INTRODUCTION

The past ten years have shown great advances in oncology, including enhanced knowledge in molecular biology and genetics, functional imaging (positron emission tomography scanning), image-guided radiation therapy and surgery, increasing use of monoclonal antibodies, as well as molecular targeted cytotoxic agents, which are increasingly applied to clinical situations (12). There have been many technical innovations in radiation oncology, which have resulted in an increasing use of image-based treatment planning in radiation therapy for three dimensional (3-D) and intensity modulated radiation therapy (IMRT), stereotactic irradiation (radiosurgery), and image-guided brachytherapy. Special particles, including protons and heavy ions, are used at some institutions.

Ling et al. (43) summarized imaging advances that have potential application in radiation oncology and emphasized the need to adequately identify various target volumes as defined by ICRU Report No. 50 (37) and ICRU Report No. 62 (38). They proposed the concept of a biologic target volume (BTV), which can be derived from biologic images that will substantially improve target delineation, treatment planning, and radiation therapy delivery. In the future radiation oncology will incorporate both physical and biologic conformality and evidence-based multidimensional conformal therapy to improve the treatment of patients with cancer using either 3-D conformal, IMRT, or other techniques (12,25,46). We update a previously published review on this subject (60).

The ultimate goal of radiation therapy treatment planning is to biologically characterize and accurately delineate the target volume, plan a course of therapy, and predict tumor and normal tissue response (TCP, NTCP).

Tumor and Normal Tissue Radiation Response

A well-known axiom is that increased doses of precisely delivered radiation are necessary to control larger tumors; because of concern with normal tissue radiation effects, physical and biologic optimization is critical to improve therapeutic ratio. A variety of factors affect the sensitivity of cells to irradiation, including intrinsic radiosensitivity, phases of the cell cycle, and environmental conditions such as oxygen tension. Our understanding of the interaction of irradiation with cells has grown increasingly complex (15). A variety of approaches, chemical and biologic, have been used to enhance cell kill, such as increased tumor oxygenation, chemical modifiers that affect hypoxia, modifiers of radiation damage repair (such as amifostine), or biologic response modifiers. Physical approaches to enhance radiation cell kill include increased precision in radiation treatment planning and delivery to enhance tumor dose distribution, improvement in tumor target definition to ensure coverage by adequate radiation doses,
differential tumor and normal tissue dose (obtained with conformal or IMRT), and dose escalation. As noted by Brahme (5) dose optimization can be obtained by exploiting the physical and biologic characteristics of innovative irradiation techniques such as intensity-modulation. An illustration of possible improvement of therapeutic ratio in clinical outcome by using biologically optimized IMRT is shown in Figure 1.

In the past, clinical, radiographic, and more recently computed tomography (CT) or magnetic resonance imaging (MRI) have constituted the basis for treatment planning in radiation therapy. Whereas CT scanning is more useful in outlining critical volume structures and providing physical density information (Hounsfield units), MRI has been found to provide better outline of soft tissues.

In recent years, positron emission tomography (PET) scanning has increased the use of this modality to more accurately stage tumors and plan treatment in oncology. It is known that most tumor cells have a high glycolytic metabolic rate (65). PET scanning measures in vivo biochemical disturbances (such as accelerated glucose metabolism) associated with malignant neoplasms. Clinical applications of PET scanning in oncology include (1) differentiating benign from malignant lesions, (2) staging of malignant tumors, (3) treatment planning including radiation therapy, and (4) monitoring treatment results and follow-up.

Deoxy-glucose labeled with fluorine (F18-FDG) is frequently used to assess functional tumor biology and metabolism. After FDG is intravenously injected, its uptake in tissues is measured for approximately 60 minutes with PET scanning. FDG is transported to the membrane of the cell; increasing the number of glucose transport molecules at the surface of the tumor cell will enhance glucose and FDG uptake through the membrane of tumor cell (65). Intercellular hexokinase will covert FDG into FDG-6-phosphate, which exists in low levels in tumor cells. Because the deoxy component of FDG blocks further degradation of FDG-6-phosphate, FDG phosphate accumulates in the cell and emits positrons. The distribution of the FDG reflects the level of glucose consumption at a specific site. A minimal size of lesions detected on PET scan is about 5 mm, depending on the uptake of the radionuclide and the activity of the surrounding tissues.

The recent introduction of PET/CT scanners in clinical practice, with image coregistration, has enhanced our capability and efficacy in treatment planning (13).

**Hypoxia and Tumor Response to Irradiation**

For fifty years, it has been known that hypoxia confers resistance to radiation damage in a wide range of cells, as demonstrated by Gray et al. (28) and Thomlinson and Gray (75). It has been shown in numerous in vitro and in vivo experiments that approximately 2.5 to 3 higher doses of irradiation are required to kill equivalent proportion of hypoxic cells in comparison with well-oxygenated cells.

A variety of methods have been used to measure oxygenation of tumors (35). Limited clinical studies have been performed with polarographic quantitative oxygen electrodes (Eppendorf, Hamburg, Germany). This technique is invasive, and it is only useful to study tumors accessible by electrodes. In addition, known heterogeneity to tumor oxygengation as well as normal tissues lead to significant sampling errors (78). Another disadvantage of the polarographic electrode is the inability to distinguish between viable hypoxic tumor from necrosis.

**Functional Tumor Imaging**

Rasey et al. (63) demonstrated the efficacy of PET scanning with 18F fluorinated misonidazole in quantifying hypoxia in head and neck and lung cancer. In their study, 36 of 37
patients with these tumors had hypoxic regions with fractional hypoxic volumes of 9% for head and neck and 47% for non-small cell lung cancer (NSCLC). Chapman et al. (12) also showed that single positron emission tomography (SPECT) with 131 iodinated axomycine arabinozide ($^{131}$IAZA) can also detect tumor hypoxia in both head and neck and lung cancer, despite the lower resolution of this imaging method. Hypoxic markers that contain the 2-mitroimidazole (azomycin), which upon reduction can covalently bind to cellular molecules were named “vanilla markers”; they include miso- and fluoromisonidazole.

