treatment	Chemo-radiotherapy	23 (76%)
	Radiotherapy	7 (24%)

Table 3.1.1. Patient characteristics

3.2 Fusion accuracy

No data is available in the literature regarding the accuracy of the rigid registration between a diagnostic PET/CT and a simulation CT scan using a commercial software for radiotherapy treatment planning system (Eclipse, Varian). The scanning and fusion methodology between PET/CT and simulation CT has been presented previously in Figure 2.8.1 and 2.9.1. A thermoplastic mask was personalised for each patient. A contrast enhanced simulation CT was acquired with the thermoplastic mask on the head&neck region with the patients positioned on a flat couch. Contrast was given only to patients with adequate renal function. PET/CT was acquired with patients lying on a flat couch. Patients were initially scanned from the lower neck to the pelvis in arm down position. Subsequently, the patients wore the thermoplastic mask and PET/CT was acquired on the head&neck region. PET/CT of the head&neck region was transferred to the radiotherapy treatment planning system (Eclipse, Varian). A rigid fusion between PET/CT and simulation CT was performed using the radiotherapy treatment planning system (Eclipse, Varian).

The fusion accuracy between PET/CT and simulation CT was assessed in 14 patients. Since the variability of the results in the two groups was small, I decided not to calculate the fusion accuracy for the 30 patients in order to limit the workload of this complex methodology. The bony structures (maxillary sinuses, C1 and C4) defined on PET/CT and simulation CT as a single volume resulted 84.4cc (47.7-117.4) and 86.3cc (47.7-117.9) respectively with no significant difference (p0.94). The fusion accuracy calculated with the reproducibility index (R) resulted 0.89 (0.83-0.92). There is no data from the literature to compare this result with. Fusion accuracy of 0.89 is a positive result considering possible minimal set-up differences between PET/CT and simulation CT and intra-observer variability in contouring the bony structures. An example of fusion accuracy evaluation has been presented previously in Figure 2.10.2.

3.3 SUVmax

SUVmax (g/ml) for both the primary and nodal disease was compared using the Wilcoxon signed rank test. In case of multiple pathological nodes, the highest value of nodal SUVmax was reported. Median SUVmax (g/ml) was 19.0 (range 9.7-40.0) and 13.7 (3.0-25.0) for primary and nodal disease respectively. A total of 27 patients had SUVmax recorded for both primary and nodal disease. Among these patients median SUVmax was significantly higher in the primary tumour compared to the nodal disease (19.0 versus 14.0 g/ml, p=0.0001). An example of calculation of SUVmax has been reported previously in Figure 2.13.1.

SUVmax was also calculated for primary tumour and nodal disease in the three risk categories of oropharyngeal cancer according to Ang et al [6]. Using this classification there were 9 low, 9 intermediate and 6 high risk patients. There were 6 patients who could not be classified because HPV status was unknown (this included 2 patients who also had unknown pack-years). T SUVmax and N SUVmax were not recorded in 2 and 2 patients respectively. Both T SUVmax and N SUVmax were lower in the HPV+ (low/intermediate risk group) compared to HPV- patients (high risk group), however differences were not statistically significant as reported in Table 3.3.1.

	T SUVmax (g/ml)				N SUVmax (g/ml)			
Risk group	N	median	IQR	p-value	N	median	IQR	p-value
low/intermediate (HPV+)	16	16.9	(12.5-22.7)	0.20	17	10.0	(7-16)	0.06
high (HPV-)	6	21.0	(20-25)		5	17.0	(15-20)	
unknown	6	19.0	(16-30)		6	11.0	(4.2-17)	

Table 3.3.1 Mann Whitney test for difference between HPV+ (low/intermediate) and HPV- (high risk) groups

In the separate 3 risk group analysis, T SUVmax was significantly lower in the intermediate (13 g/ml) compared to the low (21.3 g/ml) and high risk group (21 g/ml). N SUVmax was also lower in the intermediate risk group (8.8 vs 15 vs 17 g/ml) but this was not statistically significant as reported in Table 3.3.2. The analysis does not tend to support the original observation that low risk patients have lower SUVmax.

	T SUVmax (g/ml)				N SUVmax (g/ml)			
Risk group	N	median	IQR	p-value	N	median	IQR	p-value
low	9	21.3	(16-25)		9	15.0	(7.5-16)	
intermediate	7	13.0	(10.5-18)	0.042	8	8.8	(5.7-11)	0.07
high	6	21.0	(20-25)		5	17.0	(15-20)	
unknown	6	19.0	(16-30)		6	11.0	(4.2-17)	

Table 3.3.2 Kruskal Wallace test of difference between low, intermediate and high risk groups

CHAPTER 4

RESULTS (B): STAGE MODIFICATION DUE TO PET

Contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) and positron emission tomography/CT (PET/CT) are widely used to determine the presence and extent of head &neck tumours both before and after treatment. However, PET/CT is superior to both CT and MRI in detection of carcinoma of unknown primary (CUP), cervical lymph node metastasis, distant metastasis, residual tumour, recurrent disease and second primary tumours leading to possible alteration in treatment planning [220-223]. Before treatment, PET/CT can be used for delineation of the extent of primary, detection of unknown primary or synchronous primary tumour (T), detection of regional lymph node and distant metastases. Standard staging of head&neck squamous cell carcinoma follows the TNM classification according to the American Joint Committee on Cancer. The primary tumour extension (T stage) varies from site to site given differences in specific anatomic detail of each site, while regional lymph node involvement (N0 to N3 stage) shares similar classification with the exception of thyroid and nasopharyngeal cancers. Metastases outside head&neck regions (e.g. mediastinal and axillary lymph nodes) represent distant disease (M stage) [224]. Precise tumour staging is critical for treatment planning and prognosis. Prior to initiation of treatment, HNC is clinically staged by using clinical examination, imaging, and endoscopy with tissue biopsy or fine needle aspiration. Multiple studies suggest that PET/CT is superior to conventional imaging (CT or MRI) in initial staging and may alter management and treatment especially when unexpected cervical lymph nodes and/or distant metastases are discovered. The National Comprehensive Center Network issued an update in clinical practice guidelines in HNC and PET/CT imaging in 2013, and suggested using PET/CT for initial staging of the oral cavity, oropharyngeal, hypopharyngeal, glottic, and supraglottic cancers for stage III-IV disease as well as mucosal melanoma and nasopharyngeal carcinoma (World Health Organization class 2-3 and N2-3 diseases [225]. The accuracy of staging is increased when the information of clinical assessment and multiple imaging modalities are analysed [226].

In this Chapter the results of the comparison between TNM staging defined with baseline contrast enhanced CT and pre-radiotherapy PET/CT are reported. To be noted that TNM classification 7th edition was used in this thesis and no pre-radiotherapy MRI data was available for this patient series.

4.1 T stage modification

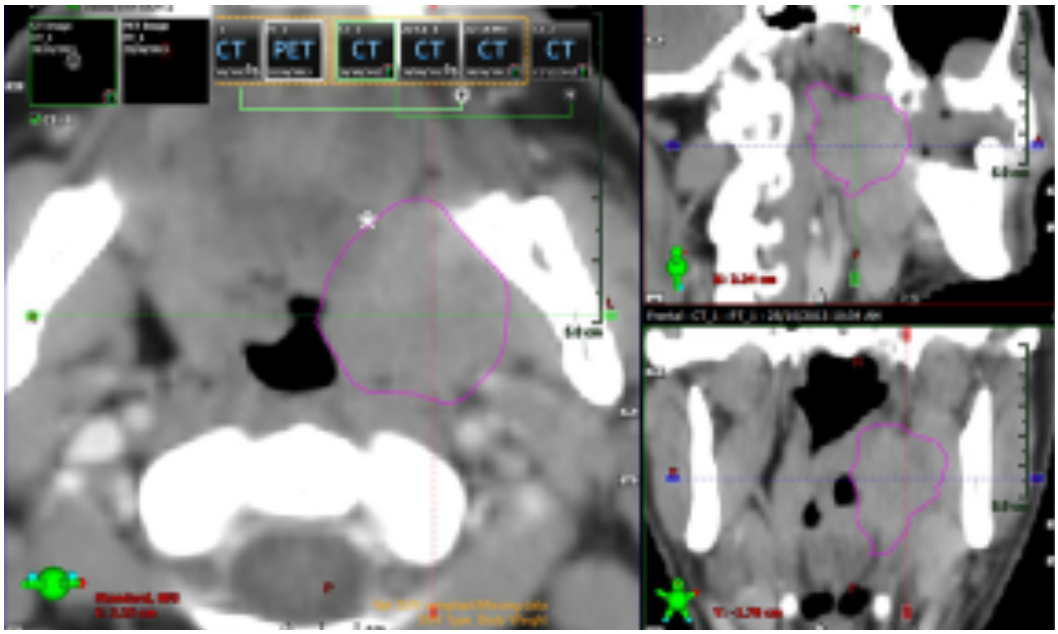
There is no clear recommendation for routine use of PET/CT in initial T staging. MRI is recommended for the assessment of nasopharynx, oral cavity, oropharynx, perineural spread and bone marrow invasion. However, MRI can be affected by motion artefacts due to prolonged imaging time [227,228]. CT is the imaging modality of choice for larynx, bony cortex invasion and ill-defined tumour with submucosal extension and diffuse infiltration. Dental amalgam artefacts can affect CT imaging in the oral cavity and oropharynx [229]. PET/CT can be affected by false positive results due to normal lymphoid tissue uptake in oral cavity and oropharynx, and limited resolution in detecting small, superficial lesions and lesions obscured by dental artefacts [230]. Accuracy is increased when the information of multiple imaging modalities is available [226].

In my project, PET/CT and simulation contrast enhanced CT defined different volumes for the primary tumour. The details are reported in Chapter 5 "Target volume variability". For the purpose of the TNM classification, PET/CT down-staged the primary tumour in 20% of the patients due to changes in the tumour greatest dimension (i.e. from T3 >4cm to T2 ≤4cm). An example is reported in Figure 4.1.1. For clinical use, the volume defined with PET (visual assessment) was considered along with the anatomical information of the contrast enhanced radiotherapy planning CT in order to generate a hybrid volume minimising the risk of geographical miss.

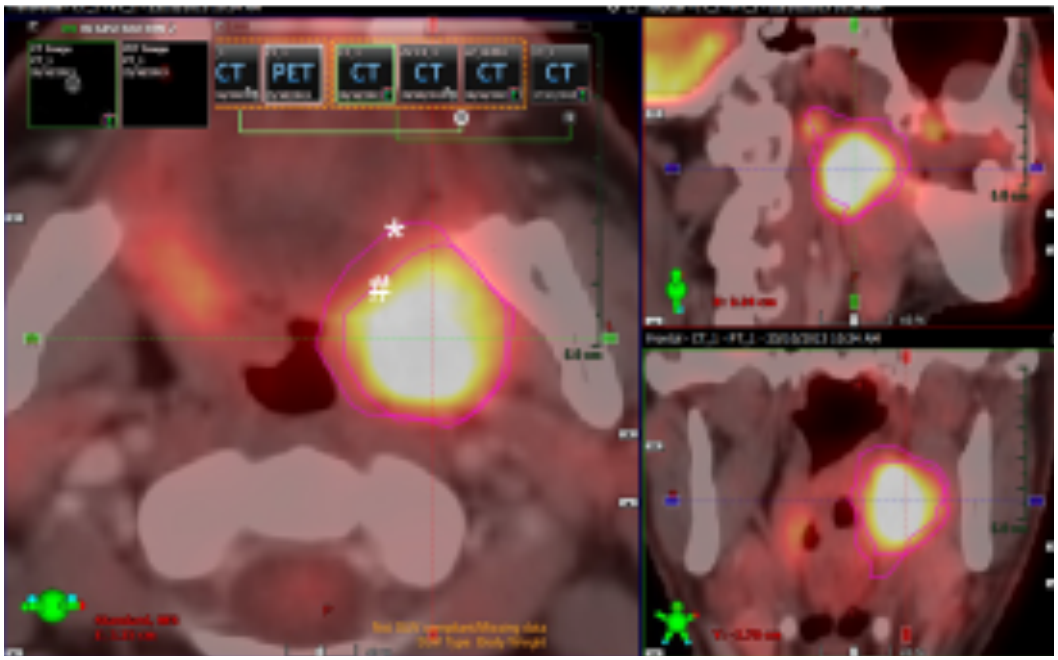
PET/CT did not modify the T staging in 80% of the patients due to non-relevant change of the tumour greatest dimension and/or anatomical reasons according to TNM 7th edition. An example is reported in Figure 4.1.2. T-stage modifications due to PET/CT are summarised in Table 4.1.1. Overall these results are in agreement with the data from the literature. The definition of a smaller primary tumour with PET/CT may lead to reduction of radiotherapy related short and long-term side effects, however this cannot be always clinically relevant because of nodal disease upstaging with PET/CT (e.g. bilateral vs unilateral pathological nodes) as reported in Paragraph 4.2.

Stage modification	n=30
Up-staged	-
Down-staged (from T3 to T2)	6 (20%)
No change	24 (80%)

Table 4.1.1 T stage modification due to PET/CT according to TNM 7th edition

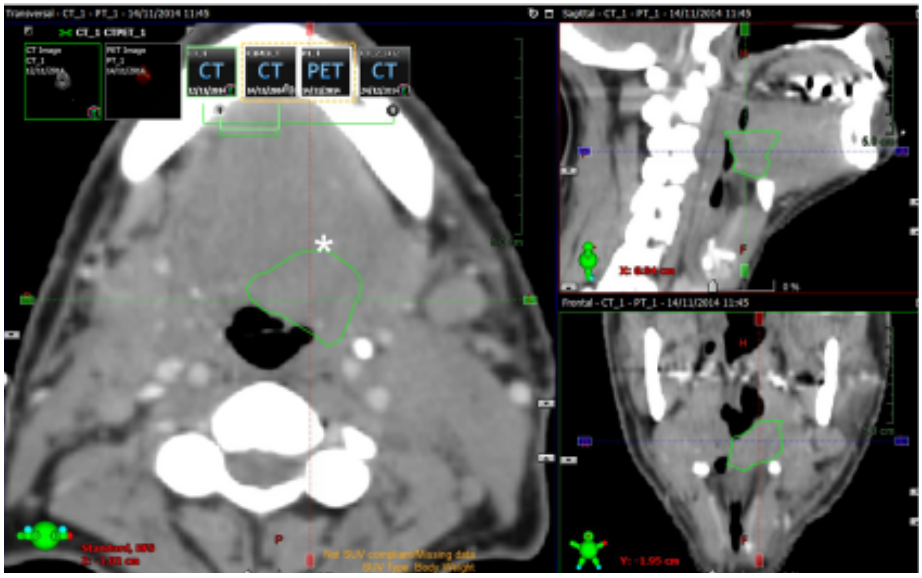


(a)

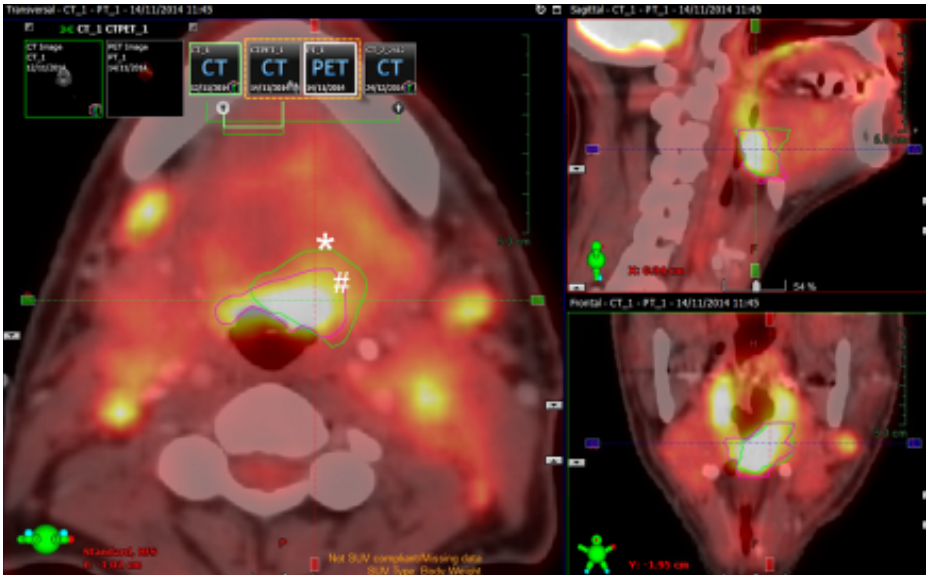


(b)

Figure 4.1.1. Patient with left tonsillar tumour initially staged as (*) T3 (tumour greatest dimension >4cm) with contrast enhanced CT (a). The primary tumour defined with PET/CT (b) can be classified as (#) T2 (tumour greatest dimension ≤4cm).



