December 9, 2009

Tamara Syrek Jensen, J.D.
Acting Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Blvd., Mail Stop C1-09-06
Baltimore, MD 21244

Re: Public Comment on CAG-00181R3 (Limited-Scope Reconsideration of CAG-00181R Regarding Certain Restrictions on Coverage of FDG-PET for Initial Treatment Strategy Evaluation)

Dear Acting Director Jensen:

We are writing in support of the decision of the Centers for Medicare & Medicaid Services (CMS) to open a limited-scope reconsideration of NCD CAG-00181R for the purpose of reconsidering the restriction of coverage of FDG-PET to one scan per patient for initial treatment strategy evaluation. We believe that the clinical evidence demonstrates significant health benefit outcomes from performing more than one PET scan as part of the initial antitumor treatment strategy in certain clinical circumstances.

This letter is submitted jointly on behalf of the Academy of Molecular Imaging (AMI), the American College of Nuclear Medicine (ACNM), the American College of Radiology (ACR), the American Society for Radiation Oncology (ASTRO), and the Society of Nuclear Medicine (SNM). These groups collectively are composed of clinicians, academicians, researchers and nuclear medicine providers utilizing molecular imaging technologies, including integrated positron emission tomography/computed tomography (PET/CT). We represent tens of thousands of physicians, providers, and patients with regard to this technology, and have worked closely with CMS over the past several years to increase beneficiary access to PET/CT through the development of the National Oncologic PET Registry (NOPR).

As articulated in our October 14, 2009 reconsideration request, we believe that there is substantial evidence that — in certain limited clinical circumstances — the restriction of PET coverage to a single scan for initial treatment evaluation is contrary to good clinical practice. Several examples of such circumstances are detailed in the reconsideration request itself. We also believe that the existing literature available to CMS provides clinical justification for second

initial scans in certain radiation planning and prolonged evaluation situations. Part III of our reconsideration request contains an extensive summary of this literature. We would also like to bring to the attention of CMS two additional recent publications that provide further support for easing the single-scan restriction.

Kidd et al. (2009)[1] evaluated a cohort of patients with locally advanced cervical cancer treated with brachytherapy and intensity-modulated radiation therapy (IMRT), in which the IMRT was guided by the results of FDG-PET. The PET studies in these patients were performed as repeat examinations, after an earlier initial staging study, so that the PET data could be acquired in the treatment position and thus properly fused with the simulation CT for planning of the IMRT. By comparison with a historical control group of similar patients treated with brachytherapy and conventional external radiation, the patients who underwent PET-guided IMRT had better overall and cause-specific survival and less treatment-related toxicity. This study provides important evidence that FDG-PET used for radiation treatment planning leads not only to altered treatment plans, but also to actual improvement in patient outcomes. As we noted in our original request, there is broad consensus that FDG-PET to be used for this purpose must be obtained in the treatment position, and this will generally require a separate study from the one performed for initial staging of the patient's tumor burden.

Simpson et al. (2009)[2] conducted a survey of a random sample of 1,600 radiation oncologists regarding their utilization of advanced imaging technologies for target delineation in radiation therapy, and their future plans for such use.[3] The study found that 95% of the responding physicians, reported using advanced imaging technology for target delineation, and that FDG-PET was the most common technology employed (by 76% of respondents). The most common cancers treated using image-guided target delineation were lung (83%), central nervous system (79%), and head and neck (79%). Finally, among users of advanced imaging technologies, 66% planned to increase use of such technologies, while 30% of nonusers planned to adopt these technologies in the future. This study indicates the significant expansion of the use of FDG-PET for target delineation over the past decade, and suggests that oncologists find such imaging to have clinical value.

In conclusion, we continue to believe that the strict one-scan limitation cannot be reconciled with either the prevailing standard of care or the existing literature, and therefore encourage CMS to amend CAG-00181R to accommodate and cover clinically necessary "second

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[1] Kidd EA et al. Clinical outcomes of definitive intensity-modulated radiation therapy with fluorodeoxyclucose-positron emission tomography simulation in patients with locally advanced cervical cancer. *Int J Radiation Oncolgy Biol Phys* (in press, available online Nov. 2, 2009, http://www.redjournal.org/article/S0360-3016(09)00954-7/abstract).

[2] Simpson DR et al. Technologies for target delineation in radiation oncology. *J Am Coll Radiol* 2009, 6:876-883.

[3] Of the sample (identified through the American Society for Radiation Oncology directory), 1089 were contactable. The response rate was 36%, or 394 physicians.

initial" scans in situations such as those described in our reconsideration request. Such a policy would harmonize the omnibus PET coverage policy with the existing evidence on the clinical value of certain "second initial treatment strategy evaluation" scans.

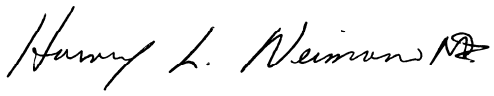
As we noted in our reconsideration request, we remain cognizant of the desire of CMS to avoid situations in which limited coverage of second initial scans could lead to attempts to obtain reimbursement improperly for second initial scans beyond such circumstances. However, we believe that it is possible to extend coverage for certain limited radiation therapy purposes and in the other scenarios we describe without allowing the exception to consume the general rule.

We look forward to working closely with CMS throughout this limited-scope reconsideration process, and to providing any additional information that CMS may require.

Sincerely,

Timothy J. McCarthy, PhD
President, AMI

Jay A. Harolds, MD, FACNP
President, ACNM



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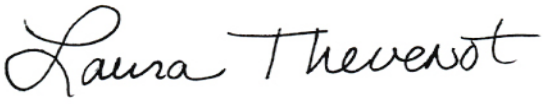

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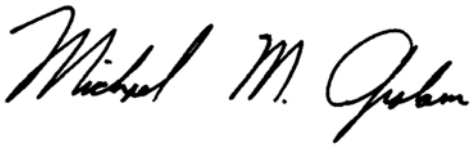

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CLINICAL INVESTIGATION

CLINICAL OUTCOMES OF DEFINITIVE INTENSITY-MODULATED RADIATION THERAPY WITH FLUORODEOXYGLUCOSE–POSITRON EMISSION TOMOGRAPHY SIMULATION IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER

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Purpose: This study aimed to evaluate the toxicity and clinical outcomes for cervical cancer patients treated definitively with intensity-modulated radiation therapy (IMRT) compared with non-IMRT treatment.

Methods and Materials: This prospective cohort study included 452 patients with newly diagnosed cervical cancer treated with curative intent (135 IMRT and 317 non-IMRT). Treatment involved external irradiation and brachytherapy, and 85% of patients received concurrent chemotherapy. All IMRT patients underwent an F-18 fluorodeoxyglucose positron emission tomography (FDG-PET/CT) simulation. A 3-month post-therapy PET was obtained to evaluate treatment response. Toxicity was scored by the Common Terminology Criteria for Adverse Events Version 3.0.

Results: The IMRT and non-IMRT groups had similar stage distribution and histology. For all patients, the post-therapy FDG-PET response correlated with overall recurrence risk ($p < 0.0001$) and cause-specific survival ($p < 0.0001$). Post-treatment FDG-PET findings were not significantly different between the IMRT and non-IMRT patients ($p = 0.9774$). The mean follow-up for all patients alive at the time of last follow-up was 52 months (72 months non-IMRT, 22 months IMRT). At last follow-up, 178 patients (39 IMRT, 139 non-IMRT) had developed a recurrence. The difference in recurrence-free survival between the two groups did not reach statistical significance ($p = 0.0738$), although the IMRT group showed better overall and cause-specific survivals ($p < 0.0001$). Of the patients, 62 patients (8 IMRT and 54 non-IMRT) developed Grade 3 or greater bowel or bladder complications, and by cumulative hazard function analysis the risk was significantly less for patients treated with IMRT ($p = 0.0351$).