Fujibayashi et al. (22,23,24) found that a copper chelate, (Cu(II)-diacetyl-bis(N$^4$-methylthiosemicarbazone) ($^{60}$Cu-ATSM) was retained in the ischemic heart while washed out from the normoxic tissue (21). The Cu(II) of Cu-ATSM is quickly and irreversibly reduced to Cu(I) and retained due to the lack of electron carrier and the mechanism of its selective retention within hypoxic cells, whereas the compound is rapidly washed out in well oxygenated cells (Figure 2) (42). The retention of Cu-ATSM indicates the presence of intact mitochondria (viable tumor cells) but disturbed electron flow (namely, high NADH) caused by the depletion of final electron acceptor, oxygen. Chao et al. (10) published an innovative approach to use $^{60}$Cu-ATSM PET scanning correlated with CT scans in patients with head and neck cancer to improve the planning for IMRT. To achieve exact co-registration of the images obtained with both modalities, they carried out an experiment using fiducial markers to acquire the information required in imaging acquisition, processing, and registration (Figure 3). An elaborate co-registration schema of images as outlined by Chao et al. (10) will minimize this technical problem but it is eliminated with a PET-CT scanner (3,79,70). An example of the fusion of Cu-ATSM and PET and CT scans images as well as the dose distribution for IMRT for a carcinoma of the tonsil are illustrated in Figure 4. Other hypoxic markers are under development (12).

Multimodality image fusion will be a powerful tool for definition of target volumes in radiation therapy planning. Image fusion is generally achieved through the use of software techniques that minimize the pixel by pixel differences between the imaging modalities. Successful implementation of hypoxia PET imaging in IMRT planning may allow the physician to select hypoxic subvolume within GTV for higher dose to overcome radiation resistance (10).

**Head and Neck Cancer**

In 75 patients (67 with larynx and 8 oral/hypopharynx cancer), who had 109 FDG PET scans and 160 laryngoscopies performed during and after treatment, local recurrence was diagnosed in 37 patients. All patients with recurrent tumor had positive FDG scans. In 34 of 48 patients, the first FDG scan was positive but in 9 of 12 with initial false-positive results, the FDG scan became negative. The sensitivity and specificity of the first scan with regard to recurrence were 92% and 63%, respectively. In subsequent scans the sensitivity and specificity were 97% and 82%, respectively. False positive results may be caused by several factors including patients who speak or swallow extensively after the injection of the FDG or patients with inflammation. Furthermore, radionecrosis or edema may mimic a local recurrence (74).

Greven et al. (29) studied 45 patients with head and neck cancer treated with radiation therapy using FDG PET scans. The standard uptake values normalized for blood glucose and mean body mass, were not useful for predicting outcome following treatment. One month after treatment, PET scans were inaccurate to predict the presence of persistent tumor, but 4-month post radiation therapy scans were more accurate. None of 18 patients with negative PET scans had persistent tumor whereas 6 of 7 with positive and 2 of 3 with equivocal scan had positive biopsies. Rege et al. (64), in a study of 12 patients with head and neck cancer, also showed that
tumors with greater than 50% decrease in metabolic activity after irradiation had improved local tumor control.

Preliminary results of 12 patients treated with IMRT for carcinoma of the nasopharynx reported by Chao et al. (11) showed substantial sparing of the parotid gland with 93% receiving less than 30 Gy, in comparison to lower percentages for the MLC IMRT (48%) or the conventional radiation therapy techniques (66%). In an analysis of 2-year results of patients treated with carcinoma of the nasopharynx, the addition of chemotherapy to IMRT substantially improved the tumor control and disease-free survival (Table 1). Preliminary analysis of patients with carcinoma of the oropharynx also showed substantially improved 2-year local tumor control and disease-free survival in the patients treated with IMRT compared with conventional techniques, either irradiation alone or with surgery (Table 2). Late complications of treatment have been only about 17% to 30% incidence of grade 2 xerostomia with IMRT techniques compared with 75% to 80% with conventional techniques. The incidence of grade 3 xerostomia or other soft tissue complications has been significantly decreased with the IMRT technique (Table 3).

**Lung**

Plain radiographs and CT scans are frequently used to identify abnormal pulmonary lesions and to distinguish benign from malignant tumors, with over 50% of the indeterminant lesions resected at surgery representing benign abnormalities (47).

FDG PET scanning is increasingly used in the evaluation and treatment planning of patients with lung cancer (Figure 5). Minimal size of lung lesions detected on PET scan is about 5 mm, depending on the uptake of the radionuclide and the activity of the surrounding tissues. FDG PET scan has been shown to have a sensitivity ranging from 83% to 100% and specificity ranging from 63% to 90% in differentiating benign from malignant tumors (7,33, 40,41,44,45).

Graeber et al. (27) reported on 96 patients with lung cancer evaluated with preoperative FDG-PET; 66 had histologic malignant tumors and 30 benign masses. FDG-PET had an accuracy of detecting malignancy in pulmonary lesions of 92% (sensitivity 97%, specificity 89%). Further, the FDG-PET accurately predicted lymph node metastasis in 91% of 111 surgically sampled sites, whereas CT was correct in only 64%. In six patients distant metastases were demonstrated on PET scan, significantly helping to define the therapeutic approach.

