VIEW POINT

FDG-PET/CT: New horizons in anal cancer

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Summary Anal cancer is an uncommon tumor with an incidence of about one case per 100,000 in most countries. Its incidence seems to be increasing because of exposure to human immunodeficiency virus (HIV) and human papillomavirus (HPV). Traditional pretreatment evaluations include physical examination and CT imaging of the pelvis. Current treatment guidelines include fluorodeoxyglucose positron emission tomography integrated with computed tomography (FDG-PET/CT) as part of the standard pretreatment workup of patients diagnosed with anal cancer. At diagnosis, FDG-PET/CT is used to evaluate primary tumor size, lymph node status and to evaluate for distant metastases. FDG-PET/CT can also be used for radiation therapy treatment planning by clearly defining sites of metabolically active tumor. Posttherapy FDG-PET/CT to determine response to therapy is highly predictive of long-term clinical outcomes. This imaging modality can also be used to evaluate sites of recurrent disease. FDG-PET/CT is an imaging modality which greatly affects the management of patients with anal cancer.

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Pretreatment staging

The clinical staging of patients with anal cancer is in accordance with the American Joint Committee (AJC), TNM staging system. This classification addresses the three important issues: primary tumor size, lymph node status and distant metastases. The primary tumor size is assessed by direct visualization and palpation. However, for large and deeply invasive tumors, it is often difficult to determine the true extent of the primary disease. CT assessment of the size of the primary tumor is also difficult for these large lesions since tissue planes are indistinct and tumor margins may blend with surrounding normal tissues. Lymph node status is determined by palpation of the groins and by CT evaluation of the groins and true pelvis. There are no specific radiographic size criteria for defining abnormal lymph nodes in the groins. Reactive nodes in the groins are often enlarged but do not contain metastatic tumor cells. Fine-needle aspiration (FNA) of suspicious groin nodes is often performed to determine nodal status. The evaluation for distant metastases often includes a chest x-ray and/or CT scan of the abdomen and pelvis.

FDG-PET/CT for patients with carcinoma of the anus can address all three staging criteria of the TNM system in a single whole-body imaging procedure \cite{1,2}. Primary tumor...
size is a significant prognostic factor. Increasing tumor size portends a greater propensity for lymph node and distant metastases. Miller and Grigsby [3] developed a methodology for determining primary tumor size based on FDG-PET imaging for patients with invasive carcinoma of the cervix. The primary tumor size is determined in cm³ from the 40% isocontour of the SUV_max of the tumor. This methodology has also been applied to patients with anal cancer and validated as a predictor of clinical outcome and response to therapy [4]. In addition, Nguyen et al [5] reported that 98% of their patients with anal cancer demonstrated avid FDG uptake in the primary tumor as compared to visualization of the primary tumor by CT in only 58% of cases. These results are similar to our findings of 91 and 59%, respectively [6].

Lymph node status in patients with anal cancer is a significant prognostic factor. Widder et al. [7] reported that the single most important factor for disease-free survival in their patient population was lymph node status. They reported a hazard rate of 2.40 for recurrence when the lymph nodes were positive for the presence of tumor. Cotter et al. [6] compared the detection of abnormal lymph nodes by CT and PET/CT. They reported that PET/CT detected abnormal lymph nodes in 20% of the groins that were normal by CT and in 23% without abnormality on physical examination. Similar findings were reported by Nguyen et al. [5]. They reported that, compared to CT, PET upstaged 17% of patients with unsuspected pelvic/inguinal nodal disease.

The evaluation of patients with anal cancer for the presence of distant metastatic disease has not been standardized. Patients may present with metastases to the lungs, liver and bone. Often these sites are not fully evaluated unless the patient is symptomatic. Therefore, the true incidence of metastasis at diagnosis is unknown but may be as high as 5—10%. In an unpublished update of our series of 102 patients with anal cancer who underwent PET/CT at the time of initial diagnosis, four in 102 (4%) had distant metastases.

Implications for prognosis and treatment

The prognosis for patients with anal cancer depends on the size of the primary tumor and the sites of metastatic disease, primarily lymph node metastases. FDG-PET/CT has been shown to be superior to conventional imaging studies for evaluating the primary tumor, lymph node metastases and distant metastases.

Primary chemoradiation therapy has been established as the first-line treatment for squamous cell carcinoma of the anal canal. Multidrug chemotherapy is preferable to single-drug chemotherapy with radiation [8—10]. In most cases, the specific chemotherapy regimen is determined by institutional policy and is not altered based on sites of disease. However, tumor size and sites of disease are critical for radiation dose prescriptions and treatment planning.

