PET has become an important diagnostic modality in the assessment of cancer. In contrast to CT and MRI, which detail the anatomy of the body, PET provides an assessment of biochemical processes by way of uptake and retention of radiopharmaceuticals by tissues. While structural imaging can allow identification of enlarged or distorted internal structures, PET scanning provides information about whether these derangements are likely tumour, scarring from previous treatment, or other biological processes. PET aids management by answering critical questions regarding the presence and extent of disease.

In clinical practice, PET is most often performed using the glucose analogue, fluorine-18 fluorodeoxyglucose (FDG). Enhanced glucose metabolism has long been recognised to be a feature of malignant cells, but is now known to be directly driven by key genomic changes in cancer cells. Because of significantly increased uptake of FDG in most cancers compared to normal tissues, FDG PET provides high diagnostic contrast. Consequently, FDG PET has superior diagnostic accuracy compared to structural imaging in a wide range of cancers and in a number of different clinical scenarios. These include initial diagnosis, primary staging, therapeutic planning, response assessment, restaging at relapse and post-treatment surveillance. The evaluation of tumours by PET is not, however, limited to use of FDG since there are many other potential tracers that can be utilised to characterise other processes pertinent to tumour biology. For example, cellular proliferation can be assessed with thymidine analogues such as fluorine-18 fluoro-L-thymidine (FLT), while tissue hypoxia can be imaged using nitroimidazole-like compounds such as fluorine-18 fluoromisonidazole (FMISO).

Evaluation of head and neck cancer

Head and neck cancer is one of the most common cancers in the developed world and is a major cause of cancer death. In Australia, the incidence in males has been decreasing since the early 1980s, but has increased slightly in women during the same period consistent with smoking trends and emphasising the link between this type of cancer and tobacco use.

The primary treatment of head and cancer is determined by disease stage. Some early cancers, such as T1 laryngeal squamous cell carcinomas (SCC), can be cured by radiotherapy alone, or by laser surgery, maintaining the functions of speech and swallowing. However, the majority of patients currently present with loco-regionally advanced disease, requiring selection of combined modality therapies individualised to achieve the best chance of cure while minimising treatment-related toxicity. In particular, preservation of organ function and quality of life are important yardsticks of the success of therapy, in addition to the more general goal of increasing survival. With this objective in mind, radiotherapy with concurrent platinum-based chemotherapy often precedes surgery in order to minimise the volume of tissue requiring resection, or to obviate surgery in a proportion of cases. In such cases, the additional morbidity of salvage surgery at the primary site and in the neck dictate that initial radiotherapy should be highly targeted to macroscopic tumour, confined to the neck in order to maximise the chance of cure, but also reduce the toxicity to adjacent normal tissues.

The likelihood of cure with any given therapeutic strategy is also related to the stage of disease. With increasing tumour and nodal stage, survival is reduced and the likelihood of relapse is increased. Overall, the five-year survival rates for patients with advanced (stage 3 and 4) head and neck cancer are low (<30%) and a high percentage will develop recurrent loco-regional disease or systemic metastasis within two years of initial treatment. These rates have remained largely unchanged over the past three decades despite improvements in loco-regional control. Clearly,
improvements in the selection and delivery of treatment as well as the development of more effective therapies are required. The choice of the most appropriate treatment and the delivery of that treatment are critically dependent on accurate delineation of tumour sites. There is growing evidence that PET can significantly improve on current techniques with respect to these roles.

Rationale for PET in head and neck cancer evaluation

Most SCCs, the predominant histological subtype of head and neck cancer, have increased glycolytic metabolism, leading to high FDG-avidity. Several authors have reported the use of FDG PET scanning in cancer of the head and neck, both in the setting of primary staging and evaluation of patients after primary therapy, suggesting significantly higher accuracy than conventional evaluation. These studies have, however, generally focused on patients who have been first evaluated and selected by structural imaging techniques including CT and MRI.