Primary tumor, hilar or mediastinum lymph nodes have been outlined with CT scans or MRI to determine whether they may contain metastatic tumor, with reported sensitivity of 52% and 48% and specificity of 69% and 64%, respectively (81). Invasive procedures, such as bronchoscopy and transthoracic needle aspiration, are frequently used for definitive diagnosis and staging.

Pieterman et al. (61) evaluated PET scanning in detection of mediastinal lymph nodes in 102 patients with resectable NSCLC in comparison with CT scans. The sensitivity and specificity values of PET scanning in detection of mediastinal metastases were 91% and 86%, respectively. The corresponding values for CT scanning were 75% and 66% (p <0.001). PET identified distant metastases not detected by standard methods in 11 of the 102 patients. The use of PET resulted in lowering the clinical stage in 20 patients and raising it in 42 patients. Many studies have demonstrated improved staging of mediastinum lymph nodes with FDG PET scanning (8,14,31,51A,69,71,73,80).

Farrell et al. (20), in a study of 84 patients with stage I NSCLC, reported that PET scanning, compared with histopathologic data, accurately staged the tumors in 72 patients (86%), overstaged 10 (12%), and understaged 2 (2%). The overall sensitivity, specificity, and positive
and negative predictive values for PET scanning in assessing regional lymph node metastases were 82%, 86%, 47%, and 97%, respectively.

Marom (51), in a review of 100 patients with bronchogenic carcinoma, found that 83 patients were accurately staged by FDG PET whereas conventional imaging staging was accurate in 65 (p < 0.005). Staging of mediastinal lymph nodes with PET scanning was correct in 67 of 83 patients (85%) in contrast to 46 (58%) with CT scanning (p < 0.001). Nine patients (9%) had demonstration of distant metastasis on PET scan that were not suspected on conventional imaging studies. Also, FDG accurately staged 98% of the patients with bone metastasis (11 of 12) whereas the bone scan had a sensitivity of only 50%.

Dwamena et al. (18), in a meta-analysis of 29 studies in which FDG PET scanning and or CT scans were reviewed, the sensitivity and specificity for FDG were 79% and 95%, respectively, and for CT scans 60% and 77%, respectively. The positive predictive value and negative predictive value were 90% and 93% for FDG and 50% and 85% for CT scans, respectively. FDG scanning also has the advantage of detecting previously undetected metastatic sites in 10% to 29% of the patients at initial evaluation (6,32A,51).

Bury et al. (6) evaluated 110 patients with various stages of NSCLC and found a prevalence of bone metastases of 19%. The sensitivity and specificity of FDG for the detection of bone metastases were 90% and 98%, respectively, with an overall accuracy of 96%. In contrast, whereas the sensitivity for bone scan was 90%, the specificity was 61%, because of other benign conditions such as arthritis giving abnormal bone scans.

Akhurst et al. (1) reported on 56 patients with NSCLC who underwent chemotherapy (40 patients), chemoirradiation (11), or radiation alone (5) followed by PET and CT scanning and a surgical procedure. FDG-PET scan was correlated with pretreatment CT scans. Lung resection was performed in 20 patients. In predicting residual mediastinal nodal disease after chemotherapy or chemoirradiation, the positive or negative predictive values of the PET scan were 46% and 79%, the sensitivity 67% and specificity 61%. In 28 patients who were pathologically N0, PET scan overstaged 12 and conversely falsely classified six patients with pathologic N1 and N2 disease as having negative lymph nodes. Ten of the 53 patients on PET scan were shown to have metastatic disease.

The use of CT and PET scanning data for treatment planning in bronchogenic carcinoma is fraught with some difficulties and challenges.

Munley et al. (55), in a retrospective study of patients with lung cancer who had preirradiation SPECT lung perfusion scans (104) and PET scans (35) in addition to standard CT scans of the thorax were used to perform radiation therapy treatment planning. In 11 of 104 (11%) patients SPECT perfusion data resulted in a change of beam orientation to reduce incidence of irradiation of well-perfused lung while maintaining adequate tumor coverage. In the 35 patients on whom CT and PET scan data were used for treatment planning, 12 (34%) portions of the beam aperture were enlarged beyond what was initially the design based on the CT scan alone. For the majority of these cases the PET defined target volume encompassed the CT defined target so the treatment planner had confidence that a difference between both target volumes was not due to a co-registration error. Beam orientation based on the CT scan defined target was generally not changed by the PET imaging data. The authors concluded that the SPECT images were not ideal for treatment planning, because of blurring images and evidence of SPECT activity in regions not corresponding to the CT defined lung volumes.

Mah et al. (49) studied 30 patients with poorly defined NSCLC on CT scans who were treated with definitive radiation therapy and underwent CT simulation and FDG-PET imaging on
the same day in the treatment position. Images were coregistered using external fiducial markers. Three radiation oncologists independently defined the GTV using first CT data alone and then the fused CT and FDG-PET images. In seven of the 30 patients (23%), FDG-PET information changed the therapy from radical to palliative. In five of the remaining 23 patients (22%), FDG-PET images demonstrated lymph nodes within 5 cm of the primary tumor, and they were included in the PTV. Using CT scan data alone, the PTV would have been inadequately outlined in 17% to 29% of the patients, depending on the physician, compared with volume defined by the CT and FDG-PET data. There were great variations in the effect of FDG-PET on target definition depending on the physicians reading the studies, leading to a reduction in PTV from 24% to 70% in some cases and an increase of 30% to 76% in others (Figure 6). The study demonstrates the difficulty in interpreting FDG-PET scan data, the requirement for some threshold activity definition and the need for training of the nuclear medicine physician and radiation oncologist in the interpretation of the imaging studies.