(a)



(b)

Figure 4.1.2. Patient with left base of tongue tumour. Contrast enhanced CT (a) (*) defined a larger primary tumour compared to PET/CT (b) (#), however the T stage (T4a) did not change due to the infiltration of the extrinsic muscles of the tongue.

4.2 N stage modification

The likelihood of cervical lymph node metastases in HNC depends on location, histology and staging of the primary tumour. Differentiation between metastatic and reactive nodes by size and morphologic criteria can be challenging. PET has higher sensitivity and specificity compared to other morphological imaging modalities (80%/86% vs 75%/79%) [238]. However, PET can be affected by inflammation and/or small necrotic hypometabolic nodes leading to false positive results of approximately 20% [239]. PET/CT is superior compared to morphological imaging modalities in detecting retropharyngeal node metastases with sensitivity and specificity of 89% and 86% vs 62% and 60% respectively [241]. PET/CT is not recommended in patients who do not present with metastatic lymph nodes at physical examination or morphological imaging (i.e. cN0). In a study on the use of FDG PET/CT prior to primary radiotherapy for HNC, PET/CT modified the N stage in 35% of the patients (n102); 23% of the patients were upstaged and 77% were downstaged [243].
In my series, PET/CT modified the N stage in 18/30 (60%) of the patients. The nodal status was down-staged from N1 to N0 in 1 patient (3%). The nodal status was up-staged in 17/30 (57%) of the patients. The introduction of PET/CT in the nodal staging led to 3 different scenarios in case of N-upstaging:

1. Patients with cN0 (i.e. no pathological nodes with clinical and morphological imaging assessment) were upstaged to ipsilateral or bilateral nodal disease (i.e. N1-N2c). This is discordant with the recommendation of not using PET/CT in case of cN0.

2. Patients with cN1 (i.e. ipsilateral single nodal disease) were upstaged to ipsilateral multiple or contralateral nodal disease (i.e. N2b or N2c).

3. Patients with cN0-N2b (i.e. no or ipsilateral nodal disease) were upstaged to N2c (i.e. bilateral nodal disease).

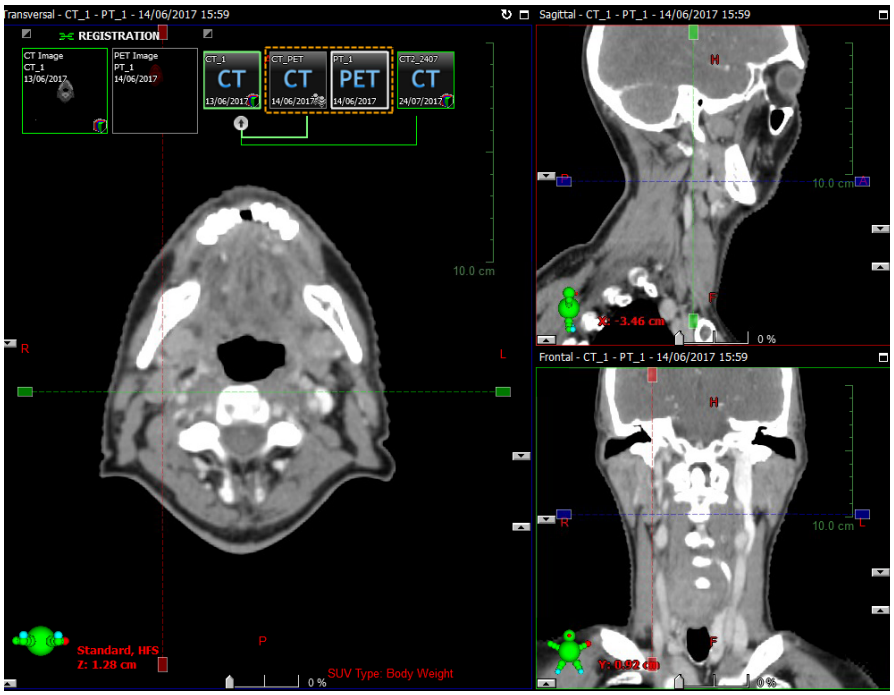
The HPV status was not correlated to either N upstaging or N2c.

Since by standard UK protocol the whole involved nodal level is treated with full radical dose (i.e. 65Gy) instead of prophylactic dose (i.e. 54Gy), the nodal upstaging can potentially increase the radiotherapy related toxicity especially in case of contralateral nodal upstaging (i.e. N2c). An example has been presented previously in Figure 2.12.1. The results of the N stage modification are summarised in Table 4.2.1.

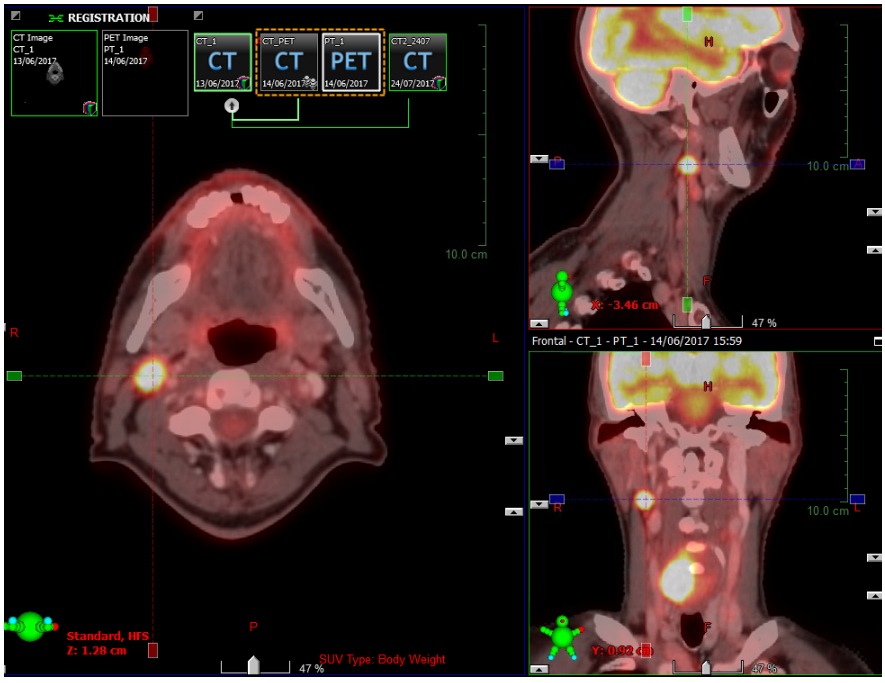
Stage modification	n=30
N0 to N1-N2c	6 (20%)
N1 to N2b-N2c	7 (23%)
N0-N2b to N2c	6 (20%)

Table 4.2.1. N stage modification according to pre-radiotherapy PET/CT

In case of N up-staging, an US+FNA was not performed if the nodal FDG uptake was clearly pathological on the basis of clinical judgement. Due to the higher sensitivity/specificity of PET/CT compared to CT and MR (80%/85% vs 75%/79%) [65], it was decided to consider the PET/CT results as true positive. Pragmatically, US+FNA was performed only in case of equivocal FDG nodal uptake to minimise the risk of false positive (20%) or negative (15%) results of PET. Only 3 patients (10%) had equivocal FDG nodal uptake. In these 3 cases (2 patients with N1 and 1 patient with N2b on CT) the US+FNA did not confirm nodal metastatic disease (N2b and N2c on PET/CT respectively) so those nodal areas were included in the prophylactic radiotherapy dose (54Gy). These 3 patients did not relapse in the neck at the time of their last follow-up. This supports the possibility of false positive results of PET (approximately 20%) in case of equivocal FDG nodal uptake in which case US+FNA should be performed. Typical examples of modification of the nodal staging are presented in Figure 4.2.1-3.

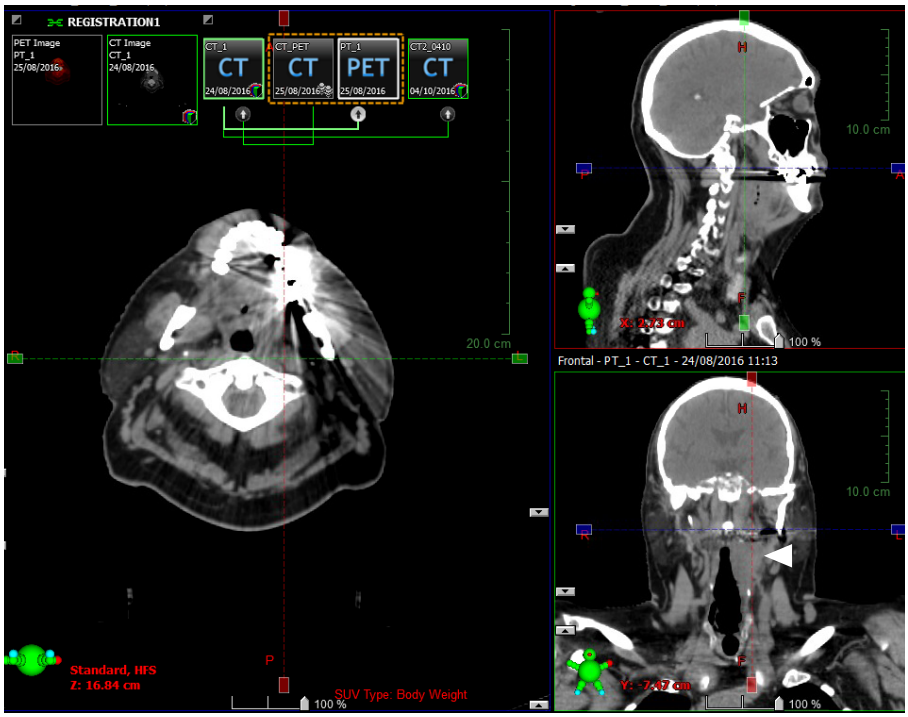


(a)

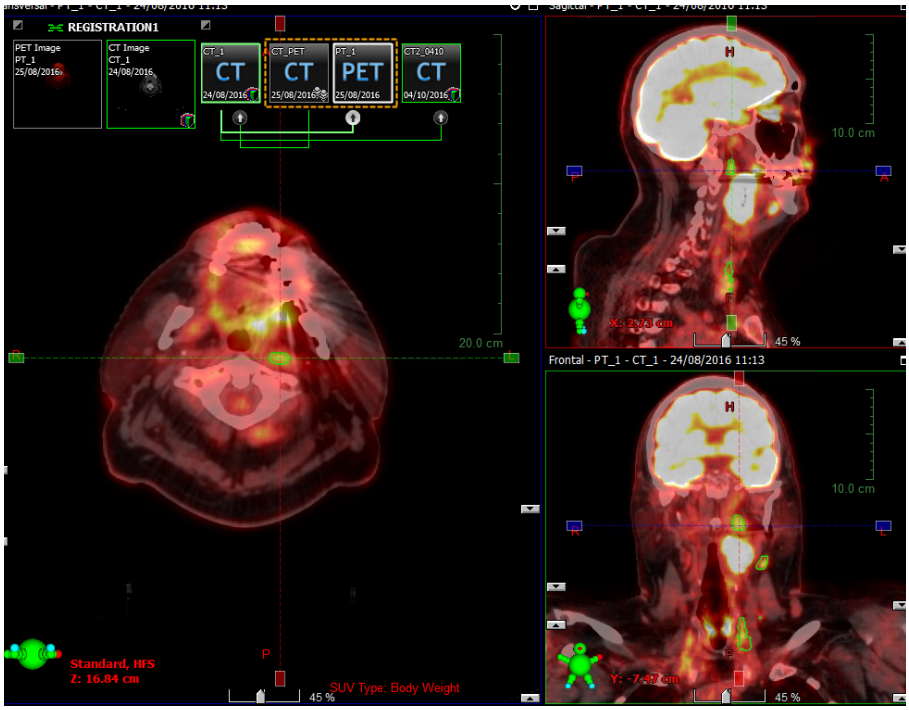


(b)

Figure 4.2.1. Patient with N0 disease in right level II on contrast enhanced CT according to morphological criteria (≤1cm, absence of necrosis or extracapsular spread) (a). PET/CT showed an intensively FDG avid metastatic right level II node (b) up-staging to N1.

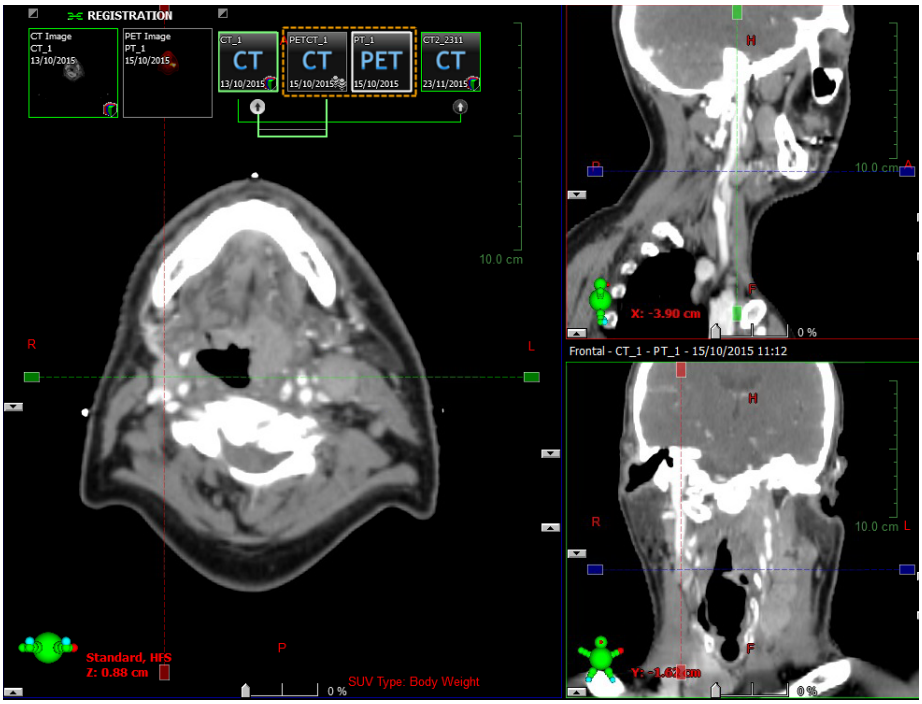


(a)

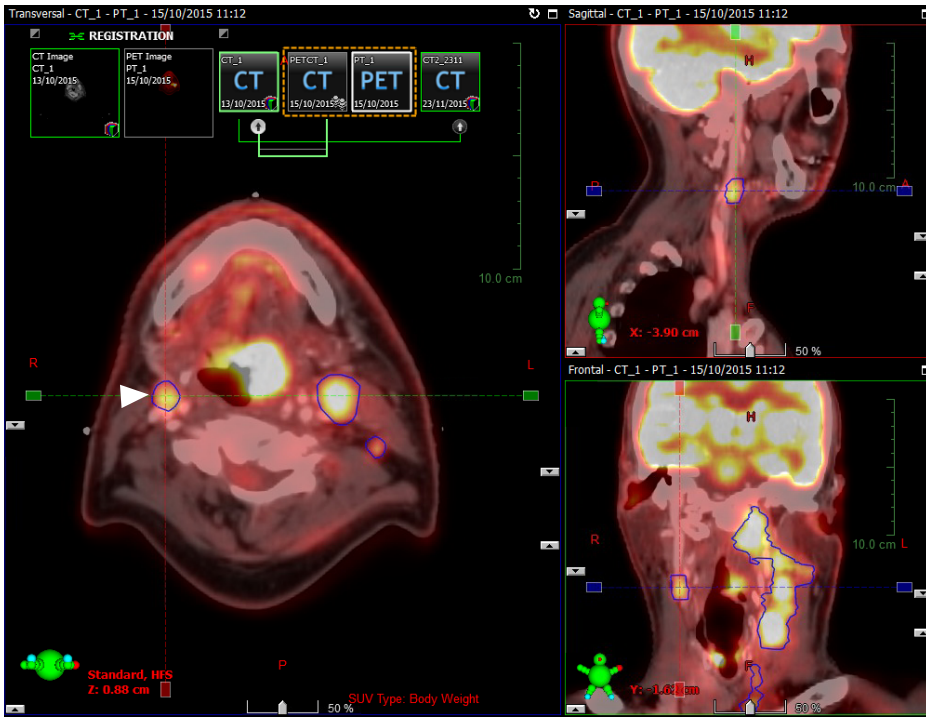


(b)

Figure 4.2.2. Patient with N2a disease in left level II on contrast enhanced CT (a, white arrow). PET/CT showed multiple FDG avid left retropharyngeal, II, III and IV nodal metastases (b, green) up-staging to N2b.