Conclusion: Cervical cancer patients treated with FDG-PET/CT-guided IMRT have improved survival and less treatment-related toxicity compared with patients treated with non-IMRT radiotherapy. © 2009 Elsevier Inc.

Cervix, IMRT, Non-IMRT, FDG-PET/CT, Image guidance.

INTRODUCTION

Cervical cancer is among the top three cancer diagnoses in women worldwide (1). In the United States, cervical cancer is a significant cause of years of life lost, as it is the third leading cause of cancer death in women 15 to 34 years old and the fifth leading cause of cancer death in women 35 to 54 years old (2). Even with recent efforts to reduce the incidence of cervical cancer with the human papillomavirus (HPV) vaccine, it has been estimated that the clinical impact will not be appreciated until after 2040 (3).

The treatment of cervical cancer has changed over time. The landmark studies showing a benefit of concurrent chemotherapy brought about a new standard in the treatment of cervical cancer. The use of concurrent cisplatin therapy along with radiation therapy significantly improved local control and overall survival (4–6). Unfortunately, concurrent chemotherapy also caused an increased incidence of hematologic and gastrointestinal (GI) side effects (6).

For other pelvic malignancies, including prostate, rectal, and anal cancer, the use of intensity-modulated radiation therapy (IMRT) has been shown to help limit dose to surrounding normal tissues and thereby decrease toxicity (7–9). The use of IMRT for prostate cancer improved pelvic nodal coverage and decreased dose to the small bowel, bladder, and rectum (7). Concurrent chemotherapy and IMRT in patients with anal cancer also showed favorable toxicity

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Conflict of interest: none.

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levels while maintaining high rates of local control (9). Pelvic IMRT appears to decrease treatment-related side effects without compromising treatment efficacy.

There have been limited studies looking at the use of IMRT for cervical cancer. Some early theoretical and dosimetric studies suggested that, for gynecologic cancers, IMRT could potentially reduce the irradiation dose to small bowel and bone marrow, as compared with standard four-field whole-pelvis treatment (10–12). A small study of 33 cervical cancer patients treated after hysterectomy with IMRT and concurrent chemotherapy showed decreased GI and genitourinary (GU) side effects, with local control comparable to that in patients treated with four-field box radiotherapy (13). Another small study of patients with locally advanced and recurrent cervical cancer suggested that a concomitant integrated boost using IMRT was tolerable, although assessment of toxicity was evaluated only up to 3 months post-therapy (14).

Given this paucity of data about the use of IMRT to treat intact cervical cancer definitively, the goal of this study was to evaluate the toxicity and treatment outcomes for cervical cancer patients treated with IMRT. Some have suggested cervical cancer is particularly difficult to treat with IMRT because IMRT requires specific target volume definition and cervical tumors are difficult to distinguish from surrounding tissue using computed tomography (CT) (15). Positron emission tomography (PET) with F-18 fluorodeoxyglucose (FDG) has good sensitivity for detecting sites of disease in cervical cancer and, at our institution, we have significant experience in using FDG-PET to aid radiation treatment planning in patients with cervical cancer (16, 17). In addition, we have found, in a prospectively validated study, that treatment response in cervical cancer, as evaluated on the 3-month post-therapy FDG-PET, predicts overall survival (18). This surrogate outcome measure could help to compensate for the shorter follow-up in an IMRT population versus patients treated in the pre-IMRT time period. All patients with cervical cancer treated definitively with IMRT in this study underwent an FDG-PET simulation to aid in target volume delineation.

This is a study of cervical cancer patients treated with curative intent. All patients underwent whole-body FDG-PET before treatment to identify sites of metabolically active disease. We evaluated the toxicity and clinical outcomes of patients treated using our long-standing institutional step-wedge technique and compared these results to those in patients treated with the PET-guided IMRT technique (an institutional treatment policy change as of March 2005).

METHODS AND MATERIALS

Patients

This analysis included 452 consecutive patients with newly diagnosed cervical cancer who were treated with curative intent with definitive radiation from June 1997 to September 2008 at Washington University in St. Louis. This registry study was approved by the Washington University Human Research Protection Office.

All patients underwent a complete pretreatment staging workup including history and physical examination, examination under anesthesia, cervical tumor biopsy, diagnostic abdominal and pelvic CT scan, and whole-body FDG-PET or FDG-PET/CT. Patients were staged using International Federation of Gynecology and Obstetrics (FIGO) clinical staging. A repeat PET or PET/CT scan was performed 3 months after completing radiation treatment to evaluate response and any residual or progressive disease.

Treatment

Before March 2005, a total of 317 patients were treated with a combination of whole-pelvis and split-field irradiation using our institutional step-wedge technique (19). Thereafter, an additional 135 patients were treated with PET-guided IMRT, using pseudo–step-wedge intensity modulation as described previously (20). The dose distributions from our IMRT treatment plans were designed to replicate the step-wedge technique plans with the pelvic lymph nodes receiving the full external beam dose (~50 Gy) and the central pelvis or cervical region receiving approximately 20 Gy from the external irradiation. The goal of the IMRT plans was to provide additional sparing of normal tissues compared with our traditional technique (20). The change in treatment technique from non-IMRT to IMRT occurred because of a change in our institutional policy in March 2005. There was no lead-in period. All patients received an average of 50 Gy to the pelvic lymph nodes and approximately 20 Gy to the central pelvis from external beam irradiation.

All patients underwent a pretreatment FDG-PET. All IMRT patients underwent an additional FDG-PET/CT simulation, as well as a CT simulation for localization and alignment. To minimize bladder activity, patients had a Foley catheter placed in the urinary bladder before receiving FDG. They received 20 mg furosemide intravenously approximately 20 minutes after FDG injection and had intravenous fluid administration (1,000–1,500 ml of 0.9% or 0.45% saline) during the study. The PET/CT and CT simulation images were registered using point and anatomic matching (21). The fused PET/CT images allowed easy contouring of the metabolically active primary cervical tumor and involved lymph nodes.

Target volume contour delineations

The FDG-avid, metabolically active primary cervical tumor (MTV_{CERVIX}) was defined as the 40% threshold volume, as described previously (22). The common, external, and internal iliac nodal regions were contoured as ''vessels'' from the bifurcation of the common iliac arteries superiorly to the middle of the femoral heads inferiorly. To create the nodal clinical target volume (CTV_{NODAL}) contour, a 7-mm margin was added in all directions to the ''vessels'' contour while pelvic bones, femoral heads, and vertebral bodies were excluded. A 7-mm margin was added uniformly to CTV_{NODAL} to create the final planning target volume (PTV_{FINAL}). For patients with PET-positive para-aortic lymph nodes, the upper border of CTV_{NODAL} included the para-aortic lymph nodes and normal vessels with the contour going from the aorta and vena cava at the level of the renal vessels through to the bifurcation of the aorta or top of the pelvic lymph node volume. Figure 1 shows representative contours for MTV_{CERVIX} and CTV_{NODAL}. Normal structures contoured included the following: bladder, rectum (up to sigmoid colon), spinal cord, right and left femoral heads, pelvic bones (consisting of sacrum, coccyx, ilium, ischium, pubic rami and acetabulum, and ''bowel'' (a bag-like structure including the small and large intestines).

