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Positron Emission Tomography/Computed Tomography for Target Delineation in Head and Neck Cancers

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Radiation and concurrent chemoradiation are essential in the treatment of head and neck cancers because they allow a potentially curative organ preservation approach in a manner that greatly affects quality of life. Greater doses of radiation to areas of gross disease have invariably led to greater loco-regional control. Radiation delivery has undergone great strides, especially in the era of intensity-modulated radiotherapy and related technologies. With the ability to sculpt out areas of higher and lower doses of radiation to millimeter accuracy, the role of imaging to better direct the radiation beam to its target via improved localization has become an issue of great promise. The use of ^{18}F-fluorodeoxyglucose-positron emission tomography (PET) with computed tomography (CT) as a means of noninvasively staging many head and neck cancers has become increasingly popular. With its role as a functional assay of tumor metabolic activity, it is often used in conjunction with physical examination and other imaging modalities to determine levels of nodal metastases as well as the site of head and neck involvement. Several groups have used images derived from PET/CT to outline areas of gross disease to receive definitive doses of radiotherapy. Generally, no statistically significant difference exists in the volumes delineated on CT alone versus PET/CT. However, in the studied populations there is often important and significant wide individual variability. The tumors on PET/CT are either larger or smaller than tumors outlined on CT scan only, in the majority of patients. Although areas of controversy include threshold definition and image resolution, the utility of a functional assay in defining target volume helps determine areas to receive higher doses of radiation in cancers of the head and neck. Exciting new functional modalities are emerging to image other parameters including tumor hypoxia, which presents a new target with the same challenges in target delineation as PET/CT.
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The field of radiation oncology has been revolutionized in the past 15 years by the advent of more precise ways to administer radiation, such as 3-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), helical therapy, and proton beam therapy. With these new technologies, dose conformality can be increased in a manner that spares normal structures while leading to an equivalent or more radiobiological effective dose (Figs. 1 and 2). Especially in the head and neck, with its confluence of small sensitive structures, the use of the most highly conformal therapies, which are time-intensive for the radiation oncologist, has been widely accepted. "Sculpting of the dose" in the head and neck area has greatly reduced the morbidity of radiotherapy, including xerostomia[1] and parotid salivary function,[2] osteoradionecrosis, hearing loss,[3] and dysphagia,[4] which all affect quality of life. The morbidities of radiotherapy are often amplified because of the use of concurrent chemotherapy, especially in the context of locoregionally advanced head and neck cancers,[5] such that a large proportion of patients may not complete treatment.

Patients with head and neck tumors exhibit a large degree of heterogeneity in pathology and locoregional extent of disease, necessitating a wide variety of treatment approaches. Factors impacting the treatment approach are predicated on location and intrinsic propensity for nodal or distant metastases, histology, and degree of locoregional advancement. Squamous cell carcinoma is the most

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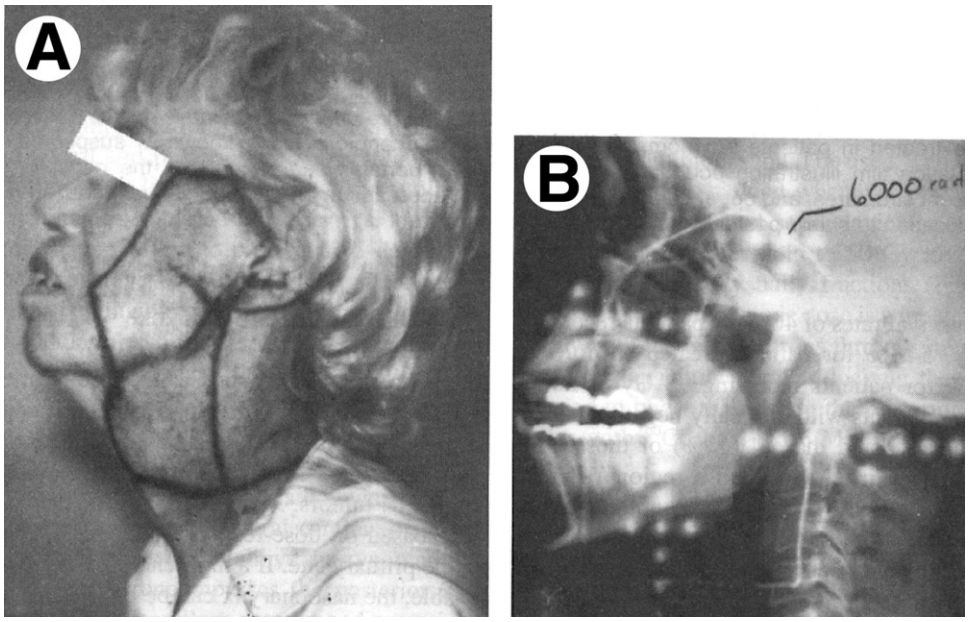