Irradiation doses to the primary tumor range from 45 to 59 Gy depending on tumor size. The size of the primary tumor and its local extent are both clearly delineated by PET/CT. Irradiation to the lymph node regions of the groins is prescribed at 30 Gy when there is no evidence of tumor in the groin nodes. But, the irradiation doses to the groins and pelvic lymph nodes may range up to 60 Gy for enlarged nodes. It is therefore important to accurately evaluate all lymph node bearing regions for the presence of lymph node metastases so that appropriate radiation doses can be administered. As with the primary tumor, PET/CT has been shown to be a superior imaging study to evaluate for the presence of metastatically involved lymph nodes. PET/CT is a whole body study and can also evaluate for the presence of distant metastases.

In order to decrease radiation doses to normal tissues (bowel, bladder and femoral heads) and to specifically target tumor tissue, intensity modulated radiation therapy (IMRT) is utilized in many clinics for the treatment of anal cancer [11]. Meyer et al. [12] have reviewed the use of IMRT for anorectal tumors and conclude that this modality has significantly reduced treatment related toxicities with disease-related outcomes similar to conventional radiotherapy approaches. Anderson et al. [13] described a technique of PET-CT fusion for target delineation and treatment planning for patients with anorectal tumors. They demonstrated that treatment fields were changed in 17% of their patients when PET-CT fusion was used for radiation planning compared to CT planning. Mell et al. [14] treated 48 patients with concurrent chemotherapy and IMRT irradiation for anal cancer. They then evaluated acute bone marrow toxicity to the volume of pelvic bone receiving 10 and 20 Gy. Their analysis found that increasing the volume of pelvic bone marrow receiving low doses of irradiation results in increased acute hematologic toxicity.

Thus, the use of IMRT irradiation decreases toxicity and is warranted in patients with anal cancer. PET-CT fusion for IMRT radiation treatment planning more accurately delineates sites of tumor than does CT.

In our clinic, it is my practice to perform a dedicated FDG-PET/CT simulation for their IMRT treatment planning. The tumor (both the primary and nodal disease) is contoured from the PET portion of the study and normal structures are contoured from the CT portion of the study. These patients undergo PET/CT simulation while positioned in their treatment immobilization devices and set-up lasers are installed in the PET/CT facility for accurate patient positioning.

Posttreatment response

Response to therapy is often difficult to evaluate in patients with anal cancer. The current guidelines for the post-treatment follow-up of patients with anal cancer include serial digital rectal examination, with biopsy of clinically suspicious lesions, beginning 8—12 weeks after therapy is completed. The clinical assessment of the anatomic region treated with chemoradiation, up to 8—12 weeks posttherapy, is often difficult to interpret because there can be significant treatment-related mucositis and dermatitis that can persist for several weeks. Controversy exists about the need for multiple random biopsies versus biopsy of suspicious lesions only.

FDG-PET has been used after completion of therapy to assess the treatment response of many tumors, including lymphoma, non-small cell lung cancer and cervical cancer [15]. For patients with anal cancer, there is a need for a non-invasive assessment of tumor response. Such a method of tumor assessment avoids unnecessary biopsy in those with
a complete metabolic response to therapy and help guide and direct biopsies in those with an incomplete metabolic response. Assessment of response to therapy is an important predictor of survival outcome. Early identification of incomplete metabolic responders allows for salvage therapy to be initiated early before there is progression of disease.

We have performed a study of 53 patients who underwent a pretreatment FDG-PET/CT scan followed by treatment with standard chemoradiation [4]. Whole-body FDG-PET/CT was performed 0.9—5.4 months (mean: 2.1 months) after the completion of therapy. Our results demonstrated that 44 patients were complete metabolic responders and their 2-year cause-specific survival rate was 94%. Nine patients had an incomplete metabolic response and their 2-year cause-specific survival rate was 39% ($P = 0.0008$). Biopsies were performed in the nine patients who had an incomplete metabolic response and six were positive for cancer.

**Conclusion**

FDG-PET/CT is utilized in many ways in the management of patients with anal cancer. Whole-body imaging at the time of diagnosis is important to demonstrate the extent of the primary tumor, detect lymph node metastases and reveal any sites of distant metastases. FDG-PET/CT radiotherapy simulation and treatment planning provides an accurate radiation treatment delivery to maximize the irradiation dose to the tumor and minimize the dose to normal tissues. Posttherapy FDG-PET/CT is important in evaluating the therapeutic response. Long-term surveillance with FDG-PET/CT can detect early asymptomatic recurrences that are amenable to curative salvage therapy.

**Conflicts of interests**

The author has no financial conflict to disclose.

**References**