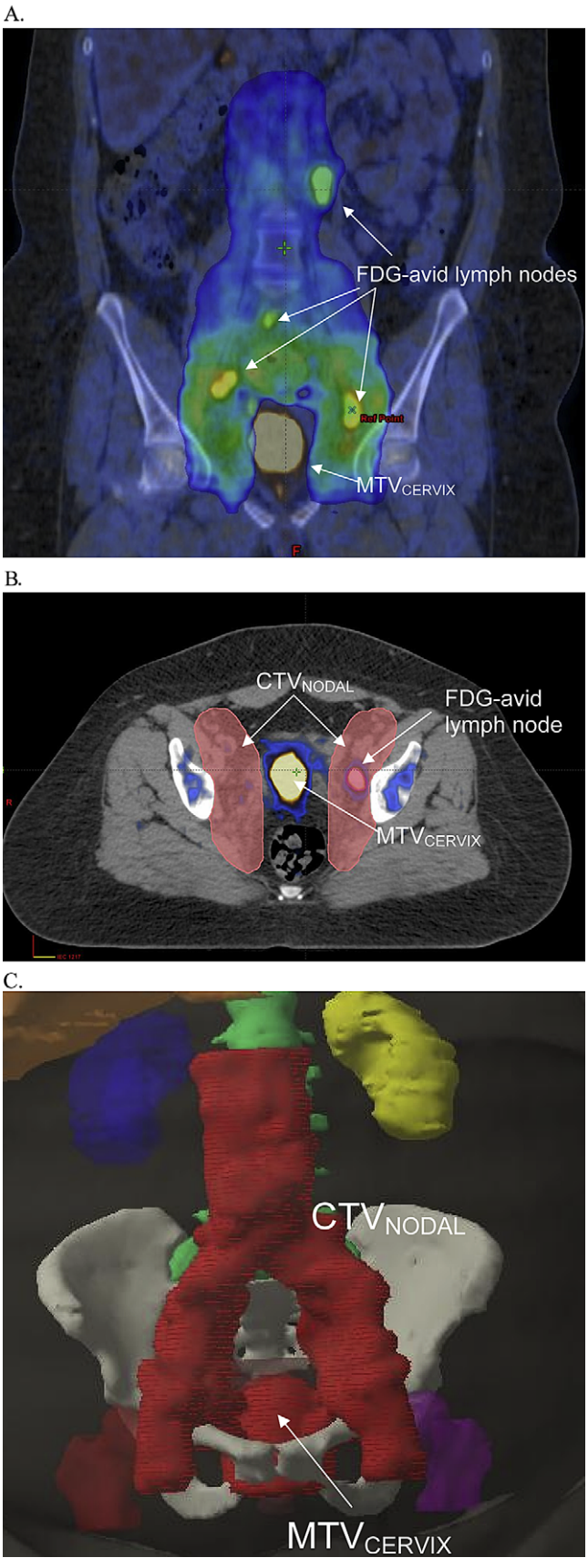

Fig. 1. Positron emission tomography (PET) fusion and intensity-modulated radiation therapy (IMRT) contours. (A)Fusion image of F-18 fluorodeoxyglucose (FDG)–PET and planning computed tomography (CT) scan showing the FDG-avid lymph nodes, metabolically active primary cervical tumor (MTV_{CERVIX}), and nodal clinical target volume (CTV_{NODAL}) contour in a coronal view. (B) Axial view of CTV_{NODAL}, MTV_{CERVIX}, and an FDG-avid lymph node. (C) Contours for CTV_{NODAL} and MTV_{CERVIX} in a three-dimensionally rendered coronal view.

Treatment planning

The IMRT planning was performed using the Eclipse Planning System (Varian Medical Systems, Palo Alto, CA). The prescription for PTV_{FINAL} was 50.4 Gy in 1.8-Gy fractions and 20 Gy to MTV_{CERVIX}. The IMRT plans were optimized to deliver 95% of the prescription dose to 100% of the volume of PTV_{FINAL} while minimizing the volume receiving 110% of the prescription dose. Dose–volume constraints for normal tissues included the following: <40% of bowel to receive 30 Gy, <40% of rectum to receive 40 Gy, <40% of pelvic bones to receive 40 Gy, and <40% of femoral heads to receive 30 Gy.

Chemotherapy and intracavitary brachytherapy

Concurrent cisplatin was received by 85% of patients (83% non-IMRT, 89% IMRT). All patients in the IMRT group received high-dose-rate (HDR) brachytherapy delivered in 6 weekly fractions of approximately 6.5 Gy per fraction to Point A using an iridium-192 source and Fletcher-Suit-Delcos intracavitary applicators. In the non-IMRT group, approximately 60% were treated with HDR and 40% had low-dose-rate (LDR) brachytherapy with two cesium intracavitary implants. For all patients, the mean overall treatment time was 52 days.

Outcome evaluation

Patients had follow-up examinations approximately every 2 months for the first 6 months, every 3 months for the next 2 years, and then every 6 months. In most patients, FDG-PET was performed 3 months after completion of treatment and then yearly or when warranted by clinical examination or symptoms. Other diagnostic imaging studies were performed as clinically indicated. The sites and timing of any recurrence were recorded. Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 was used to score the maximum late toxicity (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

Statistical analysis

The patient and tumor characteristics for the IMRT and non-IMRT groups were compared using a Chi-square test. The follow-up FDG-PET findings and recurrence and survival risk, as well as late bowel and bladder toxicity for the IMRT and non-IMRT groups were evaluated using Chi-square analysis. Survival, tumor recurrence, and actuarial complication rates were measured from the completion of treatment. StatView Version 5.0.1 software (SAS Institute, Cary, NC) was used for the analysis. A value of $p < 0.05$ was set as the threshold for significance for all study outcomes. The cumulative hazard function was used to compare the rates at conditional times for the development of Grades 3 and greater bowel and bladder complications between the IMRT and the non-IMRT groups. The Kaplan-Meier (product–limit) method was used to derive estimates of survival based on total sample size (23). The test of equivalence of estimates of survival and complications for the IMRT and non-IMRT groups were performed by the generalized Wilcoxon log-rank test (24). The Cox proportional hazards model was used for multivariate analysis (25).

RESULTS

Patient characteristics

The stage distribution, histology, and rates of lymph node involvement were similar for the non-IMRT and IMRT groups (Table 1). In both groups, approximately 90% of the tumors were of squamous cell histology, and Stages IIb and IIIb were the most common FIGO stages. The IMRT group showed a slightly lower rate of lymph nodes confined to the pelvis and modestly higher rates for no lymph node involvement and para-aortic nodal involvement.

For all patients, 80% (87% IMRT, 77% non-IMRT) underwent follow-up FDG-PET 3 months after completing radiation. Of the patients who underwent post-therapy FDG-PET, 73% (73% non-IMRT, 74% IMRT) had no persistent or recurrent disease, 14% (14% non-IMRT, 14% IMRT) had persistent disease, and 12% (13% non-IMRT, 12% IMRT) had FDG uptake in a new area. For all patients, any persistent or new disease seen on the FDG-PET correlated with overall recurrence risk ($p < 0.0001$) and cause-specific survival ($p < 0.0001$). The post-therapy FDG-PET findings were not significantly different between the IMRT and non-IMRT patients ($p = 0.9774$).