Figure 1 Representation of patient being treated with 2-dimensional radiotherapy for cancer of the head and neck, projected on the patient's skin (A) and on a radiograph (B). The entire width of the delineated field are receiving tumoricidal doses of radiation including the parotid glands, which would lead to severe xerostomia.

common pathology, often associated with a prior history of cigarette smoking, tobacco use, alcohol abuse, viral exposure, including to human papilloma virus and Epstein-Barr virus, and occupational exposure. Many of these cancers are locoregionally advanced, and organ-preservation therapies with relatively high doses of radiation (66-72 Gy daily in approximately 33-39 fractions or 74-82 Gy in 62-68 fractions twice per day) to gross tumor in the primary site and areas of gross nodal metastases with or without chemotherapy generally are preferred. In the postoperative setting in squamous cell carcinomas, in patients who present with specific findings conferring higher risk (ie, extracapsular nodal extension, close margins), the areas of high risk will often be treated to a dose of 66 to 72 Gy in 33 to 39 fractions.

Other types of tumor histology commonly found in this area include lymphomas, sarcomas, carcinomas of the skin, or salivary gland adenocarcinomas. According to the histol-

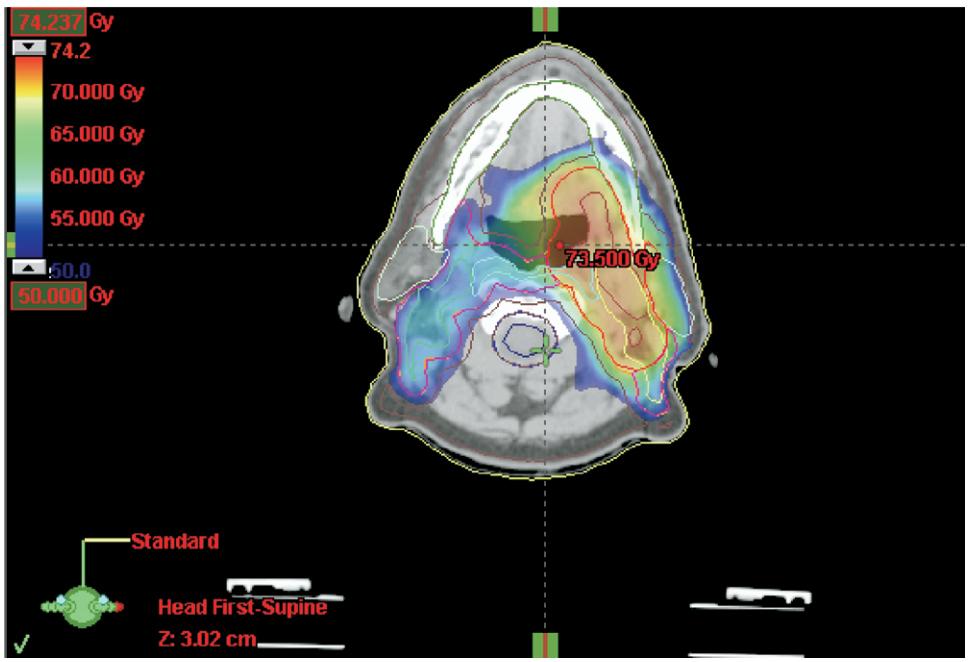

Figure 2 Axial slice of an IMRT plan. In this example the right parotid gland is spared from the highest doses of radiotherapy, sparing the patient from significant levels of xerostomia and dysgeusia.

ogy, the prescribed radiation dose to previous areas of gross disease can vary from 20 to 66 Gy and may be administered adjuvantly after a course of chemotherapy or excision. Areas at intermediate risk for disease recurrence will often be treated to a dose of 50 to 54 Gy.