(a)



(b)

Figure 4.2.3. Patient with N2b disease in the left neck on contrast enhanced CT (a). PET/CT showed an additional right level II metastatic node (b, white arrow) up-staging to N2c.

4.3 M Stage modification

Patients with locally advanced HNC present with distant metastases in 7-25% of cases [244]. PET/CT is more accurate than CT in detecting metastatic disease with sensitivity and specificity of 87.5%/95% vs 73%/80% respectively [246]. PET/CT can detect unsuspected metastatic disease and alter the treatment management in 13.7% of the patients [248].
In my series, the pre-radiotherapy PET/CT did not show unsuspected distant metastases in any of the patients, however 2 patients (6%) developed lung metastatic disease after the end of treatment. In these 2 patients neither CT nor PET/CT showed lung metastases before treatment (i.e. the lung metastases were subclinical ab initio or developed after the treatment).

CHAPTER 5

RESULTS (C): TARGET VOLUME VARIABILITY

(CTsim VS PET/CT-VIS VS PET/CT-50%)

In this Chapter the results of the variability of the target volumes generated with different imaging modalities are reported. The aim is to show how different imaging modalities can modify the absolute volume and the spatial reproducibility of the target volumes. The target volumes (T and N) were defined on the contrast enhanced simulation CT (CTsim) without the information from the PET/CT. Subsequently, the target volumes were contoured on PET/CT with visual assessment (PET/CT-vis) and segmentation (PET/CT-50%). For visual assessment purposes, SUVmax was measured in T and N, and the PET intensity scale was fixed from 0 to SUVmax of T and N separately. Volumes were defined visually as per clinical judgement taking into consideration all the clinical information (CT, PET, endoscopy, etc). For segmentation purposes, the PET intensity scale was fixed from 50% to SUVmax of T and N separately. In the literature there is no recommendation on the %SUVmax to use for segmentation purposes, so the choice of 50% threshold was arbitrary and in accordance with an ongoing clinical trial [248]. Volumes (in cc) and spatial reproducibility index R=∩/U were calculated and compared for the different imaging modalities (i.e. CTsim vs PET/CT-vis vs PET/CT-50%). R=0 and R=1 were the lowest and higher grade of spatial reproducibility. The concept of R has been previously shown in Figure 2.10.1. The volumes defined with PET/CT-vis were used for the real treatment of the patients and this was an arbitrary choice since no guidelines are available in the literature regarding the segmentation methodology to use in the clinical practice. The target volume variability was assessed in 14 patients and is presented in Paragraph 5.1 and 5.2.

5.1 Primary tumour (T)

The median volume of the primary tumour (T) defined with PET/CTvis was smaller than the volume defined with CTsim (11.5cc vs 16.5cc, p=0.31) with reproducibility index R 0.49. The median volume of the primary tumour defined with PET/CT50% was smaller than the volume defined with PET/CTvis (4.6cc vs 11.5cc, p=0.001) with reproducibility index R 0.32.

PET/CT50% identified a smaller volume which was inside the volume defined with PET/CTvis, i.e. PET/CT50% identified a hyper-metabolic sub-volume inside PET/CTvis as

proven by a DICE index (PET/CT50% ∩ PET/CTvis / PET/CT50%) of 1 for all the 14 cases. This concept is shown in Figure 5.1.1.

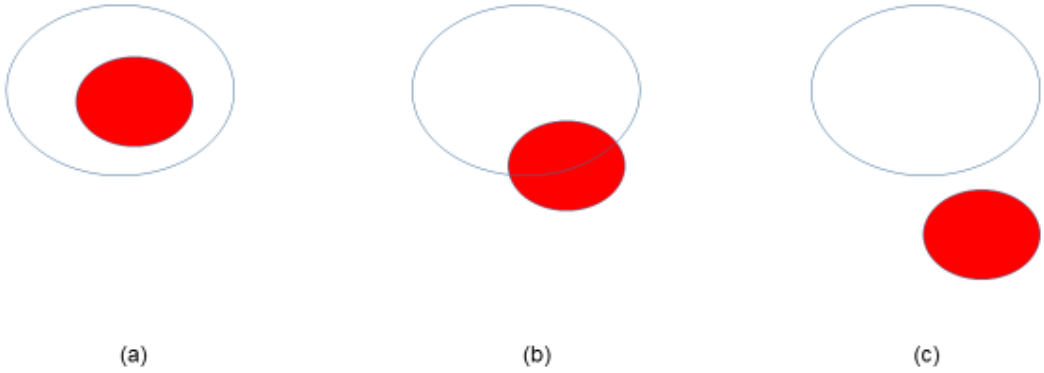


Figure 5.1.1. The volume identified by PET/CT50% (red) was a hypermetabolic sub-volume of the volume defined with PET/CTvis (blue) as shown by a DICE index (PET/CT50% ∩ PET/CTvis / PET/CT50%) of 1 (a). A DICE index <1 and 0 represents partial (b) or no overlapping (c) of the volumes respectively.

The results for the primary tumour are summarised in Table 5.1.1. An example of target variability has been previously reported in Figure 2.11.1.

<table>
<tr><th></th><th>T(cc)</th><th>R</th><th>R</th></tr>
<tr><td>CTsim</td><td>16.5*
(7-43.5)</td><td rowspan="2">0.49
(0.34-0.61)</td><td></td></tr>
<tr><td>PET/CTvis</td><td>11.5* #
(5.3-35.1)
p=0.31*</td><td rowspan="2">0.32
(0.1-0.58)</td></tr>
<tr><td>PET/CT50%</td><td>4.6#
(0.8-17.2)
p=0.001#</td><td></td></tr>
</table>

Table 5.1.1. Primary tumour (T) defined with different contouring modalities in 14 patients. CTsim= contrast enhanced simulation CT; PET/CTvis= PET/CT assessed with visual assessment methodology; PET/CT50%= PET/CT assessed with segmentation of the SUVmax with a threshold of 50% (i.e. 50% to 100% of the SUVmax); the reproducibility index was calculated as R= ∩/U of the volumes. A reproducibility of 100%, 50% and 0% is represented by R=1, R=0.5 and R=0 respectively.

These results support the use of the volumes defined with PET/CTvis for treatment because:

1. They should be considered more accurate compared to CT alone since PET/CTvis includes both the functional and the anatomical information.

2. CT alone is frequently affected by dental artefacts inducing over-estimation of the primary tumour compared to PET/CTvis. In case of dental artefacts PET/CTvis can be useful if MRI is not available as shown in Figure 5.1.2.

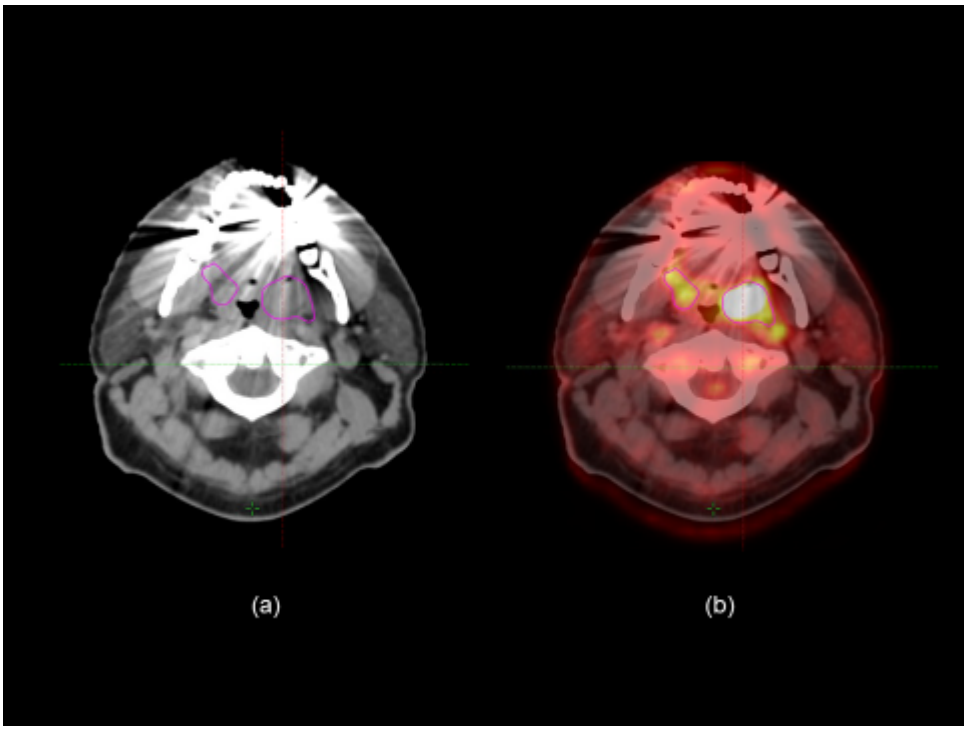


Figure 5.1.2. Dental artefacts can obscure the primary tumour in the oropharyngeal region on contrast enhanced CT (a). The functional information from PET/CT can easily identify viable tumour (magenta) if MRI is not available.

5.2 Nodal disease (N)

The median volume of the nodal disease (N) defined with PET/CTvis resulted bigger than CTsim (13.8cc vs 11.1cc, p=0.42) with reproducibility index R 0.47. The median volume of the nodal disease defined with PET/CT50% was smaller than the volume defined with PET/CTvis (3.5cc vs 13.8cc, p=0.04) with reproducibility index R 0.27. PET/CT50% identified a hyper-metabolic sub-volume inside PET/CTvis similarly to the primary tumour (T) as reported in Paragraph 5.1. The results for the nodal disease are summarised in Table 5.2.1 and an example of target variability has been previously reported in Figure 2.11.2.

	N(cc)	R	R
CTsim	11.1* (0-110.1)	0.47 (0-0.76)	
PET/CTvis	13.8* # (0-98.7) **p=0.42***		0.27 (0.14-0.7)
PET/CT50%	3.5# (0-30.7) **p=0.04#**		

Table 5.2.1. Nodal disease (N) defined with different contouring modalities in 14 patients. CTsim= contrast enhanced simulation CT; PET/CTvis= PET/CT assessed with visual assessment methodology; PET/CT50%= PET/CT assessed with segmentation of the SUVmax with a threshold of 50% (i.e. 50% to 100% of the SUVmax); the reproducibility index was calculated as R= ∩/U of the volumes. A reproducibility of 100%, 50% and 0% is represented by R=1, R=0.5 and R=0 respectively.

CHAPTER 6

RESULTS (D): OUTCOME RESULTS

The clinical results related to tumour response, tumour progression and overall survival of the patients treated with PET/CT-based VMAT are reported in this Chapter.

6.1 Tumour response

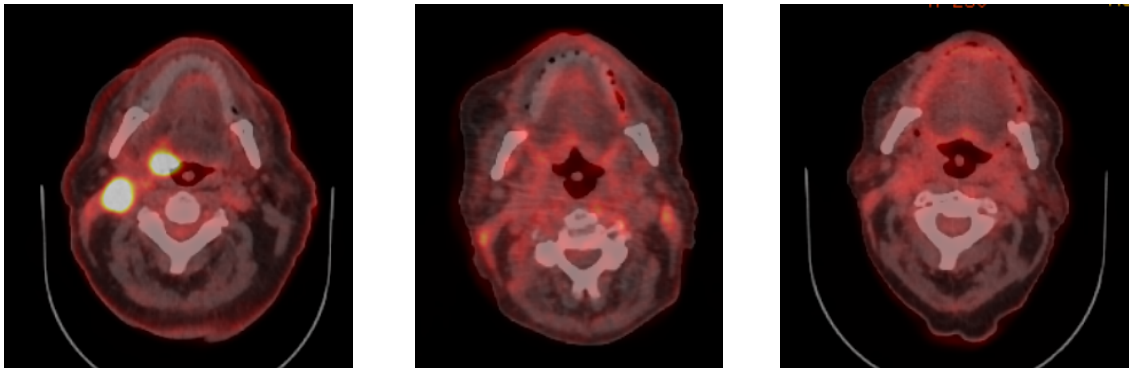
Tumour response was defined with RECIST 1.1 or metabolic criteria in patients who were assessed with CT or PET after treatment respectively as described in Paragraph 2.20. A total of 23 patients were evaluable for response at 3 months after the end of treatment. Complete response (CR), partial response (PR) and progressive disease (PD) were assessed in 18(78%), 4(18%) and 1(4%) respectively. 1 out of 4 patients with PR had residual FDG activity in both primary tumour and nodal disease and died from tumour progression 4 months after the end of treatment; this patient was HPV negative. 3 out of 4 patients with PR had residual FDG activity in the nodal disease. They had an US and FNA which did not show any residual cancer; these patients were HPV positive. These results are in agreement with the PET-neck study [249] showing the high predictive value of PET/CT for residual nodal cancer in HPV- oropharyngeal cancer.

The tumour response is summarised in Table 6.1.1.

Response	n=23	CT	PET/CT
CR	18(78%)	5	13
PR *	4(18%)	-	4
PD #	1(4%)	-	1

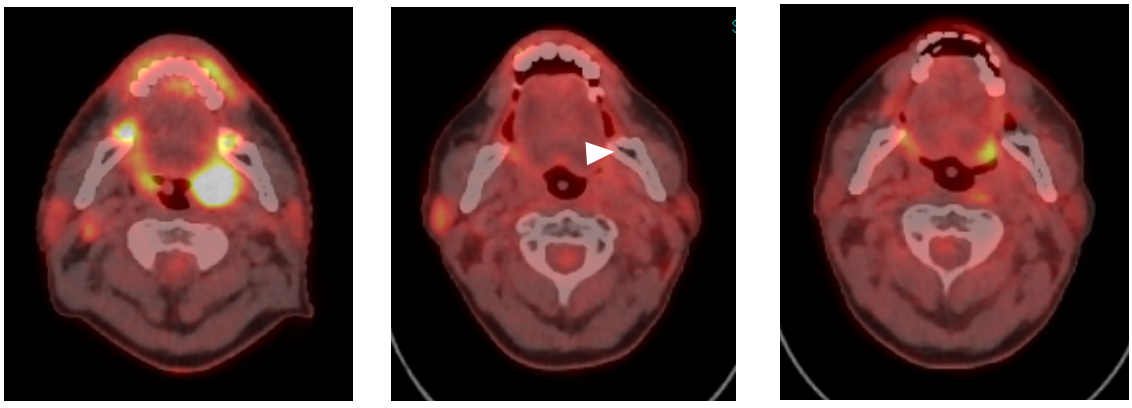
Table 6.1.1. Tumour response at 3 months after the end of treatment. Patients were assessed with CT or PET/CT. * 1 patient (HPV negative) had residual FDG activity in both primary tumour and nodal disease and deceased for tumour progression at 4 months after the end of treatment; 3 patients (HPV positive) had residual FDG activity in the nodal disease but US and FNA did not show any residual cancer. # PET/CT showed progressive metastatic disease in the lungs.

Four patients who had CR at 3 months had an additional PET/CT at 6 months confirming the CR. An example is shown in Figure 6.1.1. One patient with PR at 3 months with PET/CT had a PET/CT at 6 months showing CR. This case is shown in Figure 6.1.2. One patient had the first response assessment with PET/CT at 6 months showing residual FDG uptake in the primary tumour and nodal disease and new metastatic lung nodules. This case is shown in Figure 6.1.3.