The mean follow-up for all patients alive at the time of last follow-up was 52 months with a range of 5–117 months (non-IMRT: 72 months, range 29–117 months; IMRT: 22 months, range 5–47 months). At the time of last follow-up, 178 patients had developed a recurrence, 39 in the IMRT group, and 139 in the non-IMRT group. There was a similar pattern of recurrences between the two groups, with the majority of patients having distant recurrences and 10% or less developing a pelvic recurrence only (Table 2). The difference in recurrence-free survival between the two groups did not reach statistical significance ($p = 0.0738$), as shown in Fig. 2.

At the time of last follow-up, 247 (91 IMRT, 156 non-IMRT) patients were alive with no evidence of disease, 51 (34 IMRT, 17 non-IMRT) were alive with disease, 122 (5 IMRT, 117 non-IMRT) had died of disease, 28 (4 IMRT, 24 non-IMRT) had died of intercurrent disease, and 4 (1 IMRT, 3 non-IMRT) had died from treatment-related toxicity. The patient in the IMRT group died of chemotherapy-related toxicity, whereas the 3 in the non-IMRT group all experienced Grade 3 or greater bowel complications. The IMRT group showed better overall cause-specific survival ($p < 0.0001$) and overall survival ($p < 0.0001$), as shown in Fig. 3. A Cox multivariate analysis for cause-specific survival including stage, FDG-PET lymph node status, and treatment technique (IMRT or non-IMRT) found that all three factors were independent predictors (Table 3). All variables were complete for the analysis for all patients.

At the time of last follow-up, 62 patients had developed a Grade 3 or greater GI or GU complication. The complications for the IMRT and non-IMRT patients are listed in Table 4. Eight patients (6%) in the IMRT group developed a Grade 3 or greater bowel or bladder complication; this was significantly fewer than the 54 (17%) observed in the non-IMRT group ($p = 0.0017$). The mean overall time to developing such a complication was 16.2 months for all patients (16.5 months for non-IMRT, 14.0 months for IMRT). Figure 4 shows the significant difference in the cumulative hazard function rates for the development of bowel or bladder complications for the IMRT and non-IMRT groups ($p = 0.0351$).

Table 1. Patient and tumor characteristics for the IMRT, non-IMRT, and total groups

Characteristic	IMRT	Non-IMRT	Total	*p* Value
Mean age at diagnosis (y)	52	52	52	
Chemotherapy	120 (89%)	262 (83%)	449	0.2238
Stage				0.7003
Ia2	0 (0%)	2 (0.7%)	2	
Ib1	20 (14.8%)	33 (10.4%)	53	
Ib2	21 (15.6%)	56 (17.7%)	77	
IIa	3 (2.2%)	7 (2.2%)	10	
IIb	58 (43.0%)	126 (39.7%)	184	
IIIa	2 (1.5%)	2 (0.6%)	4	
IIIb	29 (21.5%)	82 (25.9%)	111	
IVa	2 (1.5%)	7 (2.2%)	9	
IVb	0 (0%)	2 (0.6%)	2	
Histology				0.3710
Adenocarcinoma	13 (9.6%)	17 (5.4%)	30	
Adenosquamous	2 (1.5%)	9 (2.8%)	11	
Squamous	117 (86.7%)	286 (90.2%)	403	
Other	3 (2.2%)	5 (1.6%)	8	
Lymph nodes				0.0309
None	68 (50.4%)	131 (41.3%)	199	
Pelvic only	41 (30.4%)	140 (44.2%)	181	
Para-aortic	23 (17.0%)	36 (11.4%)	59	
Supraclavicular	3 (2.2%)	10 (3.2%)	13	

Abbreviation: IMRT = intensity-modulated radiation therapy.

DISCUSSION

Over the years, the treatment of cervical cancer has evolved. After a series of related studies and the National Cancer Institute clinical alert in February 1999, concurrent chemoradiotherapy became the standard for treating cervical cancer (26). Advances in imaging, in particular with FDG-PET and MRI, have also brought about changes in the treatment of cervical cancer by helping to better define areas of disease.

Although concurrent radiotherapy and chemotherapy with radiosensitizing agents has helped to improve local control and survival for cervical cancer, compared with radiotherapy

Table 2. Distribution of recurrences for the IMRT, non-IMRT, and total groups

Recurrence	IMRT	Non-IMRT	Total	*p* Value
Overall	39 (28.9%)	139 (43.8%)	178	0.036
Pelvic	11 (8.1%)	33 (10.4%)	44	
Distant	21 (15.6%)	78 (24.6%)	99	
Both	7 (5.2%)	28 (8.8%)	35	

Abbreviation: IMRT = intensity-modulated radiation therapy.

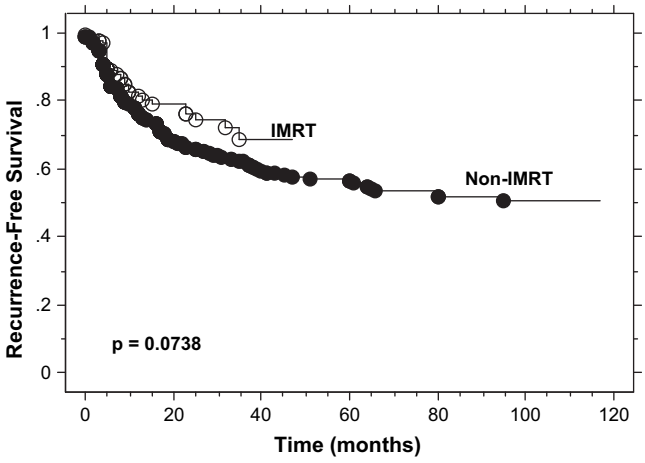

Fig. 2. Recurrence-free survival for the intensity-modulated radiation therapy (IMRT) (○) and non-IMRT (●) groups.

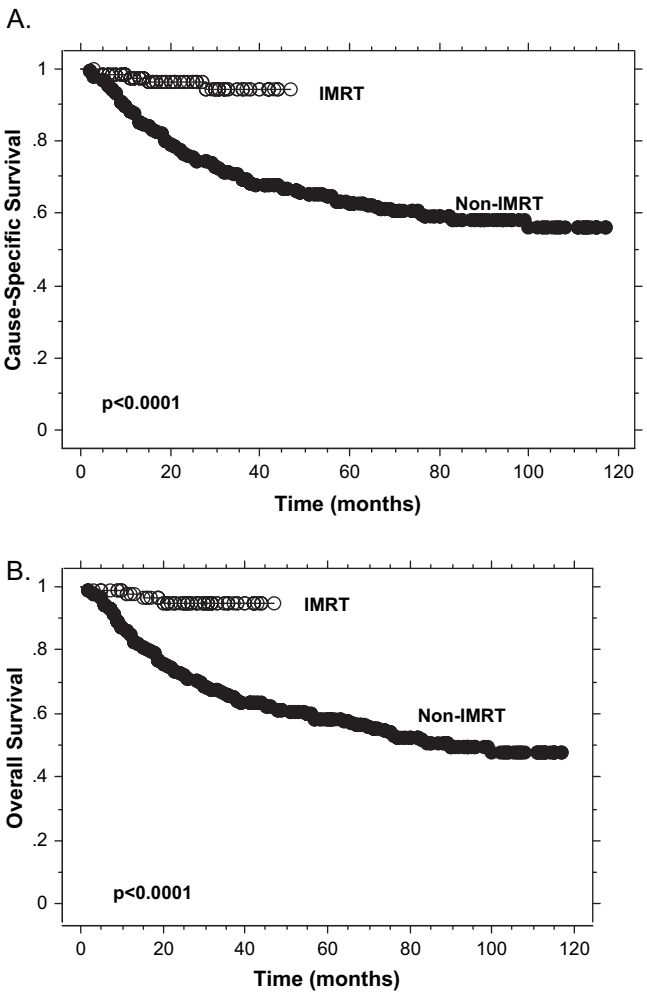

Fig. 3. Cause-specific survival (A) and overall survival (B) for the intensity-modulated radiation therapy (IMRT) (○) and non-IMRT (●) groups.

alone, it has also increased treatment-related toxicity (6). In the treatment of other pelvic malignancies, it has been shown that IMRT maintains good disease control and decreases doses to surrounding normal tissues (7–9). There seems to be more hesitation in transitioning the treatment of cervical cancer to IMRT, with only a limited number of small studies involving cervical cancer and IMRT.