Radiation dose tolerance varies widely according to the tissue being studied. Much of the data has been extrapolated from animal models.[6] Although institutional practice varies, the parotid glands are commonly constrained to a mean dose of 26 Gy, whereas spinal cord dose is often constrained to a maximum dose of 45 Gy. Maximum tolerable dose to the mandible is often quoted as 70 Gy, whereas the superior constrictor muscles are often noted to have a maximum tolerable dose of 45 Gy. In cases of reirradiation, the dose tolerances are greatly reduced and great care must be undertaken to avoid additional dose to the spinal cord.

Tumor is outlined with the aid of physical examination and imaging studies, and is defined as gross tumor (GTV). Areas of GTV are commonly expanded by 0.5 to 1.5 cm in all 3 dimensions to account for microscopic extension of disease (CTV) and for set up error to define a planning target volume (PTV); therefore, any changes in delineated GTV greatly amplifies the volume that receives high radiation dose. Because areas of tumor are in proximity to normal tissues in the head and neck and have lower tolerances for radiation than gross tumor, it is essential to define volumes that are both necessary and sufficient for tumoricidal dose delivery. Depending on the site of primary disease, the consequences of inadequate coverage to the primary site with high doses of radiation would dramatically increase the propensity for locoregional and therefore distant failure. Because nodal persistence and relapse predicts for the formation of distant metastases and therefore overall survival, adequate coverage of gross disease is essential in the treatment of patients with this disease.

The converse of increased dose conformality with IMRT and related technologies is the possibility of geographic miss of gross tumor at the primary site. The sensitivity of anatomically based assays for cancer at the primary site in the head and neck are less than ideal, with 50% to 95% for computed tomography (CT) and 68% to 92% for magnetic resonance imaging (MRI) examinations. Although large nodal areas and greatly enlarged areas of gross disease at the primary site would be a target for the higher definitive doses of radiotherapy, it is in the intermediate-sized nodes in which a more robust modality for disease identification would be of utility. The sensitivity of CT for lymph node metastases is 65% to 95%; for MRI, the sensitivity for nodal disease is 35% to 90%. For both modalities, specificity is a function of the size of the primary mass as well as that of any suspicious lymph nodes, and has been noted to be 60% to 90% in the neck. There is currently no imaging modality that is exclusively anatomically based, which is both highly sensitive and specific for gross disease in sites of the head and neck.

Impact of Positron Emission Tomography/Computed Tomography in Head and Neck Cancer

Positron emission tomography (PET) and PET/CT with ^{18}F-fluorodeoxyglucose (FDG) are nonanatomically based methods of determining tumor location, staging, persistence, and recurrence. Utilization of this modality has been increasing dramatically since early this decade. It is of utility in tumor target delineation for radiotherapy planning of the lung, especially in the setting of severe atelectasis. Because of its high sensitivity (90-96%) at the primary site and high sensitivity (85-90%) and specificity (70-95%) in the nodal areas of the neck,[7] the utility of PET in diagnosing sites of gross nodal disease in a clinically diagnosed tumor[8] as well as in carcinomas that manifest in the neck with unknown primary site[9] is widely recognized. Several groups have investigated the use of preradiotherapy PET scans overlaid on anatomic imaging to assist in delineation of target volumes. PET/CT is generally acknowledged to be superior to PET alone in identification of areas of tumor involvement,[10,11] with a sensitivity in the neck of 96% and a specificity of 98.5% in one series.[12]