Bradley et al. (4) reported on 15 patients enrolled in a prospective pilot study fusing the CT simulation scans with a PET scan obtained for treatment planning. Two 3-D radiation therapy plans were generated for each patient by separate radiation oncologists, one using the CT alone dataset and the second using the CT/PET fusion dataset. The addition of PET altered the TNM stage in six patients including two patients found to have metastatic disease (Table 4). PET identified unsuspected regional nodal disease in five patients. Fourteen of the 15 patients were eligible for definitive radiation therapy; significant changes in gross tumor volume contours occurred in seven of the 14 patients (50%) (the five patients in whom PET identified unsuspected nodal disease and in two patients PET helped differentiate tumor from atelectatic lung).

Vanuystel et al. (77) also evaluated 105 patients with NSCLC with CT scan and subsequently PET scanning with FDG. In 73 patients with positive lymph nodes on CT and/or PET scan, a theoretical study was performed delineating the GTV as defined based on either CT scan or CT and PET scanning data. Theoretical radiation treatment plans were constructed based on both sets of data including DVHs. There were 988 assessed lymph node stations in the subgroup of 73 patients with positive lymph nodes. Tumor coverage improved from 75% when the CT only data was used to 89% with CT and PET imaging (p = 0.005). In 45 patients (62%) the PET generated information would have led to a change of the treatment volume. The CT/PET based treatment plan to define the GTV resulted in an average reduction of the GTV of 29% (p = 0.002) and in the volume of lung receiving 20 Gy ($V_{\text{lung(20)}}$) of 27% (p = 0.001). Volumetric analysis of the first ten patients demonstrated that the CT-PET GTV treatment plan yielded a smaller target volume (range, 232 to 975 cm$^3$) (Figure 7A). On analysis of dosimetric data, the percentage of total lung receiving more than 20 Gy was on average reduced by 27% with the CT-PET treatment plan (Figure 7B).

Erdi et al. (19) noted that PET scanning had higher sensitivity than CT in detecting and staging mediastinal metastases from bronchogenic carcinoma. In 11 patients both CT simulation and PET scanning were performed in the treatment position using the same body cast. The GTV and PTV, as well as normal thoracic organs, were delineated using the CT scan data. Subsequently, the CT scan and PET images were fused in the treatment planning system using either manual or automated methods. In seven of the 11 cases, they observed an increase in PTV volume (average increase, 19%) to incorporate nodal metastases. In these patients the highest normal tissue complication probability (NTCP) for lung was 22% with combined CT/PET treatment plan and 21% with CT-only plan. In four patients, the PTV was decreased an average
of 18%, primarily in two patients to exclude atelectasis and in trimming of target volume to avoid delivering higher irradiation doses to the spinal cord or the heart.

MacManus et al. (48) evaluated 153 patients with unresectable NSCLC who were candidates for definitive radiation therapy after staging with PET scan. Distant metastases were detected by PET scanning in 32 patients (20%); in several patients multiple metastatic sites were detected. Of the group, 107 patients (70%) were eligible for curative treatment, which was radiation therapy with concurrent platinum chemotherapy in 68, radiation therapy alone in 34, and definitive surgery in 5 patients. The five surgical patients were initially considered inoperable before PET scan was performed. In 46 patients (30%) palliative therapy was given after PET scanning. In the 102 patients who received definitive irradiation after PET scanning, there was a significant increase in the target volume because of inclusion of structures previously considered not involved by tumor. In 16 patients the target volume was significantly reduced because the PET scan demonstrated areas of lung consolidation with low FDG uptake, which were excluded from the treatment volume or because uninvolved lymph node groups were not treated. In three patients primary tumors were visualized on PET scan that were not recognized on CT scans. Patients treated with definitive treatment had a significantly better survival than those treated for palliation; the 2-year survival rates were 44% versus no survivors after 2 years of follow-up, respectively. With both CT and PET scanning, about 75% of the patients with stage I bronchogenic carcinoma survived 2 years in contrast to 45% for stage II and III, and no survivors in stage IV group.

Seppenwoolde et al. (72) investigated the value of perfusion-weighted optimization for radiation therapy treatment planning in 116 patients with inoperable NSCLC. The treatment plans for a virtual phantom and five NSCLC patients were optimized. Seven 8 MV photon beams at equally spaced angles were set up around the tumor. Increasing the number of ports beyond seven produced only minor further gains. The GTV plus 0.5 cm margins were used to define the PTV. Using perfusion information resulted in an increase of the weights of those beams that were directed through the hypo-perfused lung regions both in the phantom and evaluated patients. For patients with one hypo-perfused hemi-thorax, the estimated gain in postirradiation lung perfusion was 6% of the prescribed dose compared to the geometrically optimized plan. To take maximal advantage of the perfusion-weighted optimization, beams that would only pass through ipsilateral, hypo-perfused lung were preferred, unless these beams exited through the contralateral (well-perfused) lung. Special attention should be paid to dose contributions to heart, spinal cord, and esophagus. Improved perfusion after radiation therapy was observed in a number of patients, however, this was not always followed by improvement of lung function as measured with classical function studies. In the 116 patients analyzed in this study, a correlation was found between the mean lung dose and the $V_{20}$. The authors concluded that only for patients with large pretreatment perfusion defect, perfusion-weighted optimization resulted in clinically well applicable treatment plans which may have caused less radiation damage to functioning lung compared with treatment plans optimized on the mean lung dose and a homogeneous target dose alone. For patients with a small perfusion difference, perfusion weighted optimization yielded a treatment plan equal to the nonperfusion weighted plan.

Nestle et al. (58) reviewed published reports on the use of PET imaging in NSCLC and compiled clinical studies on radiation therapy treatment planning (Table 5).