Some of the apprehension about using IMRT for cervical cancer seems to come from concern about missing areas of disease. It is well known that cervical cancer spreads in a predictable pattern, with the pelvic lymph nodes being the first site of metastatic disease. Therefore, the pelvic lymph nodes along with the region of the cervical tumor region represent the main clinical target volumes. Although cervical tumors are not well visualized on CT, FDG-PET greatly aids in identifying the extent of the primary tumor and lymph nodes involved by metastatic disease (16, 22, 27). It has been shown that incorporating functional imaging information, such as that from FDG-PET, significantly decreases inter- and intraobserver variation in tumor contouring (28–30). All of the cervical cancer patients treated with IMRT in this study underwent FDG-PET/CT in the treatment position to aid in target delineation and treatment planning.

In evaluating a fairly large number of patients with cervical cancer treated with IMRT, we found improvements in late bowel and bladder toxicity and equivalent recurrence rates, as compared with rates in non–IMRT-treated patients. Although both groups were treated to the same prescription dose, the IMRT group had only a 6% rate of Grade 3 or greater GI or GU toxicity, versus 17% for the non-IMRT group ($p = 0.0017$). Although the IMRT group had shorter follow-up, their average length of follow-up was longer than the mean time for developing late complications observed in this population. As pointed out by Eifel *et al.*, Grade 3 and greater rectal and urinary complications can occur up to 25 years after treatment (31). However, these investigators did note that the majority of the urinary and rectal complications occurred within 2 to 3 years after the completion of therapy and that the risk of developing complications after this time was small but continuous. The decreased toxicity with IMRT seen in the present study with a maximum follow-up of 4 years for the IMRT-treated patients is similar to that reported with other pelvic malignancies treated with IMRT (7–9). Our demonstration that IMRT decreases the rate of the development of treatment-related complications in patients with cervical cancer, while maintaining treatment efficacy, represents the most important finding of this study.

The better cause-specific and overall survivals seen in the IMRT group were unexpected results. As the treatment doses and regions of disease targeted were essentially the same between the two groups, with the exception of less normal tissues in the IMRT volumes, it is difficult to attribute the difference in outcome solely to treatment technique. The small differences between the IMRT and non-IMRT patient populations, such as the slightly higher percentages of patients in the IMRT group that had no lymph node involvement or received concurrent cisplatin might have contributed to a better survival in the IMRT group. The IMRT technique also allows specific targeting and increased dose to lymph node metastases. The decreased treatment morbidity and mortality with IMRT might also have influenced overall survival.

Table 3. Cox multivariate analysis for overall cause-specific survival for all patients

Prognostic factor	Coefficient	SE	Coefficient/SE	Chi-square	*p* Value	Exponent(Coefficient)
IMRT	1.731	0.461	3.758	14.123	0.0002	5.644
PET-positive lymph nodes	0.639	0.199	3.204	10.269	0.0014	1.894
Stage	0.654	0.612	1.069	22.621	<0.0001	0.524

Abbreviation: IMRT = intensity-modulated radiation therapy; PET = positron emission tomography; SE = standard error.

Although the IMRT group had shorter follow-up, we were able to use the 3-month post-therapy FDG-PET as a surrogate for long-term outcome. It has been previously shown, in a prospectively validated study, that the findings on 3-month post-therapy FDG-PET predict for overall outcome (18); and the results of the present study affirm this, with the post-therapy PET findings predicting recurrence and disease-specific survival. In addition, the post-treatment PET findings were not significantly different between the IMRT and non-IMRT group, suggesting that the long-term recurrence rates and disease-specific survival will be similar for the IMRT and non-IMRT patients. The use of IMRT for cervical cancer treatment takes advantage of the developments in imaging and treatment planning technology to maintain the improved outcomes of concurrent chemoradiation, while helping to decrease the treatment-related toxicity.

The findings of this analysis are significant because it represents the largest study looking at the side effects and clinical outcomes for patients with cervical cancer treated definitively with IMRT and highlights the benefits of FDG-PET simulation. There have been only limited studies of the use of IMRT for cervical cancer. Some theoretical and dosimetric studies suggest that IMRT would potentially decrease small bowel and bone marrow irradiation dose, as compared with four-field treatment (11, 32, 33) The few studies in which patients with cervical cancer were actually treated with IMRT have significant limitations for translation to larger populations. Besides being small studies with limited follow-up, these prior IMRT studies often included postoperative patients and those with recurrent disease and gave nonstandard treatment (*e.g.,* inclusion of an integrated boost or extended-field radiation to include para-aortic lymph nodes) (13, 14, 34). The largest study involved 54 patients with early-stage cervical cancer treated postoperatively with IMRT and vaginal cuff brachytherapy, and it showed good local control and low toxicity rates (35). In contrast to many of the existing studies, the IMRT group in the present study included only patients with cervical cancer treated definitively with curative intent by external beam IMRT, HDR brachytherapy, and concurrent cisplatin.

Table 4. Grade 3 or greater gastrointestinal and genitourinary complications in study group

Complication	IMRT group	Non-IMRT group	Total
Rectovaginal fistula	2	12	14
Vesicovaginal fistula	0	11	11
Small bowel obstruction	2	7	9
Large bowel obstruction	2	5	7
Cystitis, Grade 4	1	5	6
Rectal ulcer	1	5	6
Ureteral stricture	0	4	4
Rectal stricture	0	2	2
Proctitis, Grade 4	0	2	2
Ischemic colitis	0	1	1

Abbreviation: IMRT = intensity-modulated radiation therapy.

Although this study has some limitations, it also has some significant strengths. It included a fairly large patient population and generally the IMRT and non-IMRT groups had similar patient-, tumor-, and treatment-related factors and were treated with curative intent using similar dose parameters. At our institution, IMRT was instituted as a definitive change in the treatment policy for all cervical cancer patients receiving radiation at a set time point (March 2005). Therefore there was no selection bias for which patients underwent IMRT versus non-IMRT treatment. Although the IMRT and non-IMRT groups had slightly different distributions of lymph node involvement, this did not prevent the treatment technique from being an independent predictor of cause-specific survival. In addition, although the IMRT patients generally had a shorter follow-up, we were able to use the 3-month post-therapy FDG-PET findings as a surrogate for long-term outcome. This study shows the feasibility of cervical cancer IMRT with the incorporation of FDG-PET information for treatment planning, and demonstrates that PET-guided IMRT significantly decreases toxicity while maintaining disease control. These valuable findings could encourage the next transition in treating cervical cancer, expanding the use of FDG-PET-guided IMRT and thereby decreasing treatment-related toxicity.