PET/CT and Radiation Treatment Planning

The major published studies comparing PET and PET/CT with other imaging modalities are summarized in Table 1. In a study of 29 patients comparing CT-, MRI-, and PET-delineated volumes of oropharyngeal, hypopharyngeal, or laryngeal tumors, Daisne and coworkers[13] included surgical specimens in 9 patients who underwent a total laryngectomy. Nodal volumes were not delineated. The templates for the surgical specimens were created using a gelatin-casting method and areas of tumor volume contoured for comparison. The surgical specimen was significantly smaller compared with all 3 imaging modalities (CT volume = 20.8 cm^3, MRI volume = 23.8 cm^3, PET volume = 16.3 cm^3, surgical specimen = 12.6 cm^3). PET volumes were significantly smaller than the other 2 imaging modalities. Most strikingly, no imaging modality fully represented superficial extent of tumor, with underestimation of superficial tumor extension in the mucosa of the contralateral larynx and extralaryngeal extension. It is important to note, however, that 8 of the 9 patients had T4 laryngeal tumors, which therefore might not accurately represent the specificity of these imaging modalities in less-advanced tumors and at other sites. In addition, there was a high propensity for geographic mismatch both among the imaging modalities and with the surgical specimen.

Before the widespread dissemination of PET/CT scanners, Nishioka and coworkers[14] delineated PET-FDG versus MRI or CT volumes in a study of 21 patients with oropharyngeal and nasopharyngeal carcinomas. Although a PET/CT scanner was not available during the study, PET-FDG and MRI or CT

Table 1 Significant Studies Comparing PET or PET/CT versus CT in Treatment Planning for Tumors of the Head and Neck

Author (Year)	No. of Patients	Population/Modalities Imaging	Threshold Technique	CT/MRI/PET/Surgical Spec—Based Primary Volume	*P* Value Against PET	CT/MRI/PET—Based LN Volume	*P* Value Against PET	Conclusions
Daisne (2004)	20 (9 with path spec)	Stage II-IV oro-/hypopharynx, larynx (CT, MRI, PET, surgical specimen)	Source-background ratio with iso-activity level	Oropharynx: CT 32 cm^3 MR 27.9 cm^3 PET 20.2 cm^3 Larynx, hypopharynx: CT 21.4 cm^3 MRI 21.4 cm^3 Specimen: 12.6 cm^3 PET 13.4 cm^3	 0.02 0.10 <0.01 <0.01 0.06	None given	N/A	Large mismatches between CT, MRI and PET (13-80%). Imaging modalities did not estimate extent of superficial extension of tumor seen on surgical specimen
Nishioka (2002)	21	Stage I-IV oropharynx, nasopharynx (CT/MRI, PET)	Operator-chosen	Not described. 89% with "similar volumes" between CT/MRI and PET	NS	Total number of identified LN increased with PET	Not given	PET volumes are concordant except in 2 patients with nasopharyngeal cancer. Helps identify additional nodes
Ciernik (2003)	39 (12 with HN)	Stage IIB-IVA (CT, PET/CT)	50% maximal SUV by phantom	2/12 patients with ≥25% increase with PET/CT, 4/12 patients with ≥25% decrease with PET/CT	Not given for head and neck subset	Did not differentiate withprimary tumor	N/A	2 radiation oncologists contoured; volume difference decreased with PET/CT
Heron (2004)	21	Stage II-IVB larynx, pharynx, ethmoid sinus, thyroid (CT, PET/CT)	Liver uptake without background subtraction	CT 64.7 cm^3 PET/CT 42.8 cm^3	0.002	CT 29.9 cm^3 PET/CT 37.2 cm^3	NS	Significance in primary tumor reached due to 2 patients with large differences.
Paulino (2005)	40	Stage III-IV (95%) pharynx, suraglottic larynx, oral cavity, parotid, nasal cavity (CT, PET/CT)	50% isointensity	CT 37.0 cm^3 PET/CT 20.3 cm^3	Not given	Did not differentiate with primary tumor	N/A	Large individual variability. Contouring by 2 radiation oncologists. PET-volume smaller than CT volume in 75%
Riegel (2006)	16	Pharynx, nasal cavity, larynx, orbit, non-Hodgkin's lymphoma, melanoma (CT, PET/CT)	Physician preference	Not given	N/A	Not given	N/A	Contoured by 2 nuclear medicine and 2 radiation oncology physicians. Significant variations among physicians
Wang (2006)	28 (16 with vols)	Pharynx, oral cavity, larynx (CT, PET/CT)	SUV = 2.5	CT 68.8 cm^3 PET/CT 61.8 cm^3	Not given	Did not differentiate with primary tumor	N/A	Staging changed in 57% of patients; 16 patients had volume analysis, 14 of these had >11% changes in GTV.
El-Bassiouni (2007)	25	Pharynx, larynx, oral cavity, paranasal (CT, PET/CT)	Best-fit with CT volume	CT PTV 204.1 cm^3 PET/CT PTV 165.9 cm^3	0.0009	Did not differentiate with primary tumor	N/A	PET/CT delineated structures reduce size of target to receive highest dose
Ahn (2007)	46	Stage I-IVB Pharynx, oral cavity, nasal cavity, larynx, orbit, unknown primary (CT, PET/CT)	Liver uptake	CT 42.0 cm^3 PET/CT 40.5 cm^3	NS	CT 23.2 cm^3 PET/CT 20.3 cm^3	NS	Volumes on CT and PET/CT with >10% variation in approx 70% of patients