**Uterine Cervix**

PET scanning is increasingly used in the evaluation of patients with invasive cervical cancer, using FDG. FDG PET not only localizes and defines the extent of the tumor within the
pelvis, but it also provides 3-D information about the spatial orientation of the cervical tumor as well as the bladder and rectum with respect to the tandem and ovoid applicators (50,56). Rose et al. (67), in 32 patients with locally advanced carcinoma of the cervix, observed uptake in 91% of the primary tumors. Compared with surgical staging, PET scanning had a sensitivity of 72% and specificity of 92% in detecting para-aortic node metastasis.

Grigsby et al. (30) compared the results of CT and PET scanning with FDG for lymph node staging in 101 patients with carcinoma of the cervix. Patients were treated with standard irradiation and chemotherapy (as clinically indicated); median observation was 15.4 months (range 2.5 to 30 months). CT scans demonstrated abnormally enlarged pelvic lymph nodes in 20 (20%) and para-aortic lymph nodes in seven (7%) of the 101 patients while PET demonstrated abnormal FDG uptake in pelvic lymph nodes in 67 (67%), in para-aortic lymph nodes in 21 (21%), and in supraclavicular lymph node in eight (8%). The 2-year progression-free survival based on pelvic lymph node status was 73% with both CT and PET scanning negative, 49% for CT negative with positive PET scan and 39% when both, the CT and the PET scan, were positive (Figure 8A). The 2-year progression-free survival, based solely on para-aortic lymph node status, was 64% in CT-negative and PET-negative patients, 18% in CT-negative and PET-positive patients, and 14% in CT-positive and PET-positive patients (p <0.0001) (Figure 8B). A multivariate analysis demonstrated that the most significant prognostic factor for progression-free survival was the presence of positive para-aortic lymph nodes on PET imaging (p = 0.025).

A principal finding of this work is that tumor volume is strongly correlated with progression-free survival and overall survival (Figure 9) in patients with advanced cervical cancer treated by radiation therapy. The previously reported observation in many of these same patients, that lymph node status also predicted survival (30) was noted (52). Without evidence of lymph node metastasis, in patients with tumors less than 60 cm$^3$ and lymph node negative, the 3-year overall survival was 100% compared to 50% in the other patients (52).

**PET Scanning in Irradiation of Para-aortic Lymph Nodes**

With conventional radiation delivery methods, the dose to the para-aortic lymph node region cannot be safely increased beyond 45 Gy due to tolerance of the surrounding critical structures, namely kidneys and small bowel. The radiation dose delivered to para-aortic lymph node region could be escalated with IMRT as this treatment modality is associated with better dose conformity to target volumes and sparing of critical structures (54,62,66). This would be of significant clinical interest since the current standard of practice advocates the use of concurrent chemotherapy and radiation therapy for the treatment of advanced cervical cancer (53).

Improved visualization of positive para-aortic lymph nodes using PET scanning with $^{18}$FDG could identify areas for dose escalation with IMRT.

In the proposed method, the whole pelvis area is treated using the conventional AP/PA and lateral ports while the para-aortic lymph node bed is treated with static multileaf collimator (SMLC) IMRT, which allows positive lymph nodes and para-aortic lymph node bed to be treated to higher radiation doses while keeping dose to surrounding critical structures at acceptable levels (62). With isocenter beam placement the whole pelvis fields and IMRT area are abutted using treatment machine’s independent jaws, which produce a nearly uniform dose distribution in the abutment region (best achieved when the superior and inferior jaws abut at the central axis).
The two imaging studies were registered using point matching and anatomical matching. The accuracy of this registration process has been previously reported by us to be better than 2 mm (10).

Para-aortic lymph nodes visualized on the PET scan were outlined as GTV. The virtual simulation software displayed all contours on both sets of images regardless of where they were contoured (Figure 10). Often, positive para-aortic lymph nodes were visible on the CT scan as well. However, these lymph nodes were sometimes difficult to identify on the CT scan alone. The para-aortic lymph node bed was outlined as the CTV on the CT scan (57).

Portelance et al. (62) reported no significant difference in dose distribution between treatment with four, seven, or nine fields for IMRT treatment of cervical area and para-aortic region.

The dose to the GTV was escalated from 45.0 Gy to 59.4 Gy in 1.8 Gy/fraction, for a total of 33 treatment fractions, and the dose delivered to the para-aortic bed (CTV) was 50.4 Gy. With this treatment planning system all of the targets are treated concomitantly; therefore the dose prescription per fraction to the CTV was decreased from the conventional 1.8 Gy to 1.53 Gy/fraction. Using the linear-quadratic approximation and an $\alpha/\beta$ ratio of 10 and 4 for early and late responding tissues, respectively, the dose-equivalence for the CTV was approximately 49.1 Gy and 47.0 Gy at 1.8 Gy/fraction to the tumor and normal organs, respectively.

In four patients, an average of 97.6% and 89.0% of the PTV2 and PTV1 volumes received the prescription doses of 59.4 Gy and 50.4 Gy, respectively. With the exception of the kidneys and the small intestine, all critical structures received relatively low doses of radiation.

Figure 11 shows IMRT calculated dose distributions for the para-aortic lymph node bed and positive lymph nodes in axial, sagittal, and coronal planes. The four plans were normalized to either 85% or 87% of the maximum dose (57).