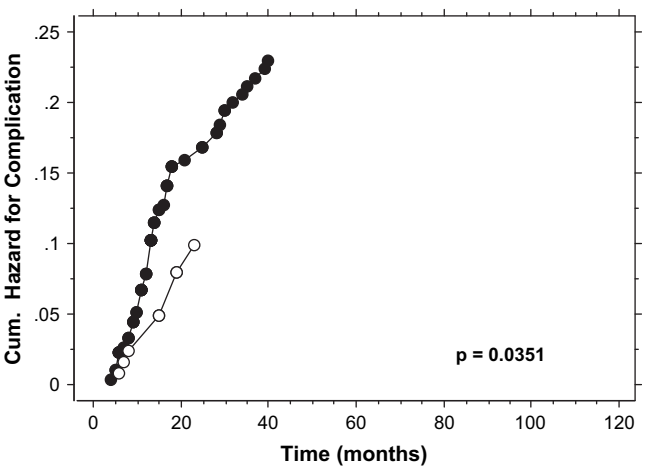

Fig. 4. Cumulative hazard function rates of bowel or bladder complication for the intensity-modulated radiation therapy (IMRT) (○) and non-IMRT (●) groups.

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Utilization of Advanced Imaging Technologies for Target Delineation in Radiation Oncology

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Purpose: The aim of this study was to evaluate the utilization of advanced imaging technologies for target delineation among radiation oncologists in the United States.

Methods: A random sample of 1,600 radiation oncologists was contacted by Internet, e-mail, and fax and questioned regarding the use of advanced imaging technologies, clinical applications, and future plans for use. Advanced imaging technologies were defined as any of the following that were directly incorporated into radiation therapy planning: MRI, PET, single-photon emission CT, 4-D CT, functional MRI, and MR spectroscopy.

Results: Of 1,089 contactable physicians, 394 (36%) responded. Of respondents, 65% were in private practice and 35% were in academic practice. The proportion using any advanced imaging technology for target delineation was 95%. However, the majority reported only rare (in <25% of their patients; 46.6%) or infrequent (in 25%-50% of their patients; 26.0%) utilization. The most commonly used technologies were 2-[^{18}F]fluoro-2-deoxyglucose PET (76%), MRI (72%), and 4-D CT (44%). The most common cancers treated using image-guided target delineation were those of the lung (83%), central nervous system (79%), and head and neck (79%). Among users of advanced imaging technologies, 66% planned to increase use; 30% of nonusers planned to adopt these technologies in the future.

Conclusions: Advanced imaging technologies are widely used by US radiation oncologists for target delineation. Although the majority of respondents used them in <50% of their patients, the frequency of utilization is expected to increase. Studies determining the optimal application of these technologies in radiation therapy planning are needed.

Key Words: Image-guided radiation therapy, IGRT, target delineation, survey, radiation oncology

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INTRODUCTION

Accurate target definition is fundamental to radiation therapy (RT) planning. In defining the target, a radiation oncologist draws on a number of sources, including physical examination, operative and pathology reports, and knowledge of the patterns of tumor spread and failure. Imaging, however, is perhaps the single most important tool to guide target definition.

In the early days of radiation oncology, x-ray (fluoroscopic) simulators were the primary imaging tool used for targeting. Treatment ports were based on visualizing radio-opaque landmarks, such as bones, surgical clips, or intraluminal contrast [1,2]. Over the past 20 years, the advent of 3-D image guidance, principally CT, has revolutionized the approach to target definition and RT planning. In most radiation oncology departments today, patients undergo simulation CT, permitting developments such as 3-D conformal RT [3-5]. Target volumes are contoured on axial CT slices, a process known as "target delineation."

Recently, there has been increasing availability of advanced imaging technologies to guide target delineation,

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particularly MRI [6-11] and 2-[^{18}F]fluoro-2-deoxyglucose (FDG) PET [12-19]. A variety of specialized imaging approaches have also been investigated to improve target delineation, including single-photon emission CT (SPECT) [20,21], MR spectroscopy (MRS) [11,22-28], non-FDG-PET [13,29,30], and 4-D CT [31,32].

Despite the growing interest in such advanced technologies for target delineation, little is known about their use in the general radiation oncology community. It is unclear how many radiation oncologists use these technologies, to what extent they are used, and how they are currently applied. To answer these questions, we conducted a nationwide survey of practicing radiation oncologists. Herein we summarize our results and discuss the implications of our findings.

METHODS

Sample

We randomly selected 1,600 of approximately 5,000 radiation oncologists listed in the 2008 American Society for Radiation Oncology directory. All physicians designated as active and allied members were included. All emeritus professors and radiation oncologists practicing outside of the United States were excluded. We attempted to contact each physician using the listed e-mail address or fax number. If neither was valid, we searched for updated contact information in the 2009 American Society for Radiation Oncology online directory. If no information could be found or if the fax or e-mail information was invalid, the physician was designated as uncontactable and was excluded from further analysis. Those who had retired or returned the surveys blank were also excluded. The survey was sent in 3 forms: as an e-mail attachment, as a link to an online survey, and by fax.

Survey

A 10-question survey was designed to collect demographic information and address the use of advanced imaging technologies to augment target delineation in patients undergoing RT (Table 1). This survey on target delineation was part of a larger, comprehensive survey on image-guided RT conducted between February 1, 2009, and March 31, 2009. The results of other aspects of the image-guided RT survey are the subject of a separate report.

Survey responses were considered evaluable if the survey was at least partially completed. For the purposes of this survey, we defined advanced imaging technologies as any of the following: MRI, PET, 4-D CT, functional MRI (fMRI), MRS, and SPECT. Conventional CT and planar imaging approaches were not included. To be considered as used in target delineation, these imaging modalities had to have been fused to the simulation CT (as opposed to being viewed side by side) for treatment planning. Accompanying the survey was a cover letter outlining the purpose of the project and the confidential nature of the results obtained. Our intention was to evaluate the prevalence and practice of various modalities described.

In addition to inquiring about practice type (academic vs private) and size of practice group, physicians were asked about the types of technologies used, the year they had adopted them, the percentages of patients in their practices they had treated with advanced imaging technologies, disease sites treated, and future plans for use. Nonusers were asked whether they intended to adopt these technologies in the future. Survey results are presented as percentages of evaluable responses.

Statistical Analysis

Differences in proportions between various groups were analyzed using the χ^2 and Fisher's exact tests. The Holm step-down method was used to adjust P values for multiple comparisons [33]. With this method, P values are ranked from lowest to highest, and with each successive test, the factor is successively stepped down in size. It is similar to the Bonferroni test, in that P values are multiplied by a factor that depends on the number of tests being performed, but is more powerful (ie, less prone to type II error) [34]. Significant values were defined as those with P values $< .05$.

RESULTS

Of 1,600 randomly selected physicians, 1,089 physicians (68%) were contactable (Figure 1). From the 1,089 contactable physicians, we received a total of 394 responses (36%). Of the 394 respondents, 7 were retired, and 1 returned the survey blank; thus, a total of 386 responses were evaluable.

Responses were received from 45 states (Table 2). One hundred thirty-three responses were from academic physicians (34.5%), and 249 responses were from private practice physicians (64.5%). Four respondents returned the survey without demographic information.