Abbreviations: path, pathology; spec, specimen; vols, volumes, HN, head and neck; LN, lymph node; NS, not significant; N/A, not applicable; PTV, planned target voulme.

were both performed in treatment planning position. Nineteen of the 21 patients did not have a significant change in delineated volumes between treatment modalities; in one patient with nasopharyngeal cancer there was a volume increase of PET-FDG of 49% and a decrease of 45% in another patient with nasopharyngeal cancer. Four patients had an increase in their nodal staging. There was no local recurrence from the areas that were not outlined as GTV.

Ciernek and coworkers[15] coregistered PET-CT with noncontrast treatment planning CT and the volumes of tumor were compared in 12 patients with carcinoma of the head and neck. A total of 50% of these experienced a change in GTV of 25% of greater on PET/CT compared with CT alone. Of these 12 patients, 6 had an increase in GTV of ≥10% on PET/CT compared with CT alone; 4 patients had a decrease in GTV of ≥10% on PET/CT, and 16% of these patients were found to have distant metastases on initial staging PET-CT.

Heron and coworkers[16] conducted a study of 21 head and neck cancer patients, including 2 who had thyroid carcinoma. Volumes of primary disease delineated on CT with contrast were 3-fold larger than volumes delineated on PET/CT. A cautionary note is that this statistically significant finding may be skewed by 1 patient with carcinoma of the base of tongue in which the CT volume was 23 times larger than the PET/CT volume. In addition, in 1 patient with carcinoma of the oral tongue, the CT volume was 9.5-fold larger than the PET/CT volume. It is unclear what role any streak artifacts from dental implants may have played in the wide variability between CT and PET/CT volumes in these 2 patients. There was no statistically significant difference in nodal volumes outlined between CT and PET/CT. PET/CT also influenced treatment management, as an additional 3 patients were found to have nodal metastatic disease.

Paulino and coworkers[17] studied 40 patients in a similar fashion. A large proportion of patients (30/40 = 75%) had a decrease in size delineated by PET/CT compared with CT alone, while a much smaller proportion (7/40 = 18%) had an increase in size on PET/CT compared with CT. Median GTV on CT is larger than that on PET/CT (37 cm^3 versus 20.3 cm^3, respectively), although there are no values given for mean volumes and there is no mention of any statistically different volumes between the 2 groups. In addition, GTV has not been separated according to gross disease at the primary site versus gross nodal disease.

Riegel and coworkers[18] examined 16 patients, whose gross tumor on CT and PET/CT were contoured by 2 radiation oncologists and 2 neuroradiologists; gross nodal volumes were not contoured. Thirteen had squamous cell carcinomas, 2 had lymphoma, and 1 patient had melanoma. Although there were no significant differences in the volumes drawn between radiation oncologists and neuroradiologists, there was significant interobserver variability within the 2 specialties. However, much of the differences appeared to be accounted for by the observed method and level of sophistication with which the physician contoured. As defined in the article, physicians who contoured properly—integrating both the PET and CT portions of fused PET/CT—delineated larger volumes than physicians who contoured based on the PET portion alone.