**Prostate**

Oyama et al. (59) reported on two groups of patients with prostate cancer PSA recurrence; group A 30 patients after prostatectomy and group B, 16 patients after radiation therapy. After administration of 1,110 MBq (30 mCi) of $^{11}$C-acetate (AC), whole-body PET images were obtained. After allowing for $^{11}$C decay, 555 MBq (15 mCi) of $^{18}$F-FDG were administered and repeated whole-body whole-body imaging was performed. Twenty-seven of 46 AC PET studies (59%) had positive findings, whereas only 8 $^{18}$F-FDG studies had positive findings (17%). Limiting the analysis to patients with findings confirmed by CT, bone scintigraphy, or biopsy or considered highly likely to represent tumor, 14 (30%) had disease identified by AC PET, whereas only 4 (9%) had disease identified by $^{18}$F-FDG PET. CT was performed on 22 patients and had positive findings in 3 (14%). Thirteen of 22 patients (59%) with serum PSA >3 ng/ml had positive AC PET findings; whereas only 1 of 24 patients (4%) with serum PSA levels $\leq$3 ng/ml had positive findings.

Dehdashti et al (16) evaluated PET using 16β-[18F]Fluoro-5α-dihydrotestosterone (FDHT), an androgen analogue developed at Washington University, in 15 men with advanced prostate cancer to assess androgen receptor binding selectively of FDHT. Patients with one or more foci of abnormally increased FDHT accumulation were studied after administration of an androgen-receptor antagonist (flutamide; Eulexin). Metastatic disease was confirmed by biopsy and/or radiologic studies. FDHT-PET findings were correlated with bone scintigraphy and/or CT. Abnormal FDHT uptake was seen in the lesions of 10 patients (metastatic disease in 10 and primary cancer in 2 of 10) on FDHT PET; one had widespread osseous metastatic disease and one had extensive lymph node metastases. Similar extensive disease was seen on bone
scintigraphy and CT, respectively. In eight patients, FDHT PET detected 10 of the 16 known osseous lesions seen on bone scintigraphy and also detected all 9 lymph node metastases seen on CT scans. In addition in these 8 patients, FDHT PET detected more extensive nodal involvement in two patients (7 more lesions) and unsuspected lymph node metastatic disease in one patient (6 lesions). All 10 of these patients underwent repeat FDHT PET after receiving flutamide for one day (250 mg tid; in all there was a decrease in tumor FDHT uptake after flutamide.

**Anal Canal**

Ung et al. (76) published a pilot study on 8 patients with carcinoma of the anal canal. The primary tumor was clearly visualized by PET (8/8) with only 4 of the 8 detectable by CT scans alone. Two patients had biopsy-proven inguinal nodes, and both of these were positive on FDG. One patient had an indeterminate inguinal node by size criteria, and this node was negative on FDG. In this pilot study, significantly improved primary tumor volume definition was achieved with hybrid PET/CT images.

**PET Scanning and Brachytherapy**

Malyapa et al. (50) compared conventional two dimensional (2-D) orthogonal radiograph-based brachytherapy treatment planning for cervical cancer with a 3-D treatment planning technique based on FDG-PET in 11 patients (1 patient with FIGO stage IB1 disease, 4 with IB2, 1 with IIB, and 5 with stage III carcinoma). One tandem and 2 vaginal ovoids were inserted in each patient followed by conventional orthogonal radiographs, 2-D treatment planning and treatment with either low dose-rate (LDR) or high dose-rate (HDR) brachytherapy was carried out. The patients underwent FDG-PET of the pelvis to visualize the tumor followed by a second FDG-PET scan with the FDG isotope placed inside the tandem and ovoids to visualize the position of the treatment sources for 3-D treatment planning. The tumor volumes were delineated using a binary threshold technique where the threshold FDG-PET image intensity was 40% of the peak tumor intensity.

In the FOCUS treatment planning system, the three tubes with $^{18}$F-FDG contained in the tandem and ovoids and visible on axial images were contoured for applicator reconstruction. The tandem and ovoid applicators have similar appearance on FDG-PET images and were uniquely identified by their expected positions (Figure 12).

Dose distributions were calculated to determine the tumor volume covered by the 650 cGy isodose line (Figure 13) and the minimal isodose surface covering 100% of the tumor volume. Point A was identified according to the classical definition relative to the reconstructed applicators. The ICRU-38 bladder and rectal points were identified. Dose volume histograms (DVH) were calculated for tumor, bladder, and rectum.

There were no significant differences in the calculated doses at the ICRU-38 (36) defined point A, bladder, and rectum points between conventional 2-D and 3-D FDG-PET approaches. However, DVH analysis showed that the maximum bladder and rectal doses were significantly greater than those obtained from conventional 2-D planning or from ICRU-38 defined points. This method may enhance the precision with which brachytherapy is delivered to patients with carcinoma of the uterine cervix.

**Image Registration and Fusion**

A variety of methods have been published regarding image registration (2,9,63,82) and they were reviewed in a previous publication (60A). Landmark registration works by identifying common objects (i.e., points, lines, surfaces, etc.) in each image set, and somehow minimizing the distance between these objects (chamfer matching). Intensity-based registration relies on correlation between the color (gray scale) of pixels in one image and the corresponding pixels in
the second image. With this method, if the images are not coregistered the pixels in one will have no relationship to the pixels in the other image and will be a random pattern of fusion. On the other hand, if the images are well registered but they are from different modalities (CT, MRI, PET), the scatter plot will contain well-defined areas (called a trace), because of gray scale correlation between the images (68). Functional imaging may allow performing biologic in vivo dosimetry by indicating levels of acute radiation damage to normal tissue (17). Such technique could totally replace portal imaging and might act as a method to determine when normal tissue tolerance is reached to prevent radiation complication (63). Changes in the areas of tumor hypoxia during radiation therapy will allow more specific dose optimization, to deliver high doses of irradiation to residual hypoxic subpopulations as illustrated by Chao et al. (11).