Of 386 evaluable respondents, 364 (94.3%) reported using at least one advanced imaging technology for target delineation. However, the majority reported using such technologies only rarely (in <25% of their patients; 46.6%) or infrequently (in 25%-50% of their patients; 26.0%). The percentages of respondents who reported using sophisticated imaging frequently (51%-75% of their patients) and routinely (>75% of their patients) were 14.5% and 8.3%, respectively.

The most commonly used imaging modalities were FDG-PET (78.3%) and MRI (73.1%). The percentage of respondents using one or both of these modalities was 90.9%. Four-dimensional CT was used by 42.3% of

Table 1. Image-guided target delineation survey

1. Type of center at which you practice?
   _____Academic _____Private Practice
2. Total number of radiation oncologists in your practice? _____
3. What is your gender?
   _____Male _____Female
4. What year did you graduate from residency? _____
5. Do you limit your practice predominantly to select disease sites? If so, which sites? (If you don't limit your practice to select sites, skip to the next question)
   _____CNS _____Breast _____Lung _____GU/Prostate
   _____Other (please specify):
6. Which of the following sophisticated imaging techniques have you used in treatment planning to aid in target delineation? Include only techniques that have been directly integrated into your treatment planning system (i.e., fused). For each technology you have used, please specify when you adopted it (including experience in residency, if any) and whether you currently still use it. If you have never used a specific technology, leave the corresponding answer space(s) blank.

Technology	Year Adopted	Currently Use? (Yes/No)	If NO, What Year Did You Stop?
4-D CT			
^{18}FDG-PET/PET-CT			
Other PET Tracers (e.g. ^{18}F-MISO, ^{11}C-Methionine, etc.)			
MRI			
Functional MRI (e.g., T2*, BOLD, etc.)			
MR Spectroscopy			
SPECT			

*If you do **not** CURRENTLY use any of the technologies listed in question 6, skip to question 10*

7. Mark the disease site(s) with an "x" for which you CURRENTLY use any of the following sophisticated imaging techniques for target delineation. Again, include only techniques that have been directly integrated into your treatment planning system (i.e., fused). If you don't currently use a specific technology in a particular disease site, leave the corresponding answer space(s) blank.

Disease Site	4-D CT	^{18}FDG-PET/ PET-CT	Other PET Tracers (e.g. ^{18}F-MISO, ^{11}C-Methionine, etc.)	MRI	fMRI (e.g., T2*, BOLD, etc.)	MRS	SPECT
CNS							
Head/Neck							
Breast							
Lung							
GI							
GU/prostate							
GYN							
Pediatrics							
Lymphoma							
Palliative							
Other (specify)							

8. In approximately what percentage of your patients do you currently use any of the sophisticated imaging technologies listed in question 6?
   _____None
   _____<25%
   _____25-50%
   _____51-75%
   _____>75%

Table 1. Continued

9. Which of the sophisticated imaging technologies listed in question 6 do you most commonly use currently?_____
10. What are your future plans for the use of the sophisticated imaging technologies to aid in target delineation listed in question 6?
    _____Do not plan to adopt
    _____Maintain current use
    _____Start using/Increase use
    _____Stop using/Decrease use

Note: BOLD = blood oxygen level–dependent; CNS = central nervous system; FDG = 2-[^{18}F] fluoro-2-deoxyglucose; fMRI = functional magnetic resonance imaging; GI = gastrointestinal; GU = genitourinary; GYN = gynecological; MISO = misonidazole; MRS = magnetic resonance spectroscopy; SPECT = single-photon emission CT.

respondents. Less commonly used modalities were fMRI (9.9%), SPECT (8.1%), MRS (7.6%), and non-FDG-PET (2.9%).

The exact modality used differed by disease site. Sites that were most commonly treated were the lungs (83%), the central nervous system (CNS) (79%), and the head and neck (79%) (Table 3). MRI was used most commonly in the treatment of CNS tumors (92.9%), whereas FDG-PET was used most commonly in lung and head and neck malignancies (89.0% and 88.3%, respectively), and 4-D CT was used most commonly in lung cancer (87.0%) (Figure 2). Highly specialized technologies such as fMRI and MRS were most commonly used in CNS tumors (8.5% and 6.6, respectively).

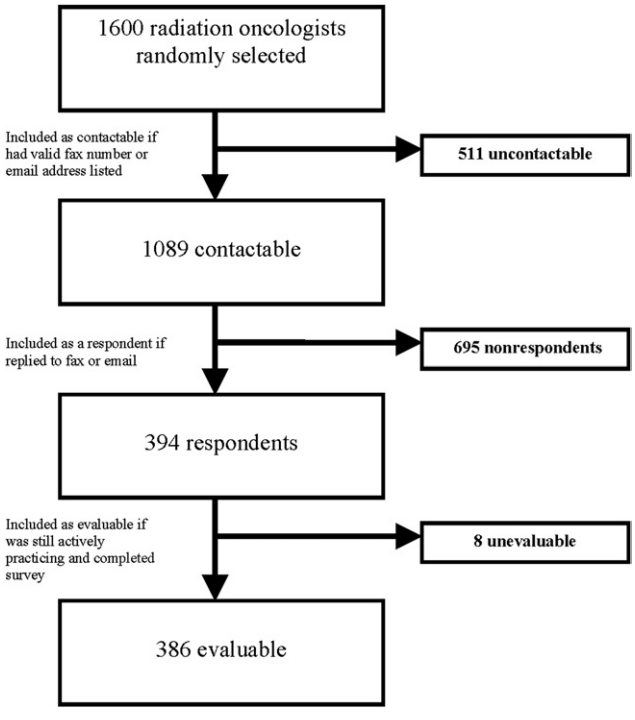

Fig 1. Survey flow chart.

Overall, no difference in the prevalence of advanced image guidance use was observed between academic and private practice radiation oncologists (94.7% and 95.1%, respectively, $P = 0.88$). As shown in Figure 3, similar proportions of academic and private practice radiation oncologists used FDG-PET and MRI. However, academic physicians were more likely to use 4-D CT ($P < .001$), fMRI ($P < .001$), MRS ($P = .02$), and SPECT ($P = .02$) than private practice physicians. In

Table 2. Characteristics of evaluable respondents

Variable	Value
Number of physicians	386
Sex, n (%)	
Male	284 (73.6)
Female	97 (25.1)
Geographic location,* n (%)	
Midwest	109 (28.2)
South	101 (26.2)
East	84 (21.8)
West	77 (20.0)
Practice type, n (%)	
Academic	133 (34.5)
Private	249 (64.5)
Specialist,† n (%)	107 (27.7)
Years in practice, median (range)	16 (1-44)
Number of physicians per practice, median (range)	5 (1-55)

*East: Connecticut, District of Columbia, Delaware, Massachusetts, Maryland, Maine, New Hampshire, New Jersey, Pennsylvania, Rhode Island, Vermont, West Virginia; South: Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Texas, Virginia; Midwest: Iowa, Illinois, Indiana, Kansas, Kentucky, Michigan, Minnesota, Missouri, North Dakota, Nebraska, Ohio, Oklahoma, South Dakota, Wisconsin; West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montano, New Mexico, Nevada, Oregon, Utah, Washington, Wyoming.
†Specialties included: central nervous system, breast, lung, prostate, other.