El-Bassiouni and coworkers[19] examined 25 patients with carcinomas of the head and neck, in which volume derived on PET/CT was found to be significantly smaller than the volume contoured on CT alone. Wang and coworkers[20] found that PET/CT changed staging in 16 out of the 28 (57%) patients with head and neck cancer studied. Of 16 patients who had volume analysis, 14 had significant changes in the contoured volume between PET/CT and CT. On average, the CT-based volume was larger than the PET/CT volume by 9%.

In our institution, Ahn and coworkers[21] analyzed 46 patients with head and neck carcinoma for CT alone and PET/CT volume differences in both the primary site and the neck; 21% of patients had an increase in the number of nodes detected on PET/CT compared with CT, whereas 14% had a decrease in the number of nodes detected on CT; 23% of patients had a larger volume (>110%) drawn on PET/CT than on CT, whereas 54% of patients had a smaller volume (<90%) delineated on PET/CT than on CT (Figs. 3 and 4). In general, PET/CT volumes of the primary lesions tend to be smaller than CT ones, as one clearly separates inflammatory mucosal and submucosal components of the mass lesion; in a smaller number of cases, especially base of tongue, PET/CT adds volume by identifying disease lying within or adjacent to muscle layers and infiltrative neoplastic processes which appear normal on CT. As far as nodal disease is concerned, there is little volume variability but PET/CT adds value by identifying abnormal uptake in nodes that appear normal on CT by volume only (smaller than 1 cm). In this case, there is a change in the patient's TNM staging, leading to a transformation of CTV dose for microscopic disease into GTV dose for gross disease. The importance of this added dose cannot be overemphasized, as it may lead to improved outcomes. Accounting for differences in volumes and doses, the authors estimated that the addition of PET/CT to CT alone changed radiation planning in approximately 55% of patients.

With anatomically based imaging such as CT, the personal experience and bias of the individual who contours increases interobserver variability in outlining the GTV. The use of PET/CT can decrease this variability by introducing an additional parameter that is useful in standardizing volumes. In the study by Ciernik and coworkers, 2 radiation oncologists contoured CT and PET/CT volumes including head and neck as well as pelvic and abdominal sites, the use of PET/CT was found to significantly decrease the mean volume difference between the 2 observers by a multiple of 4, or 17 cm^3. This observation appears to conflict with the findings of Riegel and coworkers noted above, and is likely due to a standardized threshold algorithm used by Ciernik.

When delineating tumor on PET, selection of the threshold algorithm can lead to large differences in outlined volume. The issue of threshold determination is controversial, and investigators have used several different techniques. Nishioka and coworkers used an arbitrary, operator-chosen threshold level, which presents a weakness in the study. Heron and coworkers and Ahn and coworkers normalized volumes according to liver uptake. Ciernik and coworkers