In the primary presentation setting, there has been a tendency to use PET primarily in cases with equivocal findings after conventional evaluation. Accordingly, they have addressed its complementary role as a problem-solving tool. The need for accurate anatomical localisation of disease sites for radiotherapy and surgical planning mandates the use of CT as part of the staging process of histologically-confirmed cases, however, with development of combined PET/CT scanners, there is now the possibility of obtaining this information with a single convenient and highly accurate test. Indeed, we believe that there is a strong rationale for the routine use of PET/CT for the staging, treatment selection and planning of patients with clinical evidence of locally-advanced head and neck cancer. The ability of PET to simultaneously provide a wide survey for remote nodal disease, including involvement of non-enlarged nodes, has potential implications for therapeutic selection and planning and the more reliable exclusion of remote metastatic sites is also an important diagnostic advantage. More sensitive detection of synchronous malignancies would be an added bonus.

Although the structural relations of head and neck cancer are vital for planning primary treatment, they are of less relevance in recurrent tumour. Additionally, distortion of normal anatomy renders structural imaging of limited value following aggressive local therapy. Since PET with FDG is likely to demonstrate recurrent disease with higher specificity than CT scanning, it may allow patients with negative scans to be observed. PET may be helpful in patients being considered for surgery or local radiotherapy, as the sole treatment for apparently localised disease in which detection of more widespread disease would change the treatment strategy to combined modality treatment. In patients suitable for salvage treatment of regionally-confined recurrence, determination of the local anatomy is often required. Again, combined PET/CT can potentially provide this information as a single, convenient and accurate test. By providing more accurate information about the true disease status than conventional evaluation, PET can allow more appropriate management decisions to be made. In particular, avoidance of unnecessary active treatment for patients without disease provides economic and patient benefits. Timely introduction of salvage treatment of patients with localised recurrence may also improve survival.

Finally, characterisation of the biological characteristics of head and neck cancer may be of clinical utility since these features may be important to treatment selection and to prognosis. An important example of this principle is the presence of tissue hypoxia. It is known that hypoxia is prevalent in head and neck cancer and carries an adverse prognosis with respect to the likelihood of response to radiotherapy. It is now possible to non-invasively image hypoxia with PET and derive similar prognostic information. This may enable selection of patients for new therapeutic approaches, including metabolically-guided radiation dose painting or use of molecular targeted chemotherapeutic agents.

Peter Mac experience of PET in head and neck cancer evaluation

Carcinoma of unknown primary

Presentation with malignant lymphadenopathy in the neck without a clinically obvious primary lesion is a well-recognised clinical problem, as detailed above. Various groups, including our own, have evaluated the role of PET to detect occult primaries. Although definite primary sites were only detected in around 25%, most series have reported a substantial rate of incremental metastatic site detection consistent with the high predilection for these tumours to metastasise. Furthermore, failure to detect a primary on PET was generally associated with an ongoing failure to detect it on follow-up using other techniques. Presumably a proportion of these cases have tumours that spontaneously involute. The advent of PET/CT allows more precise determination of the anatomical site of FDG uptake and ought to improve the differentiation between physiological uptake in muscle and mucosal abnormalities suspicious for primary malignancy. FDG PET/CT is now our preferred method for evaluating malignant lymphadenopathy in the neck in the absence of tumour in the upper airways on examination (Figure 1). This should ideally be performed prior to examination under anaesthesia to allow selection of sites for biopsy.

Staging of locally-advanced head and neck cancer

Relatively little primary head and neck surgery is performed at our institution. Rather we act as a major quaternary referral site for radiotherapy services, with referrals from a number of surgical oncology groups in our region. FDG PET has been used for almost 10 years at Peter Mac for the staging of most patients with locally-advanced disease being planned for radiotherapy with curative intent. This experience has demonstrated the capability of PET to detect disease in non-enlarged nodes, unexpected distant metastatic sites and second primary malignancies. In particular, PET findings are commonly incorporated into radiation treatment volume planning (Figure 2). A significant issue in judging the accuracy of PET staging in such patients is the lack of
pathological material to externally validate the imaging results. Many of these patients have already deemed to be unsuitable for surgery based on the burden of disease or co-morbidity. Furthermore, where a histological diagnosis is already available and clinician confidence in the imaging result is sufficiently high to warrant empirical treatment, it is often difficult to justify further biopsy to confirm discordant results between conventional evaluation and PET. Nevertheless, where surgical, biopsy or serial imaging follow-up has been available to validate such results, PET has been shown to be correct in the vast majority of cases.