**Conclusions**

PET scanning and other functional imaging techniques play a major role in the definition of tumor extent and staging of patients with cancer. In several anatomical sites, it has been demonstrated that image fusion of CT and FDG-PET scanning integrated in 3-D simulation and radiation therapy treatment planning will significantly improve the accuracy of planning and delivery of irradiation. The recent introduction of a combined CT and PET scanner will substantially simplify image acquisition and treatment planning. At this time it is uncertain whether PET scanning or other imaging studies accurately represent the true extent of the tumor or even if the abnormal images are indeed a malignant lesion. Pathologic confirmation will validate the accuracy of this methodology and clinical outcome studies will be necessary to establish the value of functional imaging in delineating target volumes.

**REFERENCES**


79. Wahl RL: The next big thing: Development of a combined PET/CT scanner. Imaging Econ December, 2000, p 10-22


Table 1. Intensity Modulated Radiation Therapy and Cisplatin in Nasopharyngeal Carcinoma: Preliminary Results

<table>
<thead>
<tr>
<th></th>
<th>P value</th>
<th>Radiation Therapy Alone (n = 103)</th>
<th>Radiation Therapy and Chemotherapy (n = 13)</th>
<th>IMRT and Chemotherapy (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Year disease-free survival</td>
<td>P &lt;0.05</td>
<td>53.6%</td>
<td>90.5%</td>
<td>100%</td>
</tr>
<tr>
<td>2-Year local tumor control</td>
<td>P &lt;0.05</td>
<td>69.6%</td>
<td>91.3%</td>
<td>100%</td>
</tr>
</tbody>
</table>

IMRT = Intensity modulated radiation therapy.
Chao KSC et al., Personal communication, 2000.
### Table 2. Local-Regional Control, Disease-Free and Overall Survival of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Preoperative Conventional Radiation Therapy (n = 109)</th>
<th>Postoperative Conventional Radiation Therapy (n = 142)</th>
<th>Definitive Conventional Radiation Therapy (n = 153)</th>
<th>Postoperative Intensity Modulated Radiation Therapy (n = 14)</th>
<th>Definitive Intensity Modulated Radiation Therapy (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (years)*</td>
<td>4.5 (1.5-23)</td>
<td>3.9 (1.3-19.8)</td>
<td>3.5 (1.6-17.7)</td>
<td>2.2 (1-3.2)</td>
<td>2 (1-2.8)</td>
</tr>
<tr>
<td>2-Year local-regional control (%)</td>
<td>78</td>
<td>76</td>
<td>68</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>2-Year disease-free survival (%)</td>
<td>68</td>
<td>74</td>
<td>58</td>
<td>92</td>
<td>80</td>
</tr>
<tr>
<td>2-Year overall survival (%)</td>
<td>67</td>
<td>71</td>
<td>57</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*Figures in parentheses represent ranges.

### Table 3. Intensity Modulated Radiation Therapy in Oropharyngeal Cancer: Moderate to Severe Late Complications*

<table>
<thead>
<tr>
<th></th>
<th>Preoperative CRT (n = 101)</th>
<th>Postoperative CRT (n = 139)</th>
<th>Definitive CRT (n = 143)</th>
<th>Postoperative IMRT (n = 12)</th>
<th>Definitive IMRT (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>5 (5%)</td>
<td>21 (15%)</td>
<td>24 (17%)</td>
<td>1 (8%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucosa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>2 (2%)</td>
<td>24 (18%)</td>
<td>17 (12%)</td>
<td>0</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Salivary gland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>32 (32%)</td>
<td>107 (75%)</td>
<td>114 (80%)</td>
<td>2 (17%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>3 (2%)</td>
<td>6 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Trismus</td>
<td>3 (3%)</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>6 (6%)</td>
<td>4 (3%)</td>
<td>9 (7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Soft tissue necrosis</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Excludes patients with persistent or recurrent disease.

CRT = Conformal radiation therapy; IMRT = intensity modulated radiation therapy.

### Table 4. Alterations in TNM Staging by PET in Patients with Carcinoma of the Lung

<table>
<thead>
<tr>
<th>CT Stage</th>
<th>PET/CT Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1A</td>
<td>T1N0 (n = 6) ←————→ T1N0 (3)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1N2 (n = 2) ←————→ T1N2 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2N2 (n = 5) ←————→ T2N2 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3N2 (n = 1) ←————→ T3N2 (1)</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T4N1 (n = 1) ←————→ T4N2 (1)</td>
</tr>
</tbody>
</table>
Table 5. Clinical Studies on the Impact of FDG-PET on Radiation Therapy Planning in Lung Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Method</th>
<th>Possible Impact of PET on Target Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hebert (34)</td>
<td>20</td>
<td>Visual comparison x-ray/PET</td>
<td>All Patients: 6/20 Patients with Poorly Demarcated Tumors: 6/13</td>
</tr>
<tr>
<td>Kiffer (39)</td>
<td>15</td>
<td>Anatomical comparison PET/simulator films</td>
<td>All Patients: 7/15 Patients with Poorly Demarcated Tumors: 3/3</td>
</tr>
<tr>
<td>Nestle (58)</td>
<td>34</td>
<td>Anatomical comparison PET/simulator films</td>
<td>All Patients: 12/24 Patients with Poorly Demarcated Tumors: 9/17*</td>
</tr>
<tr>
<td>Munley (55)</td>
<td>35</td>
<td>Comparison of GTVs† (CT vs. PET + CT)</td>
<td>All Patients: 12/35 Patients with Poorly Demarcated Tumors: NA</td>
</tr>
<tr>
<td>Vanuytsel (77)‡</td>
<td>73</td>
<td>Comparison of CT vs. PET + CT-GTVs† with pathology results</td>
<td>All Patients: 45/73 Patients with Poorly Demarcated Tumors: NA</td>
</tr>
<tr>
<td>Giraud (26)</td>
<td>12</td>
<td>Comparison of CT vs. CT + FDG-CDET RT plans after image fusion</td>
<td>All Patients: 5/12 Patients with Poorly Demarcated Tumors: NA, impact in one patient with atelectasis</td>
</tr>
</tbody>
</table>