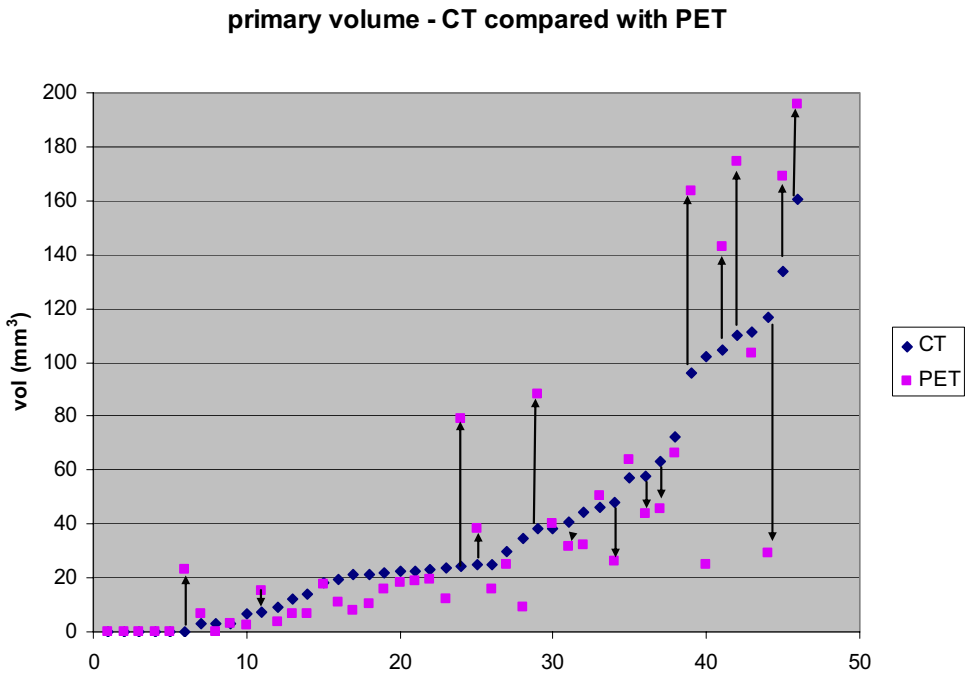

Figure 3 Comparison of primary tumor volume (GTV) between CT alone and PET/CT. (Color version of figure is available online.)

used a 50% of maximal SUV value as determined by PET phantom. A popular technique has been fixed threshold of the background-subtracted tumor maximum uptake, usually 40% to 50%; Paulino and coworkers used a 50% isointensity level. Riegel and coworkers used an arbitrary threshold depending on physician preference. Wang and coworkers contoured on the basis of an arbitrary SUV value of 2.5, whereas El-Bassiouni used an individualized thresholding algorithm that took into account tumor maximal signal. Ashamalla and coworkers have suggested inclusion of the "halo" of the PET-avid mass.[22]

PET-FDG is not an inherently accurate test, with a spatial resolution considered to be approximately 0.4 to 0.7 cm. This is dependent both on the intrinsic physical properties of the scanner, as well as the distance traveled by the positron from the ^{18}F-moiety of FDG before photon-electron pair annihilation. The magnitude of the spatial resolution uncertainty is considered to be a function of tumor size. However, as the portion of the GTV expansion to generate PTV includes margin to account for microscopic extension of the tumor which may not be evident on imaging. At our institution, common practice in the head and neck is to have a 0.5 cm expansion on GTV in the PTV to account for this microscopic extension, with a further 0.5 cm expansion to account for

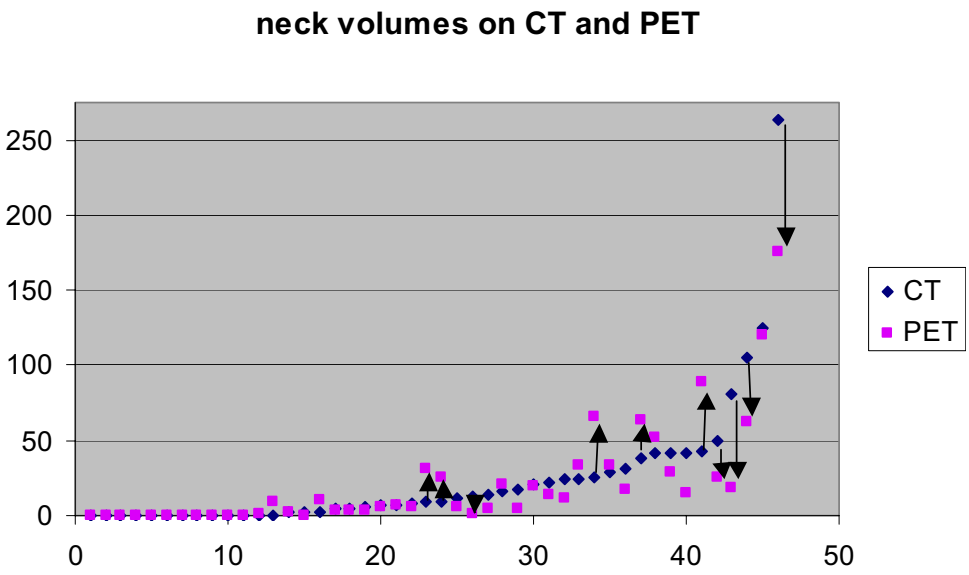

Figure 4 Comparison of neck volumes between CT alone and PET/CT. (Color version of figure is available online.)

setup error or patient movement. In this case, considering that the most likely spatial resolution error would be 0.5 cm, for a worst case scenario the delineated tumor in one dimension could be overestimated by 1 cm. At the other extreme, there would be enough margins to account for setup error with a GTV + 0.5 cm expansion.