We recently reviewed our preliminary experience using combined PET/CT scan in 35 patients who were all conventionally assessed with CT or MRI, as well as clinical examination. Twelve patients (34%) had a change in staging as a result of PET/CT (95% CI 19-52%), primarily due to upstaging (unpublished results, Connell et al. 2006). One patient had a second primary lung malignancy identified on PET/CT that had been regarded as equivocal on conventional imaging. This was treated separately with radical surgery.

Staging PET/CT changed treatment modality or intent in 10% and 29% had a change in their radiotherapy plan.

Therapeutic monitoring

Due to the high specificity and sensitivity of FDG PET in detecting lymph nodal metastases pre-treatment, we have previously performed a study to assess the utility of PET in detecting viable tumour in nodes that had shown continuing but incomplete regression early following radical treatment. The ultimate aim of the study was to validate the safety of continued observation of patients whose PET showed no metabolic activity in the residual mass, as opposed to surgical intervention, in the expectation of maintaining organ function. Given the high local complication rate with radiotherapy to the neck followed by neck dissection, neck surgery should be avoided if it is unnecessary (no residual disease) or futile (uncontrolled disease present beyond the neck). The likelihood of achieving a complete response is reduced with increasing nodal size following radiotherapy. The median potential follow-up time from presentation was 34 (16-86) months. Twenty-six patients were alive at the time of analysis. The median size of the residual anatomic mass was 1.5 (0.8-3.5) cm. In 32 of the 39 patients, PET showed no metabolic activity in the residual mass. Five of these patients had a neck dissection and were all pathologically negative. The remaining 27 patients were observed for a minimum of 16 months with only one loco-regional failure (in both the primary site and neck). There were no isolated neck failures. The negative predictive value of PET for active disease in a residual anatomic abnormality was 97%.

Restaging of suspected residual or recurrent disease

In another study evaluating patients with residual masses or symptoms suggestive of disease beyond three months from therapy and who were planned for salvage therapy, we found that PET was clearly superior to conventional restaging techniques and induced
management change in 40%. This included avoidance of unnecessary planned surgery in patients with negative PET. Appropriate management change was confirmed in 95% of evaluable cases. Disease presence and extent assessment by PET were significant predictors of survival (P < 0.0001), whereas the extent of disease determined by conventional evaluation was not.

![Figure 3](Image)

**Figure 3**

Demonstration of tumour hypoxia by F-18 FAZA.

The upper panel demonstrates active tumour in the left base of tongue and an upper cervical node. Co-registered FAZA PET images in the lower panel indicate that these lesions are hypoxic. Such lesions are likely to be resistant to radiotherapy.

**Tumour characterisation**

In a phase I trial of the hypoxic cytotoxin, tirapazamine, we have reported a high prevalence of hypoxia based on FMISO PET. In a cohort of patients with very advanced disease FMISO PET was positive in 13/15 cases at baseline including 12/15 of primary sites and 8/13 neck node regions. All sites of corresponding FMISO abnormality at baseline showed marked qualitative reduction of uptake within four weeks of commencing therapy consistent with effective hypoxia-targeted therapy. With a median follow-up of 6.9 years, there were only four local-regional failures, while three other patients have died of metachronous lung cancer. The five-year overall survival was 50% (95% CI: 27-73%) and the five-year freedom from loco-regional failure was 68% (95% CI: 38-88%). We have subsequently demonstrated that imageable hypoxia is associated with a poor outcome in patients receiving standard radiotherapy and an excellent local control in patients receiving tirapazamine in a randomised phase II clinical trial. We have now moved to a second generation hypoxia tracer called FAZA which provides higher tumour to background tissue contrast (Figure 3).

We have also evaluated FLT as a marker of cellular proliferation in various diseases including head and neck cancer, demonstrating the feasibility of using this as a tracer for evaluation of therapeutic response, particularly for tumorigenic as opposed to conventional cytotoxic therapies.

**Conclusion**

PET is an exciting modality for the evaluation of head and neck cancer with roles across the whole temporal domain of the disease process. In particular, it is likely to be the most important modality in all those situations where local anatomy is distorted. PET/CT with FDG should be a routine tool for patients with locally advanced disease being contemplated for treatment with curative intent.

**References**