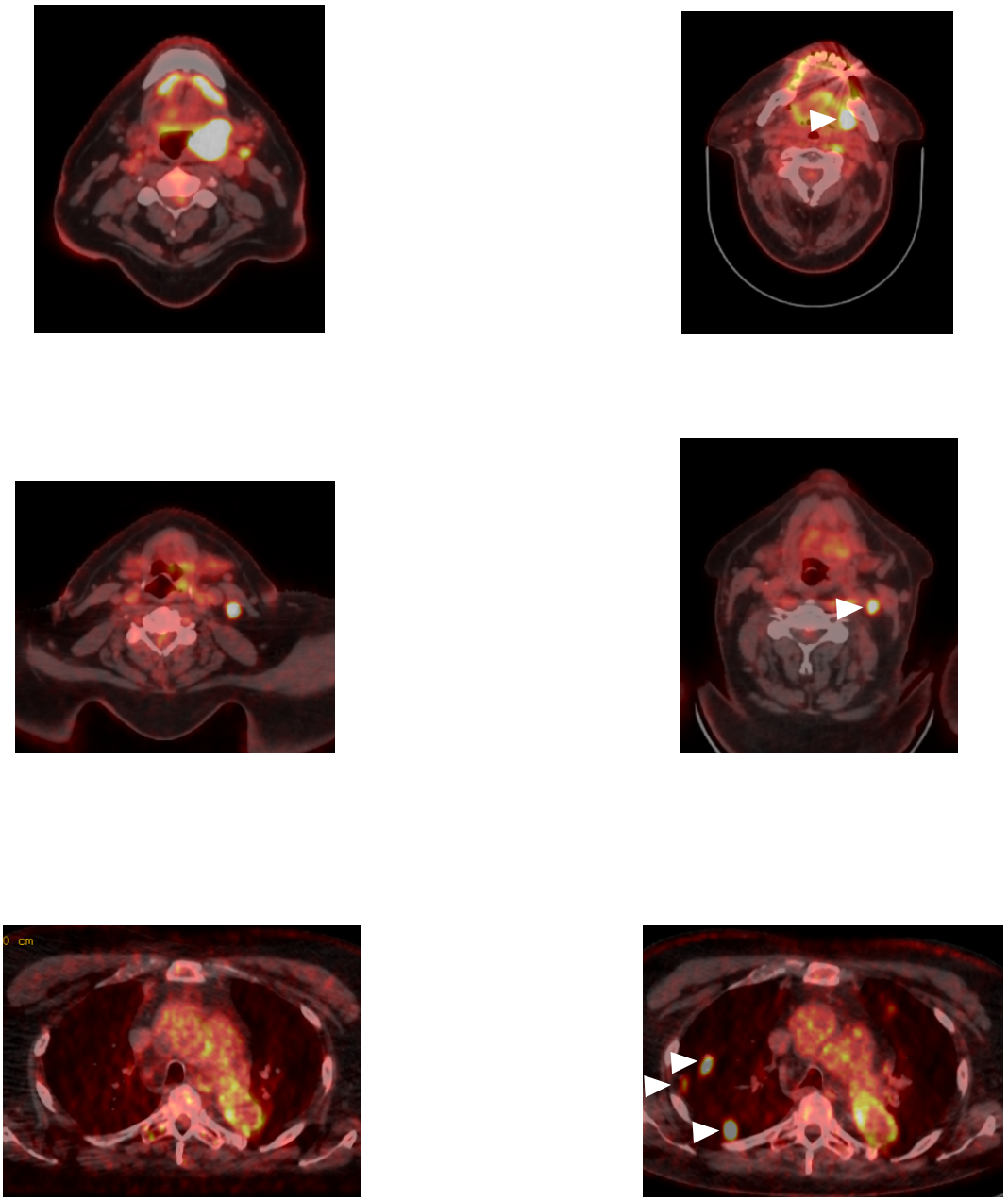
(a) (b) (c)

Figure 6.1.1. Patient with T4a N2b SCC of the right base of tongue (a). PET/CT at 3 (b) and 6 months after the end of treatment (c) showed complete response.



(a) (b) (c)

Figure 6.1.2. Patient with T2 N2c SCC of the left tonso-lingual angle (a). PET/CT at 3 months after the end of treatment (b) showed residual FDG uptake in the primary tumour (white arrow) which disappeared at 6 months (c).



(a) (b)

Figure 6.1.3. Patient with T4a N2b SCC of the left tonsil (a). PET/CT at 6 months after the end of treatment (b) showed residual FDG uptake in the primary tumour, ipsilateral nodes and new lung metastases (white arrows).

6.2 Tumour progression and overall survival

Follow-up information was available for 27 patients. Patients were followed-up for a median of 16 months (range 1-44). Twenty patients (74%) were assessed as having complete response. Progressive disease was recorded in 6 patients (22%) with a median time-to-progression (TTP) of 6.1 (3.1-15.9) months. One patient (4%) died 1 month after the end of treatment from a non-cancer related cause (myocardial infarction). Loco-regional and distant metastatic progressive disease was assessed in 3 and 3 patients respectively. Survival was calculated from date of completion of radiotherapy until date of last follow-up or death. Kaplan Meier methodology was used to illustrate survival following radiotherapy and produce estimates of overall survival (with 95% confidence intervals) at 2-years. Difference in survival between patient subgroups was assessed using the log-rank test. A total of 6 patients (22%) died. Overall survival at 2 years was estimated as 73.6% (95%CI 43.9 to 87.5%). The cumulative overall survival (OS) plot is presented in Figure 6.2.1.

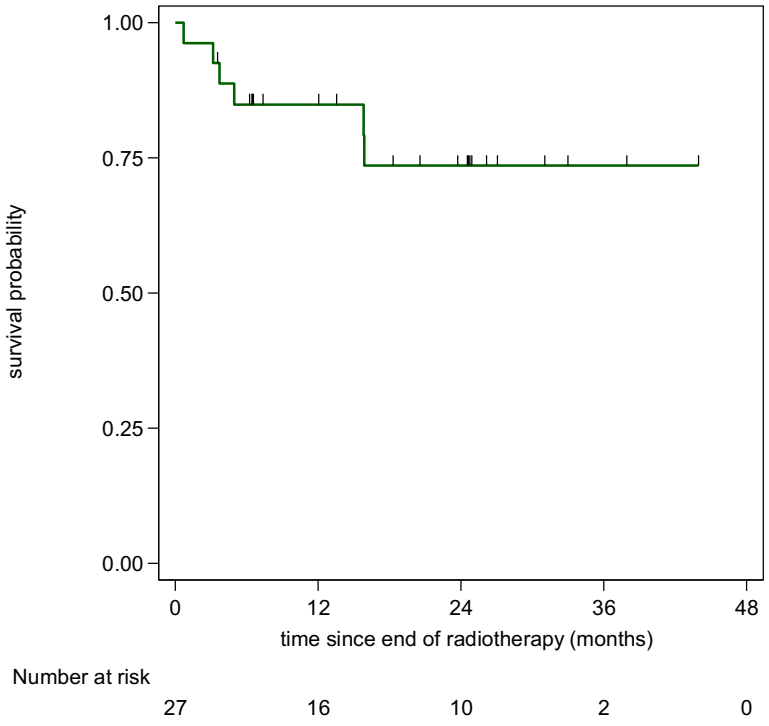


Figure 6.2.1. Cumulative overall survival (OS) curve

Among the 27 patients 21 could be classified by risk category. Estimated overall survival at 2 years was 83% (95%CI 27-97%), 87% (39-98%) and 67% (19-90%) in the low (HPV+, ≤10 pack years smoking history), intermediate (HPV+, >10 pack years smoking history) and high risk (HPV-) category respectively. The survival curves for the 3 risk categories (log rank test p=0.42) are presented in Figure 6.2.2.

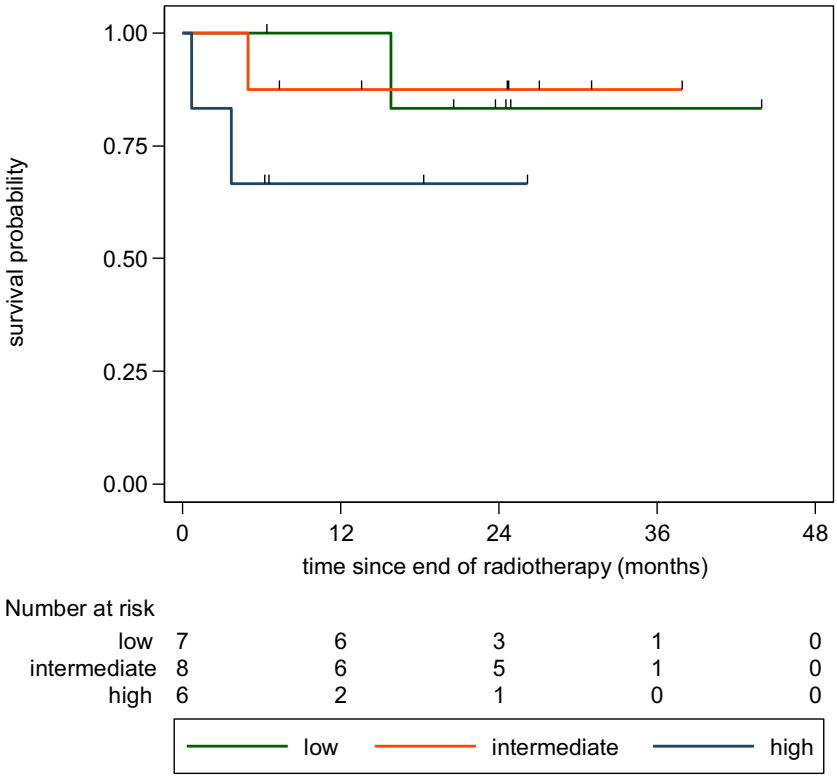


Figure 6.2.2. Overall survival (OS) curves by risk category

CHAPTER 7
RESULTS (E): OUTCOME AND LATE TOXICITY COMPARISON BETWEEN PET/CT-BASED COHORT AND NON-PET/CT-BASED RETROSPECTIVE SERIES

In this Chapter outcome and late toxicity results of the PET/CT-based VMAT cohort are compared with the results of a retrospective series of oropharyngeal cancer patients who received non-PET/CT-based VMAT at the Beatson. The comparison is exploratory and descriptive since differences should be formally assessed within a prospective randomised study.

7.1 Patient selection criteria in the non-PET/CT-based series

I retrospectively reviewed a cohort of oropharyngeal cancer patients who received VMAT 65Gy/30 fractions without PET/CT definition of the target volume. This was a mono-institutional retrospective series of patients treated at the Beatson. I identified patients with biopsy proven stage III/IV squamous cell carcinoma of the oropharyngeal region who received VMAT with bilateral neck irradiation only (as the 30 patient PET/CT cohort) with curative or post-operative intent between September 2010 and November 2012.

7.2 VMAT treatment planning in the non-PET/CT-based series

Patients were immobilised in a thermoplastic mask. Patients with adequate renal function had contrast enhanced simulation CT with 2.5mm slices without spacing from the vertex to carina. The gross tumour volume (GTV) included the radiologically and clinically evident tumour (on CT, MRI if available, endoscopy). The GTV-primary tumour and GTV-nodal tumour were expanded with a margin of 15mm and 10mm respectively and modified taking account of air and anatomical barriers. Two clinical target volumes (CTVs) were created. The first (CTV1) encompassed GTVs and the whole nodal regions at high risk of tumour dissemination. The second (CTV2) was defined as the nodal regions at low risk of tumour dissemination. Nodal areas were outlined following the criteria reported by Grégoire et al [218]. CTV1 and CTV2 were expanded with a margin of 3mm to generate PTV1 and PTV2. Margins for CTV and PTV were applied as per internal institutional protocol. Organs at risk (eyes, optic nerves, chiasm, brainstem, spinal cord, parotids, trachea, oesophagus and larynx)

were defined as per institutional protocol. A dose of 65-68Gy and 54-60Gy in 30-34 fractions was prescribed to PTV1 and PTV2. Various constraints were applied to PTV1, PTV2 and the Organs at Risk as summarised in Table 7.2.1. Treatment planning was optimised with the AAA algorithm for Rapid Arc (Varian).

	Constraint	**Dose %**
PTV1	D99%	>90
	D95%	>95
	D5%	<105
	D2%	<107
PTV2	D99%	>90
	D95%	>95
	Mean	53-56Gy
	D5%	<117
	D2%	<122
		Dmax (cGy)
PRV Spinal Cord	D1%	4400
PRV Spinal Cord	point max	4800
PRV Brainstem	D1%	4800
Optic Nerve	D1%	5000
Optic Chiasm	D1%	5000
Left Parotid		2400 (Dmean)
Right Parotid		2400 (Dmean)
Larynx		4000(Dmean)
Cochlea		5000

Table 7.2.1. Head&Neck VMAT dose constraints. PTV= Planning Target Volume, PRV= Planning Risk volume

7.3 Clinical evaluation in the non-PET/CT-based series

Patients were followed up at 3, 6, 12, 18 months after VMAT and every 12 months thereafter for 5 years in accordance with the local standard protocol. Tumour response was defined with RECIST 1.1 or metabolic criteria in patients who were assessed with 3-months post-

treatment CT or PET respectively. After the 3-months scan, patients were followed-up without imaging unless clinically indicated. Late toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [252].

7.4 Statistical analysis in the non-PET/CT-based series

Descriptive summary statistics for demographic, clinical and treatment-related information are reported as medians (with range) or counts and percentages as appropriate. Pearson's chi-square test and Fisher's exact test were used to test differences in proportions. Fisher's exact test was used when expected numbers were low (<5). Stata v14.2 was used for the analysis.

7.5 Patient characteristics in the non-PET/CT-based series

A total of 114 patients with stage III/IV oropharyngeal cancer were identified (median age 58 years, 75% men). HPV status was available for 58 (51%) patients among whom 50% were HPV positive. A total of 94 (84%) patients were treated with chemoradiation with radical intent and 20 (18%) treated with adjuvant chemoradiation following surgery. Induction chemotherapy (docetaxel+cisplatin+5FU or carboplatin+5FU) had been given to 30/94 (32%) patients treated with radical intent. Ninety (79%) patients received concomitant chemo-radiotherapy (with cisplatin, carboplatin or cetuximab) and 24 (21%) received radiotherapy alone. The patient characteristics are summarised in Table 7.5.1.