The use of hypoxia markers has been of great interest during the last several decades, and its use has been contemplated in radiation treatment planning.[23] Areas of tumor that are in chronically hypoxic areas are considered to be relatively radioresistant because of the lack of sufficient oxygen for fixation of damage generated by free radicals as well as induction of genomic and epigenetic changes in the tumor population. There is a need for differentiation between areas of acute hypoxia and chronic hypoxia. These areas can be detected using markers conjugated to misonidazole, tirapazamine and other agents that act via the inherent affinity of these molecules for electron-rich reductive states. Because of this property, these agents also act as hypoxic cell sensitizers by causing fixation of radiation-induced damage in a manner similar to that of oxygen.

Several trials have been conceived with markers of hypoxia as radiation sensitizers, with largely nonsignificant results with the notable exception of nimorazole in a subset of patients with pharyngeal and supraglottic larynx tumors.[24] An area of intense investigation is the use of these molecules to identify functional areas of hypoxia, and administer higher doses of radiation in conjunction with the same class of molecule. Theoretically, this could lead to increased local control as well as obliteration of a radioresistant cell population which is theorized to be a significant source of seeding of cancer cells into the bloodstream. Additional imaging strategies with reporter gene imaging may potentially have utility in identifying areas of tumor spread,[25] and in their delineation for radiotherapy targeting with a ^{18}F-fluoroazomycin-arabinoside marker.[26] Consideration can be given to dose escalation greater than the 70 Gy normally administered, to hypoxic areas of gross disease.

The use of PET as a noninvasive surrogate for assessing response to therapy with organ-sparing chemoradiation is controversial in patients who presented with bulky lymph node disease.[27] In general, PET for restaging had a sensitivity of approximately 80% to 95%, a specificity of 75% to 90%, and an accuracy of 80% to 90%. In a study of 28 head and neck patients, PET/CT performed 8 weeks after definitive radiotherapy had a sensitivity of 77% and specificity of 93%, in comparison with a sensitivity and specificity of 86% and 58% for contrast-enhanced CT.[28] A series of 12 patients with a clinically palpable residual neck mass found that PET/CT was highly accurate in the determination of residual tumor.[29]

Conclusion

The previous 10 years has been an exciting time in the field of radiation oncology. We are now able to administer radiotherapy in a manner that helps maintain a quality of life that is more acceptable to patients, while leading to similar or more durable levels of locoregional control. With new radiation delivery technologies, there is now consideration being given to escalate dose to areas of PET-FDG positive disease, or possibly to areas of tumor hypoxia. In the meantime, PET/CT for volume definition is beset by several technical hurdles including threshold definition and scanner resolution. While several papers have shown a trend toward decreased volumes delineated on PET/CT compared with CT alone, this was likely dependent on the threshold modality utilized. With newer imaging modalities that examine markers of hypoxia, apoptosis and cellular proliferation, questions very similar to those which have been asked about PET-FDG in target delineation are arising—how does one define edge delineation, and is dose escalation to hypoxic areas or molecular targets truly feasible? With the new capabilities afforded by improved radiation delivery modalities and methods of functional imaging, the radiation oncology community now finds itself faced with a quandary that is at once a luxury and a curse—overcoming technical hurdles to best deliver radiation to maximize tumor destruction and cancer cure while maintaining quality of life.

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Erratum

Relevant funding information was omitted from the article "FLT: Measuring Tumor Cell Proliferation In Vivo With Positron Emission Tomography and 3′-Deoxy-3′-[^{18}F]Fluorothymidine" by Salskov et al, which appeared in the November 2007 issue of the journal (Vol. 37, No. 6), pages 429-439. The article should have included the following statement:

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