*Patients with atelectasis.
†Examining mediastinal lymph nodes only.
‡Gross tumor volumes.
FIGURE LEGENDS

Figure 1: Illustration of the possible improvement of the therapeutic window and the clinical outcome by using biologically optimized intensity-modulated treatments. By three-dimensional intensity-modulation, the dose to the tumor is increased at the same time as it is reduced to the normal tissues. It should be pointed out that this figure is based on a more uniform subset of the advanced head and neck tumors with shorter treatment time and, in addition, the dose per fraction was increased instead of the number of fractions. The considerable increase of the therapeutic window and complication-free cure by using intensity-modulated dose delivery is seen (solid curves). (Brahme A: Individualizing cancer treatment: Biological optimization models in treatment planning and delivery. Int J Radiat Oncol Biol Phys 49:327-337, 2001)

Figure 2: The mechanism of ATSM trapping in hypoxic cells. The retention of CuATSM indicates the presence of intact mitochondria (viable tumor cells), but disturbed electron flow (namely, high NADH) caused by the depletion of final electron acceptor, oxygen. (Lewis JS, McCarthy DW, McCarthy TJ, et al: Evaluation of 64Cu-ATSM in vitro and in vivo in a hypoxic tumor model. J Nucl Med 40:177-183, 1999.)

Figure 3: CT-PET image co-registration based on fiducial markers (see arrows) in a patient with squamous cell carcinoma in the right tonsil and neck nodes. (Chao KSC, Bosch WR, Mutic S, et al: A novel approach to overcome hypoxic tumor resistance: Cu-ATSM-guided intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 49:1171-1182, 2001)


Figure 5: FDG PET scan in patient with T4N2 carcinoma of the lung showing the primary tumor and large subcarinal lymph node (A,B,C,D) and a 3-D conformal dose distribution (E).

Figure 6: An example of a case in which not having the FDG-PET data would have resulted in a geographic miss (Left). The co-registered images demonstrated an FDG-avid subcarinal node anterior to a vertebral body, a node not detected on CT. (Right) The CT image showing the anterior and left anterior oblique beams (multileaf collimator
and opposed beams not shown) of the plan based on CT only. In this case, less than 70% of PTV_{2CT/FDG} (light blue) would have received at least 90% of the prescribed dose on a plan based on CT only. (Mah K, Caldwell CB, Ung YC, et al: The impact of 18FDG-PET on target and critical organs in CT-based treatment planning or patients with poorly defined non-small-cell lung carcinoma: A prospective study. Int J Radiat Oncol Biol Phys 52:339-350, 2002)

Figure 7: (A) PTV volume of all ten patients based on the CT and PET-CT data. (B) Percentage of total lung volume receiving more than 20 Gy for the CT and PET-CT treatment plan for all ten patients. (Vanuytsel LJ, Vansteenkiste JF, Stroobants S, et al: The impact of 18-Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patients with non-small cell lung cancer. Radiother Oncol 55:317-324, 2000)

Figure 8: (A) Kaplan-Meier progression-free survival estimates based on pelvic lymph node status (P = 0.001) (n = 101). (B) Kaplan-Meier progression-free survival estimates based on para-aortic lymph node status (P = 0.0001) (n = 101). (Grigsby PW, Siegel BA, Dehdashti F: Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. J Clin Oncol 19:3745-3749, 2001)

Figure 9: Progression-free survival is shown for patients with relatively small volumes, V ≤60 cm³ (n = 34) and larger volumes, V >60 cm³ (n = 17). (Miller TR, Grigsby PW: Measurement of tumor volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy. Int J Radiat Oncol Biol Phys 53:353-359, 2002)

Figure 10. Axial PET and CT images showing a positive paraaortic lymph node (PALN) and kidneys. (Mutic S, Malyapa RS, Grigsby PW, et al: PET-Guided treatment for cervical carcinoma with positive para-aortic lymph nodes: A dose escalation treatment planning study. Int J Radiat Oncol Biol Phys 55:28-35, 2003.)

Figure 11. (A) Axial, (B) sagittal, (C) coronal through target, and (D) coronal through midline IMRT dose distributions for PALN bed treatment plan. Isodose lines are in 10% increments, starting with 10% isodose line. (Mutic S, Malyapa RS, Grigsby PW, et al: PET-Guided treatment for cervical carcinoma with positive para-aortic lymph nodes: A dose escalation treatment planning study. Int J Radiat Oncol Biol Phys 55:28-35, 2003)

Figure 12: (A) Axial FDG-PET image showing uterine tandem and vaginal ovoid applicators, bladder with Foley bulb and rectum. (B) Sagittal FDG-PET image showing the same structures in relation to the tumor. (Malyapa RS, Mutic S, Low DA, et al: Physiologic FDG-PET three-dimensional brachytherapy treatment planning for cervical cancer. Int J Radiat Oncol Biol Phys 54:1140-1146, 2002.)

Figure 13: (A) Three-dimensional representation of a relatively small tumor, bladder and rectum showing the tandem and ovoids source positions in relation to the critical structures. (B) 650 cGy isodose surface corresponding to ICRU-38 prescription point A. (C) Minimum isodose surface covering entire tumor (475 cGy). (Malyapa RS, Mutic S, Low DA, et al: Physiologic FDG-PET three-dimensional brachytherapy treatment planning for cervical cancer. Int J Radiat Oncol Biol Phys 54:1140-1146, 2002.)