		N or median	(%) or (range)
Sex	men	85	(74.6)
	women	29	(25.4)
Age (years)		58	(37-76)
Primary site	Tonsil	53	(46.5)
	Tongue base	51	(44.7)
	Soft palate	6	(5.3)
	Pharyngeal wall	4	(3.5)
Histology	Squamous cell carcinoma	114	(100.0)
Stage	III	21	(18.4)
	IV	93	(81.6)
	<N2c	95	(83.3)
	N2c	19	(16.7)
HPV	Positive	29	(25.4)
	Negative	29	(25.4)
	Unknown	56	(49.1)
Radical (chemo)radiotherapy		94	(82.5)
Adjuvant (chemo)radiotherapy		20	(17.5)
Induction chemotherapy	Docetaxel+Cisplatin+5FU	29	(25.4)
	Carboplatin+5FU	1	(0.9)
Concomitant chemotherapy	Cisplatin	82	(71.9)
	Carboplatin	4	(3.5)
	Cetuximab	4	(3.5)

Table 7.5.1. Patient characteristics of the non-PET/CT-based VMAT series

7.6 Outcome in the non-PET/CT-based series and comparison with the PET/CT-based cohort

The non-PET/CT-based series had a median follow up time of 20.6 (range 2.3-44.5) months. Complete response after (chemo)radiotherapy was registered in 96 patients (84%). Progressive disease was assessed in 17 cases (15%) with time to progression of 9.0 (range 3.0-23.0) months. Two-year overall survival (OS) was 79% (95%CI, 69-86%). Due to the incomplete assessment of HPV and smoking status, it was not possible to stratify the outcome results by the 3 risk categories in this group of patients. The outcome results of non-PET/CT and PET/CT-based VMAT for the whole groups (i.e. without stratification by risk category) are compared in Table 7.6.1 and Figure 7.6.1.

	n	Median FU (months)	CR	PD	TTP (months)	2y OS
Non-PET/CT VMAT	114	20.6 (2.3-44.5)	96 (84%)	18 (16%)	9.0 (3.0-23.0)	79% (95%CI, 69-86%)
PET/CT-VMAT	27	16 (1-44)	20 (74%)	6 (22%)	6.1 (3.1-15.9)	74% (95%CI, 49%-88%)
			p=0.26	p=0.41	p=0.36	p=0.36

Table 7.6.1. Outcome results of non-PET/CT and PET/CT-based VMAT. CR=complete response, PD=progressive disease, TTP=time to progression, 2y OS=2-year overall survival

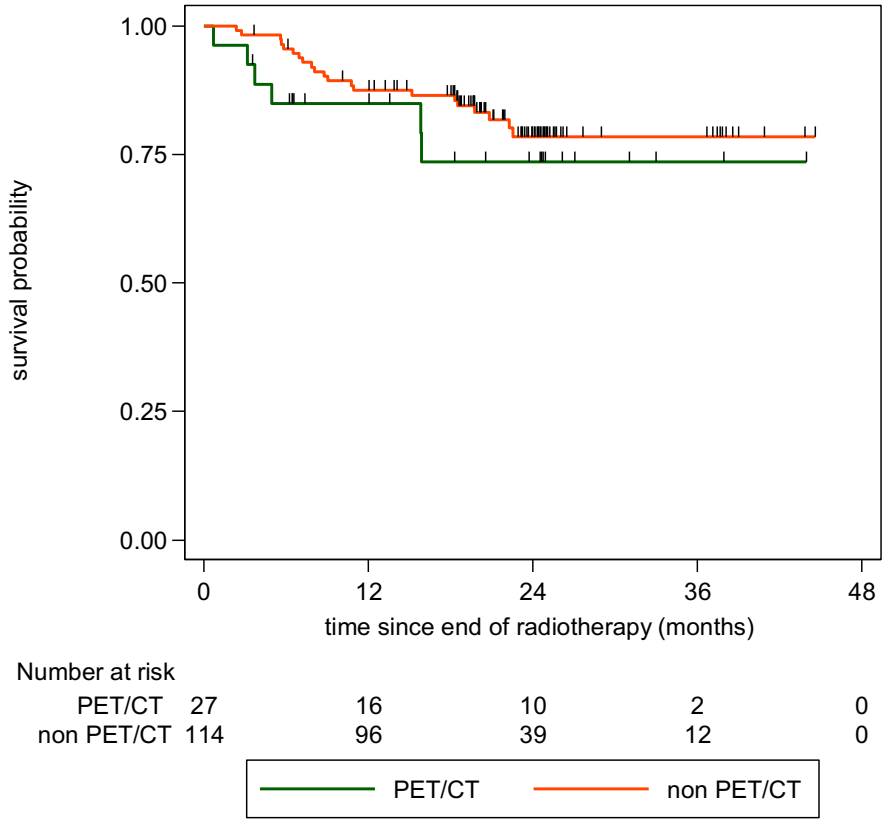


Figure 7.6.1. Overall survival curves in PET/CT and non-PET/CT-based VMAT (p=0.35). Kaplan Meier methodology was used to illustrate survival.

In summary, the analysis does not reject the null hypothesis that outcomes are the same for the 2 treatment modalities. No statistically significant difference was evident in the various results (p-values were all substantially greater than 0.05). A formal randomised study with sub-group analysis (high, intermediate, low risk) comparing PET/CT vs non-PET/CT-based radiotherapy might demonstrate the superiority of the PET/CT arm. On the basis of my findings, it is reasonable to conclude that PET/CT target definition with visual assessment did not compromise clinical outcomes compared to CT-alone target definition.

7.7 Late toxicity in the non-PET/CT-based series and comparison with the PET/CT-based cohort

In the non-PET/CT-based series the incidence of late Grade ≥2 xerostomia, dysphagia and dysgeusia was 39%, 35% and 8% respectively. The late toxicity results are summarised in Table 7.7.1.

Toxicity	Grade (CTCAEv.4)	number (%)
Xerostomia (n=110)	<2	67(61%)
	≥2	43 (39%)
Dysphagia (n=113)	<2	73 (65%)
	≥2	40 (35%)
Dysgeusia (n=91)	<2	84 (92%)
	≥2	7 (8%)
Fatigue (n=0)	<2	Not reported
	≥2	Not reported

Table 7.7.1 Late toxicity in the non-PET/CT-based series. The number of patients for which specific toxicities were measured varied and is specified for each category.

In the subgroup analysis, no significant differences were measured in the incidence of late Grade≥2 toxicity between the N2c status (with high dose 65Gy bilateral neck irradiation) compared to the <N2c status (with ipsilateral high dose 65Gy and contra-lateral low dose 54Gy neck irradiation) as summarised in Table 7.7.2.

Toxicity	Grade (CTCAEv.4)	N2c	<N2c	p-value
Xerostomia	<2	13/18 (72%)	54/89 (61%)	0.43
	≥2	5/18 (28%)	35/89 (39%)	
Dysphagia	<2	12/18 (67%)	61/92 (66%)	1.0
	≥2	6/18 (33%)	31/92 (34%)	
Dysgeusia	<2	17/17 (100%)	65/72 (90%)	0.34
	≥2	0/17 (0%)	7/72 (10%)	
Fatigue	<2	Not reported	Not reported	
	≥2	Not reported	Not reported	

Table 7.7.2 Non-PET/CT-based series. Late toxicity in the N2c (bilateral neck nodes) and <N2c (unilateral neck nodes) subgroup; p-value from Fishers exact test.

In the PET/CT-based cohort, at baseline 24 (89%) and 3 (11%) patients had PS ECOG ≤1 and 2 respectively. After the end of treatment, at a median follow-up time of 16 (range 1-44) months, PS was recorded in 20 patients: 16 (80%) and 4 (20%) patients had PS ≤1 and 2 respectively. Weight loss data was available for 22 patients: 11(50%) and 11(50%) patients had weight loss <G2 and ≥G2 respectively. A total of 17/27 (63%) patients needed nasogastric feeding after the end of treatment: 6(35%) and 11(65%) patients had NG tube for <3 and ≥3 months respectively. Among patients with NG tube for ≥3 months the median time was 4(3-12) months. Late (>3 months) xerostomia, dysphagia, dysgeusia and fatigue were not measured in all the 27 patients with follow up. Late toxicity results are summarised in Table 7.7.3 and the number of patients for which specific toxicities were measured is specified for each category.

Toxicity	Grade (CTCAEv.4)	Number (%)
Xerostomia (n=22)	<2	14 (64%)
	≥2	8 (36%)
Dysphagia (n=23)	<2	15 (65%)
	≥2	8 (35%)
Dysgeusia (n=22)	<2	22 (100%)
	≥2	0 (0%)
Fatigue (n=22)	<2	19 (86%)
	≥2	3 (14%)

Table 7.7.3. Late toxicities in the PET/CT-based cohort

In the sub-group analysis, the incidence of Grade ≥2 xerostomia and fatigue in patients with PET positive unilateral neck nodes (<N2c) was higher than in patients with PET positive bilateral neck nodes (N2c): 46% vs 29% and 23% vs 0% respectively, however these differences were not statistically significant. No patients had Grade ≥2 dysgeusia. The incidence of Grade ≥2 dysphagia was 38% in both subgroups. The subgroup analysis results are reported in Table 7.7.4.

Toxicity	Grade (CTCAEv.4)	N2c	<N2c	p-value
Xerostomia	<2	5/7 (71%)	7/13 (54%)	p=0.64
	≥2	2/7 (29%)	6/13 (46%)	
Dysphagia	<2	5/8 (62%)	8/13 (62%)	p=1.0
	≥2	3/8 (38%)	5/13 (38%)	
Dysgeusia	<2	7/7 (100%)	13/13(100%)	
	≥2	0 (0%)	0 (0%)	
Fatigue	<2	7/7(100%)	10/13 (77%)	p=0.52
	≥2	0 (0%)	3/13 (23%)	

Table 7.7.4. PET/CT-based cohort. Late toxicities in N2c (bilateral nodes) and <N2c (unilateral nodes) patients; p-value from Fishers exact test.

The late toxicity profile of non-PET/CT and PET/CT-based VMAT was similar. The incidence of Grade ≥2 dysphagia was minimally higher (36% vs 35%, p=0.96) in patients treated with PET/CT-based compared to non-PET/CT-based VMAT. The Grade≥2 toxicity results from both studies are summarised in Table 7.7.5.

	Non-PET/CT-based	PET/CT-based	
Grade≥2 (CTCAEv.4)	%PRT (N2c, <N2c)	%PRT (N2c, <N2c)	p-value
Xerostomia	39%* (28%, 39%)	36%* (29%, 46%)	* 0.81
Dysphagia	35%*(33%$^{\#}$, 34%$^{\$}$)	36%*(38%$^{\#}$, 38%$^{\$}$)	*0.96($^{\#}$1.0; $^{\$}$0.76)
Dysgeusia	8%* (0%, 10%)	0%* (0%, 0%)	* 0.34
Fatigue	Not reported	14% (0%, 20%)	-

Table 7.7.5 Grade≥2 late toxicity in VMAT for oropharyngeal cancer with and without PET/CT definition of the target volume. %PRT=percentage of patients with recorded toxicity. Toxicities were not measured in all the patients with follow-up.

CHAPTER 8
DISCUSSION

8.1 Fusion accuracy

The advantage of PET/CT is that PET functional data and CT anatomical structures can be combined providing more accurate information than images from individual modalities. It is vital that PET and CT are accurately fused. The fusion accuracy in diagnostic integrated PET/CT scanners is <1mm [253]. In radiotherapy treatment planning the correct co-registration of PET data with CT data used for planning must be verified, since a difference in spatial localization of metabolically active tumour may lead to false estimation of the gross tumour volume (GTV). Ideally, the fusion process can be executed automatically by a hybrid PET-CT-dedicated radiotherapy planning scanner using the same immobilization devices and reproducing the radiation delivery conditions [156]. This methodology can be called "1-step fusion". The dedicated PET/CT scanner should be commissioned and Quality Assurance (QA) monitored for the purpose of radiotherapy planning. This is time and financially demanding. For my project, I decided to use a "2-step fusion" approach, i.e. two separate scanners were used for acquiring the diagnostic PET/CT (in the PET Centre) and the planning CT (in the radiotherapy department) with the same set-up conditions (i.e. flat table and thermoplastic mask) [243]. I calculated that the fusion accuracy between PET/CT and planning CT is 90%. No data is available in the literature regarding the accuracy of the rigid registration between a diagnostic PET/CT and a simulation CT scan using a commercial software for radiotherapy treatment planning system. A fusion accuracy of 90% is a very positive result considering possible set-up differences between PET/CT and simulation CT, and intra-observer variability in contouring of the bony structures. The "2-step fusion" protocol gives the advantage of reducing the time and cost related to the commissioning and maintenance of a radiotherapy-dedicated PET/CT scanner. The additional biological dose of one CT scan is negligible compared to the total dose absorbed for treatment purposes and can be justified by the intent of improving the accuracy of the treatment. Additionally, the "2-step fusion" methodology can be used by radiotherapy centres that do not have a PET facility on site. The limiting factor in this case is the availability of the personalised mask in the PET Centre. Patients could take the responsibility for the transport of their own mask between distant sites. All the patients in my series tolerated well PET/CT with the mask for 10 minutes during the head&neck acquisition. However, in the routine clinical practice approximately 15% of the patients cannot tolerate the mask for a long period of time.

Relaxation techniques or mild sedation can help whilst wearing the mask. PET/CT acquisition with mask is essential to optimise the set-up especially in the region of the neck where flexion can affect significantly the fusion accuracy.

8.2 SUVmax and correlation with risk groups

In my series, SUVmax (g/ml) was calculated for both primary tumour and nodal disease. In case of multiple pathological nodes, the highest value of nodal SUVmax was reported. Median (range) SUVmax (g/ml) was 19.0 (9.7-40.0) and 13.7 (3.0-25.0) for primary and nodal disease respectively. SUVmax was significantly higher in the primary tumour compared to the nodal disease (p=0.0001). This novel result has not been reported in other studies in the literature specifically for oropharyngeal cancer. In the sub-group analysis by HPV status, I found that median SUVmax was higher in HPV- compared to HPV+ patients for both primary tumour (21.0 vs 16.9 g/ml) and nodal disease (17.0 vs 10.0 g/ml), however these differences were not statistically significant. Also, N SUVmax was higher in the high risk (i.e. HPV-) compared to the intermediate and low risk (i.e. HPV+) group (17.0 vs 8.8 vs 15.o g/ml) although again these differences were not statistically significant. My data suggests that more aggressive cancers (i.e. HPV-) are more metabolically active (i.e. higher SUVmax) than less aggressive cancers (i.e. HPV+). Since the number of patients in my series is small, this finding should be validated in a larger cohort of patients. Overall, my results suggest the hypothesis of treatment intensification in the high risk group (i.e. HPV-) because more biologically aggressive. Oropharyngeal cancer SUVmax studies are quite scarce in the literature. In a study of 71 patients with oral cancer [254], the median (range) SUVmax of primary tumours was 9.0 (7.4–13.9) in patients with nodal negative disease (cN0/pN0), while it was 11.4 (9.9–15.7) in patients with occult nodal disease (cN0/pN+). An SUVmax value≥9.5 in primary tumours was significantly associated with higher risk of occult metastatic nodal disease and worse local control. In another study of 42 patients with oral cancer [255], median tumour and lymph node SUVmax values were 23.9 (4.2-27) and 9.7 (3.5-27) respectively. Tumour-SUVmax correlated with the presence of contralateral lymph nodes (p=0.049). Univariate analysis showed that higher tumour SUVmax, stage and age were factors predicting significantly poorer OS (p=0.032, p=0.011, p=0.045, respectively). In multivariate analysis, tumour-SUVmax was an independent predictive factor for OS (HR 1.04, 95%CI 1.01-1.09, p=0.039), although the magnitude of the effect was small. The cut-off value of tumour-SUVmax for predicting survival was 22.2 (p=0.049). The results of this study indicated that tumour-SUVmax may function as an independent predictive factor for contralateral lymph nodes and worse OS in patients with locally advanced cancer of the oral

cavity. In a study on 65 patients treated with surgery for oropharyngeal cancer [256], significantly higher nodal SUVmax was associated with HPV/p16 positive vs negative nodes (SUVmax 10.8 vs 7.9). No significant differences were seen between HPV/p16 positive vs negative primary tumor SUVmax (10.3 vs 13.7). Elevated nodal SUVmax was a significant independent predictor of HPV/p16 positivity. This study is in contrast with my results (i.e. higher SUVmax in HPV negative tumours for both primary and nodal disease). My results suggest the more aggressive biological behavior of HPV negative oropharyngeal cancers (i.e. more metabolically active), however they are limited by the small sample size and the univariate analysis for SUVmax. Higher SUVmax may not be an independent factor for higher biological aggressiveness (i.e. HPV negative disease). Only multi-variate analysis in a large cohort of patients may show that SUVmax is an independent negative prognostic factor in the HPV negative subgroup. In my series T SUVmax was higher in low risk (21.3 g/ml) compared to intermediate (13 g/ml) and high risk (21 g/ml) patients. These results are difficult to interpret, however they may suggest the higher tendency of low risk patients in developing contra-lateral nodal and distant metastatic disease. No other studies are available for comparison.

8.3 TNM stage modification

8.3.1 T stage modification

In my project, for the purpose of the TNM classification, PET/CT down-staged the primary tumour (T) from T3 to T2 in 6/30 (20%) patients due to changes in the tumour greatest dimension (i.e. from T3 >4cm to T2 ≤4cm). For clinical use, the volume defined with PET (visual assessment) was considered along with the anatomical information of the contrast enhanced radiotherapy planning CT in order to generate a hybrid volume minimising the risk of geographical miss. PET/CT did not modify the T staging in 24/30 (80%) patients due to non-relevant change of the tumour greatest dimension and/or anatomical reasons according to TNM (7^{th} edition) classification. The definition of a smaller primary tumour with PET/CT may lead to the reduction of radiotherapy related short and long-term side effects, however this may not always be clinically relevant because of an upstaging of the nodal disease with PET/CT (e.g. bilateral vs unilateral pathological nodes). My results showing a change in T staging with PET/CT in 20% of cases are in agreement with data from the literature and confirm that PET/CT modifies the T staging in addition to morphological imaging.

Abramyuk et al [243] showed the capability of FDG-PET/CT to clarify equivocal findings of CT and other conventional methods with modification of the initial T-stage in 45% of patients (n 102) mainly through its downstaging. Ha et al [220] found that PET/CT upstaged T staging in 2 of 36 patients (5.5%) with subsequent changes in treatment planning. A prospective study by Scott and colleagues showed that PET changed T staging in 6 of 71 patients (8.5%) [222]. MRI remains the preferred imaging method in the assessment of nasopharynx, oral cavity, oropharynx, perineural spread and bone marrow invasion [227,228], while CT is the modality of choice for larynx and bony cortex invasion [229]. Dental amalgam artefact is a unique problem for CT imaging in the oral cavity and oropharynx. When severe, it can obscure the entire tumour particularly in the oral cavity. PET and MRI are less affected by this type of artefact. MRI, however, is prone to motion artefact, partly because it requires more imaging time. PET/CT also has a high false positivity rate due to normal lymphoid tissue uptake in the oral cavity and oropharynx. Seitz et al did not find additional value of adding PET/CT to MRI in T staging of oral cavity and oropharyngeal cancers using histopathology as the gold standard. This is thought to be due to limited resolution of PET/CT in detection of small, superficial lesions and lesions obscured by dental artefact [230]. CT has unique benefits if the tumour is ill-defined with submucosal extension and diffuse infiltration. This can help the clinician in differentiating tumour border versus normal tissue planes.

A particular concern in the oral cavity and oropharynx is assessing mandibular/bone involvement. Superficial mandibular involvement by a resectable oral cavity cancer is often treated by marginal mandibulectomy while gross mandibular invasion typically requires segmental mandibulectomy with composite free flap reconstruction [231]. Metabolic activity seen in the mandible tends to overestimate the presence of the tumour due to partial volume averaging and misregistration artefact. The CT portion of the PET/CT and contrast enhanced CT have more sensitivity and specificity than PET alone in assessment of mandibular invasion [232]. MRI is useful in detection of bone marrow changes as compared to CT, whereas CT is generally superior to MRI in the detection of cortical bone erosion. Overall, MRI has similar accuracy to CT and PET/CT.

Accuracy is increased when information from multiple imaging modalities is available [226]. Routinely, CT is performed with the patient's mouth closed and in neutral position. Apposition of oral cavity and oropharyngeal structures can obscure the tumours. Contrast enhanced CT with dynamic manoeuvres (puffed cheek technique, open mouth position or modified Valsalva manoeuvre) can enhance delineation and extent of lesions [233]. The

puffed cheek technique performed during PET/CT scanning has been proven to be practical and improved lesion detection [234].

Mandibular invasion is a major determinant of both therapeutic approach and prognosis of HNC [41]. CT and MRI are commonly used to evaluate the status of the mandible. CT has been reported to be the most accurate imaging modality in evaluating discrete cortical bone involvement [42], however MRI is superior to CT for evaluating tumour invasion into the medullary cavity of the mandible [43]. In a study in oral cancer carcinoma, the direct comparison of CT, MRI and PET/CT was evaluated in the detection of mandibular invasion [44]. The sensitivity/specificity was 47.1%/58.3%, 58.3%/100%, 97.1% /97.1% for CT, MRI and PET/CT respectively. No statistically significant difference in sensitivity and specificity was assessed between the three imaging modalities. A retrospective study compared the diagnostic performance of PET/CT and MRI for the detection of bone marrow invasion of the mandible in patients with oral cancer carcinoma (surgical specimens were used as the standard). PET/CT was found to be more specific than MRI (83% vs 61%, $p<0.05$) but less sensitive (78% vs 97%, $p <0.05$). Given the low positive-predictive value (PPV) of MRI, a positive MRI scan should be confirmed with PET, which shows higher PPV, whereas a negative MRI scan can confidently exclude the presence of bone marrow invasion [43].

In a retrospective study [39] 69 patients with oral cavity cancer and non-removable dental metallic implants at the time of the pre-treatment imaging work-up had CT or MRI plus PET/CT for the initial staging. The aim was to analyse the clinical impact of PET/CT for primary tumour detection and volume estimation. A total of 64 PET/CT, 64 CT and 27 MRI were analysed. PET/CT was more accurate in detecting primary tumours than CT when dental artefacts were present (95.3% vs 75.0%, respectively, $p<0.05$). Among the 27 subjects who had undergone all the three diagnostic modalities, the diagnostic performance for the detection of primary tumours in the oral cavity was 96.3%, 77.8% and 85.2%, respectively ($p>0.05$). In another study [40] 44 patients (66% with oropharyngeal carcinoma) who received primary tumour resection and neck dissection were retrospectively reviewed. The authors compared contrast-enhanced CT (CE-CT), PET/CT with contrast-enhanced CT (PET/CE-CT) and standard PET/CT. The primary tumour was correctly identified by CE-CT, PET/CT and PET/CE-CT in 71%, 92% and 95% of cases, respectively. Both PET/CT and PET/CE-CT were superior than CE-CT in identifying the primary site of the tumour. However, there was no statistical difference in the detection of the primary lesion between PET/CT and PET/CE-CT. In this study MRI was not evaluated. In summary, PET is particularly helpful in case of dental artefacts, however its accuracy can be improved by MRI

and CT due to the superior anatomical details especially in case of bone infiltration. PET, MRI and CT should be used ideally together in the context of multimodality imaging [175].

8.3.2 N stage modification

In my project PET/CT modified the N stage in 18/30 (60%) of the patients. The nodal status was down-staged from N1 to N0 in 1 patient (3%) and up-staged in 17/30 (57%) of the patients. The introduction of PET/CT in the nodal staging led to 3 different scenarios in case of N-upstaging: 6 patients (20%) with cN0 (i.e. no pathological nodes with clinical and morphological imaging assessment) were upstaged to ipsilateral or bilateral nodal disease (i.e. N1-N2c); 7 patients (23%) with cN1 (i.e. ipsilateral single nodal disease) were upstaged to ipsilateral multiple or contralateral nodal disease (i.e. N2b or N2c); 6 patients (20%) with cN0-N2b (i.e. no or ipsilateral nodal disease) were upstaged to N2c (i.e. bilateral nodal disease). The HPV status was not correlated to either N upstaging or N2c. Since by standard UK protocol the whole involved nodal level is treated with full radical dose (i.e. 65Gy) instead of prophylactic dose (i.e. 54Gy), the nodal upstaging can potentially increase the radiotherapy related toxicity especially in case of contralateral nodal upstaging (i.e. N2c).

Considering that PET has sensitivity and specificity of 80% and 85% in detecting nodal metastases [65], PET scans that were frankly positive or negative were considered to provide 'true' positive or negative results respectively. Hence, ultrasound (US) and fine needle aspiration (FNA) were not performed as confirmation of the PET result. This was a pragmatic approach to avoid additional procedures or delay treatment. If PET was equivocal, US and FNA were performed to minimise the risk of false positive (20%) or negative (15%) results of PET. This pragmatic approach reflects the recommendation of the PET-neck study [190] for neck dissection in case of positive or equivocal PET after chemo-radiotherapy.

In case of N up-staging, US+FNA was not performed if the nodal FDG uptake was clearly pathological on the basis of clinical judgement. Due to the higher sensitivity/specificity of PET/CT compared to CT and MR (80%/86% vs 75%/79%), it was decided to consider the PET/CT results as true positive on the basis of the clinical judgement of the oncologist and the PET radiologist evaluating the patients. US+FNA was performed only in case of equivocal FDG nodal uptake. Only 3 patients (10%) had equivocal FDG nodal uptake. In these 3 cases (2 patients with N1 and 1 patient with N2b on CT) the US+FNA did not confirm nodal metastatic disease (N2b and N2c on PET/CT respectively). These 3 patients did not relapse in the neck at the time of their last follow-up. This supports the possibility of false

positive results of PET (approximately 20%) in case of equivocal FDG nodal uptake in which case US+FNA should be performed.

In my series the percentage change in nodal status (60%) due to PET/CT is higher compared to other studies possibly because of the high percentage of males (80%), tongue base tumours (36%), stage IV disease (77%) and HPV+ cases (75%) in our patient population. Male sex, tongue base primary site, advanced stage and HPV+ status are considered risk factors for developing nodal disease, especially contralateral, which can be subclinical in morphological imaging. In a study on the use of FDG PET/CT prior to primary radiotherapy for HNC (multiple sites), PET/CT modified the N stage in 35% of the patients (n102); 23% of the patients were upstaged and 77% were downstaged. The authors did not use either neck dissection or US+FNA to confirm the PET/CT results [243]. Normal sized but nevertheless tumour cell-bearing lymph nodes are a potential source of N stage discrepancy between conventional anatomic and metabolic imaging. A retrospective study by Murakami et al [257] including 23 patients with HNSCC, reported data where the nodal stage was corrected by FDG-PET/CT in 13% for one observer and in 9% for second observer, compared to our 60% modification. From among the three different protocols used in that study (conventional imaging, additional FDG-PET/CT and FDG-PET/CT alone) FDG-PET/CT presented the most accurate lymph node staging, although lesions <15 mm in diameter may still be missed especially in case of nodal necrosis. In this study the PET/CT results were confirmed pathologically after neck dissection. At the same time, my results are in agreement with a similar large retrospective study by Fleming et al [258] showing modification of overall staging and radiotherapeutic intention after FDG-PET/CT in 30.9% of previously untreated HNC patients including finding distant and unresectable disease or secondary malignancies. Nevertheless, they did not consider FDG-PET/CT capable of replacing neck dissection in detecting occult cervical nodal metastases. The likelihood of cervical lymph node metastasis in HNC depends on location, histology and staging of the primary tumour. The presence of metastatic nodes carries poor prognosis, decreases 5-year survival and necessitates treatment in the neck [235,236]. Differentiation between metastatic lymph nodes and reactive nodes by CT/MR size and morphologic criteria can be difficult [237]. A meta-analysis showed higher sensitivity/specificity (80%/86%) of PET/CT as compared to other conventional diagnostic modalities (75%/79%) [238]. The higher sensitivity is due to the fact that PET can show hypermetabolism in normal-sized metastatic lymph nodes. However, PET is not 100% specific because inflammatory reactive nodes and adjacent granulation tissue can increase uptake yielding a false positive result of approximately 20% [239]. PET false positive results are clinically relevant because they may

induce an overestimation of the high-dose nodal areas with potential increase of the risk of radiation induced toxicity. Ideally, borderline PET positive nodes should be confirmed with US+FNA to exclude false positive results. However, US+FNA has sensitivity/specificity of 98%/95% so it should be interpreted anyway in the clinical context. Small necrotic lymph nodes may appear hypometabolic on PET especially in hyperglycaemic patients [240]. Therefore, it is important to analyse both morphologic and metabolic information derived from PET/CT. The detection of retropharyngeal lymph node metastases is particularly advantageous with FDG PET-CT. In my series FDG PET-CT identified unsuspected retropharyngeal lymph node metastases in 8 out of 30 patients (27%). This result is similar to other published studies. FDG PET-CT improves the diagnostic accuracy of pathological retropharyngeal nodes compared to the conventional CT/MRI with sensitivity and specificity of 89% and 86% vs 62% and 60% respectively [241]. It is not recommended to routinely use PET/CT to assess possible cervical lymph node metastasis in cN0 setting (i.e. patients whose metastatic lymph nodes are not palpable on physical examination or visualized on morphological imaging). However, pre-treatment PET/CT may still be useful as an optional imaging to compare with the post treatment scan to discriminate malignant tissue from physiologic uptake [242]. In summary, PET modifies the N staging in a relevant percentage of patients. Due to the 20% risk of false positive results, it would be helpful to confirm the positive/equivocal PET findings with US+FNA especially in case of detection of contralateral nodes since this is clinically important for the increased risk of radiation-induced toxicity. However, US+FNA is not feasible in case of retro-pharyngeal nodes, adds additional procedures to the work plan and can delay the treatment.

8.3.3 M stage modification

In my project, the pre-radiotherapy PET/CT did not show unsuspected distant metastases in any of the patients compared to CT alone. Two patients (6%) developed lung metastatic disease after the end of treatment. In these 2 patients neither CT nor PET/CT showed lung metastases before treatment. Possibly the lung metastases were subclinical at baseline or developed after the treatment. My results differ from other published studies probably because of the small sample size, despite the high percentage of HPV+ cases (75%) and stage IV disease (77%), which are considered as risk factors for developing distant metastatic disease. Approximately 7% to 25% of patients with advanced stage HNC have distant metastases at initial presentation [244]. The most common sites of metastases include lung, bone and abdomen. Mediastinal lymph node involvement is considered distant metastasis

[224]. Contrast enhanced chest CT is commonly used to assess intrathoracic spread with 73% sensitivity and 80% specificity [245]. Overall PET/CT is more accurate than conventional imaging in detecting metastatic foci [246]. PET/CT has sensitivity and specificity of around 87.5 % and 95% respectively. It is very important to detect distant metastases early in the workup as it changes prognosis and management. Extensive surgery and/or chemoradiotherapy with curative intent may cause significant morbidity and mortality and may be avoided in the event of documented distant metastases. PET/CT is recommended when distant spread is suspected in HNC patients with locoregionally advanced stage. However, negative PET/CT does not completely exclude absence of metastases due to the 5% false negative rate of this imaging modality (e.g. in case of small necrotic metastases) [247]. A multicentric prospective study evaluated the impact of PET/CT on the initial staging and management of patients with HNC. The group found that PET/CT improved the TNM classification of the disease and altered the management of 13.7% of the patients mainly due to the ability of PET/CT to detect metastatic or additional disease [248]. In a study on modification of staging and treatment of HNC by FDG-PET/CT prior to radiotherapy, a considerable increase in M1 patients was noted after using FDG-PET/CT for staging ($p=0.001$). Although the majority of patients remained unchanged with regard to M stage and this with no metastases (M0), 12.7% of the patients were shifted from M0 to M1. One out of 102 patients with initial distant metastasis (M1) was found to have no metastases (M0) with FDG-PET/CT [242]. In a retrospective study of PET/CT before radiotherapy, PET/CT upstaged from M0 to M1 12.8% of the patients shifting the intent of treatment from curative to palliative. In the same study, 2% of the patients were re-categorized from palliative to curative therapeutic intention. Thus, 85% of patients remained within their initial intention category (of either curative or palliative intention). The PET/CT findings were, however, not verified with biopsy in this study [243]. In summary, PET/CT is a helpful tool to detect unsuspected distant metastatic disease in the context of multimodality imaging especially in patients with high burden of disease.

8.4 Target volume variability

My series showed that PET/CT with visual assessment (i.e. based on the observer's experience) modified the absolute volume and the spatial reproducibility of both primary tumour (T) and nodal disease (N) compared to CT alone. The median volume of T defined with PET/CT was smaller than the volume defined with CT alone (11.5cc vs 16.5cc, $p=0.31$) with reproducibility index R 0.49. The median volume of N defined with PET/CT was bigger than CT alone (13.8cc vs 11.1cc, $p=0.42$) with reproducibility index R 0.47. Differences

were not statistically significant, probably due to the small number of patients. Chatterjee S et al [259] used PET/CT and contrast enhanced CT (CECT) alone for the definition of the target volumes in 20 oropharyngeal cancer patients. The authors did not use visual assessment for PET/CT but a segmentation methodology. PET/CT was segmented at 40% of the SUVmax of the tumour. PET/CT gross tumour volumes were smaller than CT volumes (mean±standard deviation: 25.1cc±35.8 versus 36.5cc±44.14; $p<0.015$) for the primary tumour. Interestingly, their study showed no significant differences in gross tumour volume for T1/T2 disease, although differences in gross tumour volumes for advanced disease (T3/T4) were significant. The nodal target volumes were not statistically different (mean±standard deviation: CECT versus PET/CT 32.4cc±36.6 versus 32.2cc±37.09; $p>0.86$). The reproducibility index between PET/CT and CECT was 0.66 (0.2-1) and 0.84 (0-1) for T and N respectively. In my series, PET/CT segmented at 50% of the SUVmax identified a smaller volume which was inside the volume defined with PET/CT with visual assessment for both primary tumour and nodal disease (median values: 4.6cc vs 11.5cc, $p=0.001$; 3.5cc vs 13.8cc, $p=0.04$). Segmentation at 50% of the SUVmax identified a hyper-metabolic sub-volume inside PET/CT with visual assessment as proven by a DICE index of 1 for all the cases. The choice of 50% of the SUVmax was made in accordance with an ongoing clinical trial. In this study the hyper-metabolic sub-volumes are considered more radio-resistant, thus amenable for an intensification of the radiotherapy dose [216]. PET/CT thresholding does not follow a particular consensus. The threshold to be applied to recover true objects is well known to vary according to the size, shape and heterogeneity of the considered object. Studies have been reported in the literature using either a maximum SUV cut-off [260-262] or a percentage of SUVmax as the threshold [260,263,264]. Other studies have used adaptive thresholding using a gradient-based method including automatic segmentation for adaptive radiotherapy with FDG PET. This modality is considered to provide a better estimate of the intra-tumoral metabolic variability [265,266]. Chatterjee S et al [259] used HNC a “static” threshold of 40% SUVmax in accordance with Erdi et al for lung cancer [267]. This made the target volume reproducible and easily implementable, however selected a hyper-metabolic sub-volume, as shown in my series. The authors used generous margins from the gross tumour volume to the clinical target volume in accordance with the UK standard [268]. Probably the wide margins compensated for the tumour volume reduction and avoided geographical misses, however the clinical outcome is not reported in that study. In summary, PET/CT modifies the radiotherapy target both in terms of absolute volume and spatial reproducibility compared to CT alone. The intra and inter-observer variability in interpreting PET/CT with visual assessment is the main concern for using such methodology, so segmentation modalities are recommended in a multimodality imaging

strategy [175], however there are no guidelines on which segmentation protocol should be used. In my project I could have used different SUVmax segmentation levels (e.g. 10%, 20%, 30%, 40%, etc) and identified which one best approximates the results from visual assessment.

8.5 Outcome

8.5.1 Tumour response, time to progression and overall survival

In my series with PET/CT-based VMAT (n=27), I assessed tumour response with RECIST 1.1 or metabolic criteria depending on post-treatment imaging and recorded complete response (CR), partial response (PR) and progressive disease (PD) at 3 months after the end of treatment in 78%, 18% and 4% of the patients respectively. After a median follow-up time of 16 (1-44) months, 74% of the patients had CR, whilst 22% had PD with median time to progression (TTP) of 6.1 (3.1-15.9) months. The estimated cumulative overall survival (OS) at 2 years was 73.6% (95%CI 43.9 to 87.5%). In the sub-group analysis, the estimated 2-year OS was 83% (95%CI 27-97%), 87% (39-98%) and 67% (19-90%) in the low (HPV+, ≤10 pack years smoking history), intermediate (HPV+, >10 pack years smoking history) and high risk (HPV-) categories respectively. In my retrospective series with non-PET/CT-based VMAT (n=114), the CR at 3 months was 84%. At a median follow-up time of 20.6 (2.3-44.5) months, 16% of the patients had PD with a median TTP of 9.0 (3.0-23.0) months. The estimated cumulative overall survival (OS) at 2 years was 79% (95% CI 69-86%). It was not possible to stratify the outcome results by the 3 risk categories in this group of patients. Survival was similar (2-year OS:74% vs 79%) for the 2 treatment modalities and no statistical difference was evident (log-rank test p=0.35) in survival curves. A prospective randomised study stratified by risk group would clarify if a true difference exists. PET/CT did not compromise the clinical outcome compared to CT-alone target definition. This support the safety of PET/CT target definition with visual assessment. My results are also similar to other published studies. Ang KK et al [6] analysed a large series (n721) of oropharyngeal cancer patients and reported 3-year OS of 93%(88.3-97.7), 70.8%(60.7-80.8) and 46%(34.7-57.7), and 3-year loco-regional-control rates of 90.4%, 80.9% and 57.3% in the low, intermediate and high risk group respectively. O'Sullivan B et al [269] showed in a prospective cohort of 800 patients that distant metastases were significantly more common in p16+ oropharyngeal patients with N2c/N3 disease and N2B smokers >10 pack-years (i.e. intermediate risk patients) who received radiotherapy alone compared to chemoradiotherapy. This data confirms that patients with intermediate and high-risk

oropharyngeal cancer (i.e. HPV+ smokers/>10 pack-years and HPV- patients) should receive chemo-radiotherapy and suggests that they are not candidates for de-escalation of treatment. Huang SH et al [270] reviewed a cohort of 810 oropharyngeal cancer patients with median follow-up of 5.1 years. The authors made a recursive partitioning analysis and defined prognostic groups combining TNM stage and non-anatomic factors. The 5-year OS was 70%, 58%, 50% and 30% ($p<0.01$) for stage I, II, III and IV respectively in HPV- patients. HPV+ patients were classified in 4 groups with 5-year median OS ($p<0.001$) of 89% (T1-3 N0-N2c M0, ≤20 pack year smoking), 64% (T1-3 N0-N2c M0, >20 pack year smoking), 57% (T4 or N3M0, age≤70 years) and 40% (T4 or N3M0, age>70 years). In summary, the oncological outcome results of my PET/CT-based VMAT series seem to be similar to non-PET/CT-based radiotherapy studies. A randomised study with sub-group analysis (high, intermediate, low risk) comparing PET/CT vs non-PET/CT-based radiotherapy could demonstrate the superiority of the PET/CT arm possibly related to better patient selection (i.e. exclusion of patients with unsuspected distant metastatic disease) and more accurate staging/target volume definition (i.e. identification of additional ipsilateral and/or contra-lateral nodal disease).

8.5.2 Late toxicity

In my series with PET/CT-based VMAT, I recorded Grade≥2 late xerostomia, dysphagia, dysgeusia and fatigue in 36%, 35%, 0% and 14% of the patients respectively at a median follow-up time of 16(1-44) months. In patients with PET positive bilateral neck nodes (N2c), it would be expected that the irradiation of the bilateral neck with high dose (65Gy) increases the risk of long-term complications compared to patients with PET unilateral neck involvement (<N2c). Surprisingly, in the sub-group analysis, the incidence of Grade≥2 xerostomia and fatigue in patients with PET <N2c was higher than in patients with PET N2c: 46% vs 29% and 23% vs 0% respectively, however these differences were not statistically significant. This is likely related to the small cohort of patients and/or specific dosimetric factors of the parotids (inducing xerostomia) and the central nervous structures such as brainstem and medulla [250] and/or the thyroid [251] (inducing fatigue). Such dosimetric factors are not further reported or discussed for the purpose of this thesis. The incidence of Grade≥2 dysgeusia was not affected by the N2c status. The incidence of Grade≥2 dysphagia was 38% in both the subgroups. Due to the higher dose to the central swallowing structures (pharyngeal constrictors muscles, upper oesophagus, etc) in the N2c patients, a higher incidence of severe dysphagia would be expected. In my retrospective review with non-

PET/CT-based VMAT, the incidence of late Grade≥2 xerostomia, dysphagia and dysgeusia was 39%, 35% and 8% respectively at median follow time of 20.6 (2.3-44.5). The N2c did not increase the incidence of late Grade≥2 toxicity compared to the <N2c status and did not show a statistically significant difference. In patients treated with PET/CT-based VMAT the incidence of long-term Grade≥2 dysphagia was minimally higher compared to non-PET/CT-based VMAT: 36% vs 35%, p=0.96; 38% vs 33%, p=1.0 in N2c. This could be related to the higher detection of N2c disease (20%) with PET/CT compared to CT alone. Overall, the long-term toxicity profile of PET/CT and non-PET/CT-based VMAT was similar, i.e. PET/CT-based VMAT did not increase the incidence of severe (Grade≥2) long term toxicity apart from a minimal increase (+1%) of Grade≥2 dysphagia. This suggests the safety of PET/CT target definition with visual assessment, however only a large prospective randomised study could confirm this.

The late toxicity profile in my series with PET/CT-based VMAT is similar to other published studies with non-PET/CT-based IMRT (Intensity Modulated Radiotherapy).

Xerostomia is clinically defined as the subjective complaint of dry mouth and can be related to salivary gland hypofunction. However, studies are contradictory as to whether there is an actual relationship between the patient's subjective perception of dry mouth and the objective measure of salivary flow rates [271]. Patients might experience xerostomia without clinical evidence of mouth dryness or hyposalivation, perhaps due to a change in saliva composition [272]. Late xerostomia is the major limiting factor in the delivery of radiotherapy to the head&neck region. Subjective late xerostomia is reported up to 64% in long term survivors [273]. Because of the anatomy, the parotids glands are often included in the irradiated volumes and despite the use of highly conformal radiotherapy techniques it is inevitable to deliver significant doses especially to the medial parts of these organs. In patients with midline tumours treated with induction chemotherapy followed by chemo-IMRT the incidence of subjective Grade≥2 xerostomia was observed in 21% of the patients at 12 months [274]. Nutting CM et al [20] reported Grade≥2 xerostomia at 12- and 24-month follow-up in 38% and 29% of patients with oropharyngeal (85%) and hypopharyngeal (15%) cancer treated with static IMRT. Kam MK et al [275] reported late severe xerostomia in 39% of patients with early stage nasopharyngeal cancer. The incidence of high-grade xerostomia at 3 and 6 months is significantly lower in patients treated with bilateral superficial lobe parotid sparing compared to contra-lateral parotid sparing IMRT [276].

Dysphagia is one of the more common acute and chronic manifesting treatment toxicities post chemo-radiotherapy. Research with head&neck populations has shown that the

presence of chronic dysphagia has considerable impact on a patient's quality of life (QoL), is highly correlated with increased rates of depression and anxiety and can lead to aspiration with associated life-threatening pneumonia [277]. Hence, there is significant clinical interest in any options that may help to decrease dysphagia-related toxicity associated with non-surgical management. With modern radiotherapy techniques such as intensity modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT), there has been increased capacity to deliver highly conformal targeted radiotherapy dose to facilitate enhanced functional sparing of key organs at risk (OAR) such as the brain, spinal cord, and parotid glands. The increased capacity to limit dose, where possible, to certain key structures has generated a body of evidence exploring the potential to minimize radiotherapy dose to key structures involved in swallowing. Key anatomical structures involved in swallowing, and whose dysfunction as a result of radiotherapy may contribute to dysphagia, have been referred to as the dysphagia aspiration risk structures (DARS). These structures include the base of tongue, pharyngeal constrictors, glottic larynx, supraglottic larynx, esophageal inlet muscle, oral cavity, crico-pharyngeal inlet, and cervical esophagus [278]. Evaluation of dysphagia and its comparison within trials are complicated by multiple patient-reported instruments, multiple end points for interpretation and summary of results, poor reproducibility in interpreting the results and low correlations between observer, patient, and objective measures, for which observers tend to underestimate dysphagia. My observer-rated results based on CTCAE v4 compare favourably with other studies, which reported rates of Grade≥2 dysphagia of 20% to 42% at 12 months after chemo-radiotherapy [279-281]. Swallowing structure sparing IMRT may contribute in reducing the rate of long-term severe dysphagia. The majority of the DARS sparing studies have applied retrospective methodology to examine swallowing outcomes. More recently, an emerging body of literature has started to prospectively apply active sparing of the DARS for patients receiving chemo-radiotherapy for HNC and has provided some early evidence of the impact on late dysphagia severity [282-285].

Dysgeusia occurs in the majority of the HNC patients undergoing radiotherapy There are not many studies conducted to assess this commonly reported side effect. Furthermore, clinical research on radiotherapy-induced taste alterations has proven to be difficult, considering a lack of reliable and validated study tools for assessing objective and subjective outcomes [286]. The majority of the patients (70-100%) experience partial or total taste loss during radiotherapy. Impairment can be observed in all five tastes. Irrespective of radiotherapy to the tip of the tongue, bitter and salty tastes are found to be most severely affected while sweet taste is least affected [287]. All tastes decline at 4th to 5th week after the start of

radiotherapy and improve on the 11th week [288]. Regardless of the taste quality, maximum impairment in taste is seen in patients during the fourth to sixth week. Loss of all taste types is most pronounced at 2 months following radiotherapy. Recovery from taste loss is seen to start as early as 4-5 weeks after completion of radiotherapy. Around 6-12 months after radiotherapy completion, recovery from dysgeusia is reported in most patients [289,290]. However, partial loss of all taste types can persist for 1–2 years after treatment as reported in some studies [290, 291].

Fatigue is frequently reported as toxicity both during and after radiotherapy. The causes of fatigue are multi-factorial including the disease, treatment, comorbidities, and other patient-related factors. High grade fatigue is described as generalised weakness that is not relieved by rest and limiting activities of daily living. Incidence of fatigue during radiotherapy has been shown to vary between tumour types [292]. In my series with PET/CT-based VMAT I recorded Grade<2 and Grade≥2 fatigue in 86% and 14% of the patients respectively. Such results are similar to other published studies. Previous studies of fatigue in HNC patients treated with radiotherapy have reported many correlating factors. Jereczek-Fossa et al [293] observed in a prospective study of 117 patients that fatigue during and after radiotherapy was correlated to pre-radiotherapy fatigue score, induction and/or concomitant chemotherapy and the need for cortisone during radiotherapy, but not the prescribed radiotherapy dose. Bjordal et al [294] in a comparison of conventional fractionation with hypo-fractionation reported that differences in Quality of Life measures including fatigue could not be explained by clinical or socio-demographic factors alone. Eardley [295] reviewed the acute side effects in 39 patients with HNC receiving conventional radiation therapy. Fatigue was reported in two-thirds of patients during treatment. Even 7 weeks after radiotherapy, 40% of patients reported persistent fatigue. Gulliford SL et al [296] showed a statistically significant increase in Grade≥2 acute fatigue for those patients who were treated with intensity-modulated radiotherapy (IMRT) compared to standard conventional radiotherapy (CRT). A statistically significant increase in maximum and mean doses to various nervous structures (posterior fossa, brainstem and cerebellum) was observed for patients who received IMRT compared to those who received CRT. Dose-volume atlases of the same structures indicated that regions representing larger volumes and higher doses to each structure were consistent with a higher incidence of acute fatigue. There was no association between the dose distribution and acute fatigue for the other neurological structures tested. Xiao C et al [297] conducted a prospective study in 46 head&neck cancer patients pre- and one-month post-IMRT. Fatigue was measured by the Multidimensional Fatigue Inventory (MFI)-20 at both time points along with the assessment of peripheral

blood inflammatory markers including interleukin (IL)-6, soluble tumour necrosis factor receptor 2, and C-reactive protein (CRP) and gene expression. Significant associations were observed between fatigue, IL-6 and CRP, which were independent of time. In addition, the change in fatigue from pre- to post-IMRT was positively associated with the change in IL-6 and CRP. Analysis of up-regulated gene transcripts as a function of IMRT and fatigue revealed over-representation of transcripts related to the defence response and nuclear factor kappa B. The authors concluded that inflammation is associated with fatigue over time in this patient population. Fatigue can also be related to hypothyroidism secondary to head&neck irradiation. Lin Z et al [251] reviewed 56 naso-pharyngeal cancer patients treated with IMRT. The authors showed that the patterns of radiation induced thyroid volume shrinkage and fT4 level reduction were similar, with both of them showing decreasing trend from 0 to 30 months. The thyroid volume and function reached a relatively steady state after 36 months. The incidence of hypothyroidism increased up to 24 months and its frequency was associated with the thyroid dose (Dmean and D50).

In summary, the late toxicity results of my PET/CT-based cohort are similar to my retrospective non-PET/CT-based series and other published studies with non-PET/CT-based IMRT. I measured late toxicity using observer-rated results based on CTCAE v4 criteria. More reliable late toxicity results could be achieved with patient-reported toxicity assessment tools as it is done in most large prospective head&neck studies.

CHAPTER 9.

CONCLUSIONS

I implemented a 2-step-fusion methodology between PET/CT done in the PET Centre and planning CT done in the radiotherapy department at the Beatson West of Scotland Cancer Centre and calculated the fusion accuracy of 90%. This is not reported in any other published studies. The "2-step fusion" protocol gives the advantage of reducing time and cost related to the commissioning and maintenance of a radiotherapy-dedicated PET/CT scanner. Additionally, this methodology can be used by radiotherapy centres that do not have a PET facility on site. PET/CT fusion has been introduced in the routine radiotherapy planning at the Beatson for selected oropharyngeal cancer patients.

I showed that SUVmax was significantly higher in the primary tumour compared to the nodal disease. In the sub-group analysis by HPV status, I found that SUVmax was higher in HPV- compared to HPV+ patients for both primary tumour and nodal disease, and nodal SUVmax was higher in the high risk (i.e. HPV-) compared to the intermediate and low risk (i.e. HPV+) group, even though these differences were not statistically significant. My data suggests that HPV- are more metabolically active than HPV+ oropharyngeal cancers. My results support the hypothesis of treatment intensification in the high-risk group because more biologically aggressive.

PET/CT down-staged the primary tumour (T) in 20% of the patients due to changes in the tumour greatest dimension. The definition of a smaller primary tumour with PET/CT may lead to the reduction of radiotherapy related short and long-term side effects, however this cannot be always clinically relevant because of an upstaging of the nodal disease with PET/CT (e.g. bilateral vs unilateral pathological nodes). My results of 20% change in T staging with PET/CT are probably biased by the small sample of patients, however they are in agreement with data from the literature (10-45%) and confirm that PET/CT modifies the T staging in addition to morphological imaging. PET/CT modified the nodal staging (N) in 60% of the patients. The nodal upstaging (57% in my series) can potentially increase the radiotherapy related toxicity especially in case of contralateral nodal disease (i.e. N2c). My percent change in nodal status due to PET/CT is higher compared to other studies (15-35%) probably because of the small number of patients enrolled. The pre-radiotherapy PET/CT did not show unsuspected distant metastases in any of the patients compared to CT alone. This result differs from other published studies which showed a rate of unsuspected metastases of 13%.

PET/CT with visual assessment (i.e. based on the observer's experience) modified the absolute volume and the spatial reproducibility of both primary tumour (T) and nodal disease (N) compared to CT alone in agreement with the literature. The segmentation with 50% of the SUVmax identified a hyper-metabolic sub-volume. The estimated overall survival and the late toxicity profile of my PET/CT-based cohort were similar to my non-PET/CT-based retrospective oropharyngeal series and other published studies showing that the methodology of PET/CT-2-step-fusion and visual assessment does not compromise outcome and safety.

My results are limited by the small number of patients and the mono-institutional design, however they support the role of PET/CT in locally advanced oropharyngeal cancer in the context of multi-modality imaging for better selection of the patients and more accurate definition of the radiotherapy target volumes.

As follow-up to my project, I envisage a multi-institutional randomised study comparing PET/CT and non-PET/CT-based radiotherapy in oropharyngeal cancer with stratification by risk category aimed to assess the evidence of the clinical impact of PET/CT on outcome and late toxicity in the 3 sub-populations (low, intermediate, high risk). The feasibility of this study may be affected by the necessity of a large number of patients and the applicability of a robust PET/CT-QA protocol in the various centres involved.

Additionally, I envisage a multi-institutional study of metabolically adapted radiotherapy with dose intensification to the hyper-metabolic tumour in the intermediate and high-risk patients. Baseline and half-way PET/CT can be used to identify hyper-metabolic tumour variations to treat dynamically with higher doses throughout the 6-weeks of treatment with the aim to improve the poor outcome in these oropharyngeal sub-populations and assess tolerability. The feasibility of this study may be affected by the applicability of a robust PET-quantitative-assessment QA protocol in the various centres involved.

APPENDIX

A2.2 PET/CT medical exposure risk assessment for clinical use

Acute Services Division

Specialist Oncology Services
Clinical Director: Dr D Dunlop
Beatson West of Scotland Cancer Centre
Gartnavel General Hospital

Diagnostic Directorate
Director: Mrs A MacLennan

NHS
Greater Glasgow and Clyde

MEDICAL EXPOSURE RISK ASSESSMENT

IONISING RADIATIONS (MEDICAL EXPOSURES) REGULATIONS (2000)

Area of Change
Introduction of PET-CT scanning for image registration with radiotherapy CT planning scans to aid target localisation for Head and Neck (H&N) Cancer.

Description of Clinical & Technical Conditions
Currently PET-CT information is available for viewing on AW server workstations sited adjacent to Eclipse treatment planning system (TPS) workstations. The H&N clinical team have identified a requirement for PET-CT images to be registered with planning CT images in Eclipse and the registered data set used during target localisation in the radiotherapy planning process.

Brief Description of Change(s)
PET-CT scans taken at the West of Scotland PET Centre will be introduced to Eclipse and will undergo image registration with planning CT scans performed at BWoSCC. Patients whose scans are used in this way will initially be included in a 10-patient pilot study with end points comparing the target volume delineated using planning CT alone with that delineated using planning CT registered with PET-CT. For patients in the pilot study, the final target volume used for clinical planning will be influenced by PET-CT data.

The study has been approved by the Radiotherapy Management Group. Depending on an analysis of the pilot study experience and of the effect of PET-CT on target volumes and plans, PET-CT image registration may then be introduced for non-study patients.

RT Physics Voluming Room staff will introduce PET-CT images to Eclipse using a DICOM query/retrieve operation from the Hermes PET server source. Image registration with the CT planning scan will be carried out according to WI 14.05.02. The registration will be approved by the Practitioner. For patients in the pilot study multiple PTVs will be created, one for each combination of imaging methods being assessed.

Date Effective

01/05/2014

Identified Areas for Risk Management

1. Geometrical distortion of PET-CT images leads to inaccurate registration and subsequent error in target delineation.
2. Influence of PET information leads to larger or smaller target volumes resulting in either over-modulation of the VMAT plan or under-treatment of the PTV.
3. Time between Decision to Treat and treatment.
4. Communication to Planning section that PET images are to be introduced
5. Confusion in planning process caused by presence of multiple target volumes
6. Training
7. Documentation

Employees involved
Practitioners; RT Physics Operators; Radiography Operators

Risk Management &Control Processes

1. Geometrical distortion of PET-CT images leads to inaccurate registration and subsequent error in target delineation.

Patients will receive their PET-CT scan in the radiotherapy position. A flat couch top, compatible with the Varian Exact indexing system will be used. The patient's BDS will be attached with indexing positions as used for planning CT planning scan and EBRT treatment. PET and CT information obtained at PET-CT have the same DICOM origin and are recognised as pre-registered by the Eclipse registration module. The intrinsic accuracy of registration between the PET and CT information is estimated by PET-CT scientific staff to depend solely on the extent of any patient movement between the PET and CT acquisitions. In this case the random error inherent in the PET-CT registration is estimated to be no more than +/- 2 mm. Quality System form DA 14.033 (Eclipse Algorithms) will be updated to note that only H&N PET-CT scans conforming the above criteria are permitted to be registered.

The slice thickness of the CT images returned from the PET scanner will be 2.5mm i.e. optimal spacing for registration with planning CT scans of the same slice spacing.

Automatic registration of the CT scan obtained at PET-CT with the planning CT scan will be performed by RT Physics staff. The registration will then be assessed by the Practitioner and approved according to WI 14.05.02.

It is the responsibility of the Practitioner to verify that the PET-CT information is of an appropriate quality, and that the intrinsic registration of the PET and CT is of sufficient accuracy, to permit clinical use in informing target volumes.

During the course of the pilot study, the PET-CT scanner will be assessed for geometrical accuracy of the CT images under the supervision of the Head of Radiotherapy Physics Imaging. This data will form a baseline for possible future routine QA. Following completion of the pilot study, and prior to further routine clinical use for radiotherapy, a process must be agreed by the Radiotherapy Physics Imaging Section for assuring the continuing geometric accuracy of the PET-CT scanner for radiotherapy image registration, and the agreed process documented. Once the QA process is agreed, a clinical use certificate should be issued for the PET-CT scanner and scanning of post-pilot study patients subject to this certificate.

2. *Influence of PET information leads to larger or smaller target volumes resulting in either over-modulation of the VMAT plan or under-treatment of the PTV.*

It is the responsibility of the Practitioner to determine if the influence of PET information results in a target volume significantly different from that delineated using current protocols, and on any subsequent action. It is acknowledged that there is a lack of consensus, both nationally and internationally, on the correct methodology for the use of PET Standard Uptake Values (SUVs) in determining radiotherapy target volumes. Therefore the additional risk associated with the use of PET information must be considered and accepted by the Practitioner on a per patient basis.

During the pilot study, clinical treatment plans will be checked by Physics Planning staff experienced in H&N checking who will assess plan all parameters. As with standard H&N VMAT, plans with unusual optimiser parameters, monitor units or dose distributions will be assessed by an experienced MPE and may require dosimetric QA.

3. *Time between Decision to Treat and treatment.*

Patients involved in the pilot study will have PET scan during week 0 then planning CT scan, target voluming and peer review carried out in week 1. Treatment planning will then be carried out, with Practitioner review and plan issue in week 2 with treatment commencing in week 3. This follows the extant Practitioner pathway.

4. Communication to Planning Section that PET images are to be introduced

The Practitioner will be responsible for ensuring that radiotherapy clinical pilot study patient identification from FM 11.22 is generated for each patient in the pilot study. Since the study is not a clinical trial, a Quality System concession will be created to concede the use of this trial form. In addition, the Practitioner and/or Specialist Radiographer (Head and Neck) will be responsible for ensuring that form FM 14.05.02 (Record of Radiotherapy Imaging) accompanies the patient to PET-CT scanners, is completed and then returned the Voluming Room. At plan completion, RT Physics planning staff will indicate on the plan FM 14.028 (plan checklist) that the appropriate PET image series has been introduced. FM 14.028 will be updated to accommodate this new check. FM 14.05.02 will be issued to the case notes.

During the clinical pilot study, the Practitioner and/or Specialist Radiographer (Head and Neck) will be responsible for completing those sections of the form noting details of the PET-CT scan sets to be introduced to Eclipse. Following completion of the pilot study, and prior to scanning further patients, the clinical team must agree on who is responsible for completion of FM 14.05.02 and implement a system for ensuring this form's completion.

5. Confusion in planning process caused by presence of multiple target volumes

For patients in the pilot study, the Practitioner will delineate 3 pairs of primary and nodal GTVs determined firstly by analysis of the CT data alone, secondly with the addition of a visual assessment of the PET, and finally with the addition of threshold SUV information. The Practitioner will then create a 4th GTV pair, labelled GTV_T and GTV_N which will be the final GVTs for clinical use. The Practitioner will then grow these clinical GTVs to create the primary and nodal CTVs and the PTVs (labelled PTV1, PTV_MR and PTV_LR) for use in clinical treatment planning. H&N planning work instruction WI 14.02.40 will be updated to note this process. The names of the PTVs for use in clinical planning are the same as those used for standard head & neck VMAT planning, and no other structures will be created which include the letters "PTV". The risk of incorrect selection of clinical PTV is therefore minimised.

6. Training

PET-CT scanning staff have received training in scanning patients on the flat table top. Training has been supervised by the Radiotherapy Physics Imaging section. A team of 4 staff in the Radiotherapy Physics Voluming Room have received training in introducing PET-CT sets carried out by the Head of Radiotherapy Imaging Physics. A team of 5 planning staff, including 2 MPEs, will receive training in PET image introduction and in the naming formalism of target structures used in the pilot study. Only these staff will be allocated for planning and checking of plans for treatments in the pilot study.

7. Documentation

WI 14.10.11 has been updated to describe the introduction of PET-CT images to the Eclipse planning system. Details of the PET-CT scan sets will be recorded, by scanning staff, on a new form, FM 14.05.02. WI 14.10.11 will require Physics planning staff introducing PET-CT images to check scan I.D. and number of slices in the scan set during the introduction to Eclipse.

Conclusions & Recommendations

The introduction of PET-CT images for registration with CT-planning scans in the Eclipse TPS should proceed as part of the proposed pilot study. Following completion of the pilot study, patient recruitment should pause, and a thorough assessment of the planning data be made. This assessment should be led by the Practitioner responsible for the pilot study with input from RT Physics, and result in the creation of a written report.

The process may continue to routine clinical use of PET images following the pilot study without further IR(ME)R PRA providing:

1) The Clinical Team agree the results of the pilot study justify this through their endorsement of the assessment report.
2) Arrangements are in place for documented on-going QA of the PET-CT scanner and Certificate of Clinical Use issued.
3) The clinical team agree on who is responsible for completion of FM 14.05.02 and implement a system for ensuring this form's completion for each patient.

Signature: ..... **Date:** 23/4/2014
Medical Physics Expert

Signature: ..... **Date:** 23/4/2014
Medical Physics Expert

Signature: ..... **Date:** 28/4/2014
Medical Physics Expert

Accepted By **Date:** 13/5/2014
Head of Therapy ~~Radiography~~

Accepted By: ..... **Date:** 23/4/14
Head of Radiotherapy ~~Physics~~

Accepted By: ..... **Date:** 15/5/14
Clinical Team Lead

Accepted By: ..... **Date:** 24/4/14.
Clinical Lead for Radiotherapy

MEDICAL EXPOSURE RISK ASSESSMEN

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Current Document list

Document No.	Document Name	Revision
WI 14.05.02	Eclipse Image Registration	
FM 11.22	Clinical Trial Information Sheet	
FM 14.05.02	Record of Radiotherapy Imaging	
WI 14.10.11	Introduction of CT Images to Eclipse	
WI 14.02.40	H&N IMRT/VMAT Planning	
FM 14.028	Plan Checklist	
DA 14.033	Eclipse Algorithms	

A2.5 Patient information leaflet for PET/CT scanning for radiotherapy planning

Radiotherapy Patient Information Sheet

PET-CT for Treatment Planning in Head and Neck Cancer

As part of your planning process for radiotherapy you have agreed to have a PET-CT scan. This is **in addition** to the routine CT planning scan which your Doctor has discussed with you.

Your Doctor will also have discussed with you the need to have a Mask or Beam Directional Shell (BDS) made. This is to ensure you stay in the same position for your treatment each day. You will need to wear your mask for part of the PET-CT scan. This part of the scan will take approximately 12 minutes. The rest of the scan will be done without your mask. Your radiographers will guide you in this process.

- **PET:** Positron Emission Tomography is a safe and easy scanning method using an injected tracer. This is generally a form of slightly radioactive sugar which allows us to produce images that show where the tumour is localised in your body. It also shows us the functional activity of these tumour cells compared to normal organs.
- **CT:** Computed Tomography uses X-rays to produce pictures showing the anatomy of your body organs and the tumour itself.

By combining these two techniques and sets of images in one scan, we are able to get important information to help your Doctor accurately plan your treatment.

The PET-CT will be carried out at the West of Scotland PET Centre in The Tom Wheldon Building, Gartnavel General Hospital. You will also be given a patient information leaflet about PET-CT scanning explaining the scan in more detail.

If you need any further information you can contact:

Dr Stefano Schipani, Consultant Radiation Oncologist: Tel. 0141 301 7072

Mrs Maureen Thomson, Consultant Radiographer: Tel. 0141 301 7424

Version 2.0 8/11/2017

A2.8 Record of Radiotherapy Imaging Form for the transfer of the PET/CT of the Head&Neck region (H&N PET/CT) from PACS to the radiotherapy planning system (Eclipse, Aria)

BEATSON WEST OF SCOTLAND CANCER CENTRE QA CONTROLLED DOCUMENT

FM 14.05.02

Record of Radiotherapy Imaging

Patient Details	Radiotherapy Practitioner
MAP ******3074	S Schipani

This form is to be used for recording images intended for registration with the primary CT planning scan except in the case of image guided brachytherapy in which the MRI scan is used without registration.

Once images are introduced to ARIA or iPlan, and all sections completed, this form should be uploaded to ARIA Encounters.

Scan Set Details	1	2	3	4
Scan Date	07/03/17	07/03/17		
Scan Type	PET	CT		
Scan ID				
Series Number	13	10		
Series Description	PET AC head neck	CT std head neck		
No of images	119	155		
Information provided by: (initials /Date)	SS 11/03/17	SS 11/03/17		
Introduced to Eclipse (initials /Date)	MS 11/03/17	MS 11/03/17		

Comments:

Doc. No: FM 14.05.02	**Active Date: 22/04/2016**	**Revision No: 2**	**Page No: 1 of 1**

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