Table 3. Prevalence of image-guided target delineation use by disease site

Disease Site	Number of Users (% of All Users)
Central nervous system	286 (79.0)
Head and neck	289 (79.8)
Breast	72 (19.9)
Lung	302 (83.4)
Gastrointestinal	193 (53.3)
Genitourinary	159 (43.9)
Gynecologic	166 (45.9)
Pediatrics	52 (14.4)
Lymphoma	203 (56.1)
Palliative	94 (26.0)

addition, academic physicians were more likely to use these advanced image guidance technologies frequently or routinely (>50% of their patients) in their practice, compared with private practice physicians (31% vs 21%, $P = .04$).

Results were compared on the basis of geography, number of years of experience, size of practice, and area of specialization. The percentages of physicians using image guidance for target delineation in the East, South, Midwest, and West were 97.5%, 97.0%, 94.4%, and 93.4%, respectively ($P = .50$).The percentages of users with 1 to 10, 11 to 20, and >20 years in practice were 98.1%, 95.2%, and 96.5%, respectively ($P = .50$). There were no significant differences in individual modalities used on the basis of years of experience. The percentages of respondents in practices with 1, 2 to 10, and >10 physicians who reported using these technologies were 88.4%, 97.6%, and 91.6%, respectively ($P < .01$). Physicians in solo practices were less likely to use them than physicians in group practices ($P = .04$). Overall, their use was similar for specialists and nonspecialists. However, specialists were more likely to use these technologies frequently or routinely (>50% of their patients) in their practices compared with nonspecialists (33% vs 19%, $P < .01$).

Figure 4 illustrates the cumulative adoption of each imaging modality. MRI was reported to be adopted the earliest, with the majority of respondents (53.9%) using MRI having implemented it by 2002. The adoption of PET was next, with the majority of respondents using FDG-PET (61.5%) having implemented it by 2005. Four-dimensional CT was reported to have been adopted the latest, with the majority of respondents using 4-D CT (50.3%) having implemented it by 2006.

Of those respondents using advanced imaging technologies, 32.1% planned to maintain their current levels of use, while 65.6% planned to increase use. Among rare or infrequent (≤50%) users, 70.0% planned to increase use, while 58.8% of frequent or routine (>50%) users planned to increase use. No current users planned to decrease or cease use. Among nonusers, 29.4% planned to start using these technologies in the future.

DISCUSSION

In this study, we attempted to assess the utilization of advanced imaging modalities for target delineation in the United States and determine the ways in which radiation oncologists were applying them. We found that the majority of physicians surveyed (>90%) used advanced imaging technologies in their practice. However, the majority of respondents used them in <50% of their patients. We also found that the types of technologies used varied greatly. MRI and FDG-

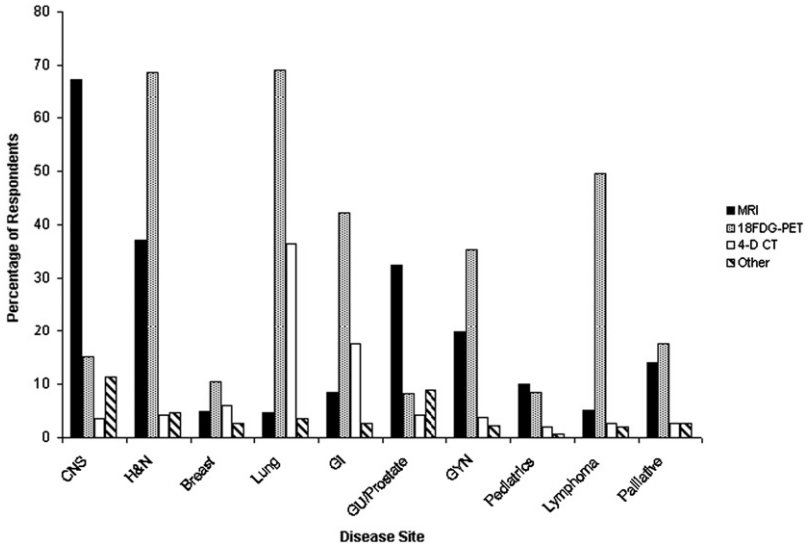

Fig 2. Prevalence of modalities used, by disease site. CNS = central nervous system; 18FDG = 2-[^{18}F]fluoro-2-deoxyglucose; 4-D CT; GI = gastrointestinal; GU = genitourinary; GYN = gynecology; H&N = head and neck. Other modalities include fMRI, MR spectroscopy, single-photon emission CT, and non–FDG-PET.

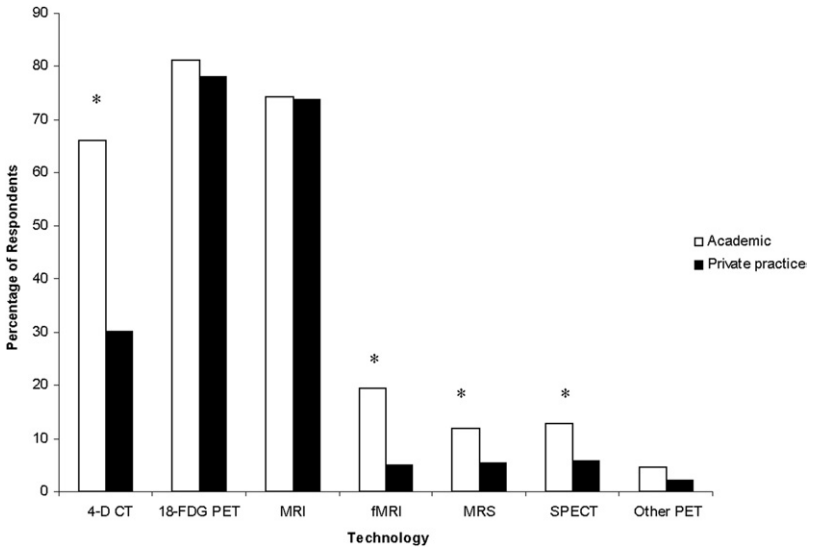

Fig 3. Percentage of academic and private practice physicians using image-guided target delineation technologies, by modality. 18-FDG = 2-[^{18}F]fluoro-2-deoxyglucose; fMRI = functional magnetic resonance imaging; 4-D CT; MRS = MR spectroscopy; SPECT = single-photon emission CT. *$P < .05$.

PET were the most common technologies used, with nearly 75% of respondents using one or both.

We noted several differences in utilization on the basis of various physician characteristics. Although there was no difference in utilization between academic and private practice physicians, academic physicians tended to use advanced imaging technologies more frequently. More specialized technologies, such as 4-D CT, SPECT, fMRI, and MRS, were less commonly used by private practice physicians. This might be due to decreased access, as well the use of highly specialized technologies for research in academic settings. Second, we found that physicians in solo practices were less likely to use advanced imaging in their practices, possibly because of decreased time and access. However, even among those physicians, utilization was near 90%. Third, we found that number of years in practice was not correlated with utilization. Finally, we noted that although similar proportions of specialists and nonspecialists used advanced imaging modalities, specialists used them more frequently.

The earlier adoption of MRI and FDG-PET is most likely due to their greater availability and the large number of clinical studies supporting their use in CNS, head and neck, and lung cancers [8,9,12,16,17]. Not surprisingly, adoption rates for fMRI, MRS, and SPECT were low, likely because of their limited availability and the fact that many are still primarily used in the research setting. One interesting finding was the high level of 4-D CT utilization in both private practice and academic settings alike. This is particularly noteworthy, because 4-D CT, unlike other advanced imaging technologies, requires additional time, specialized software and hardware, and specially trained staff members within the radiation oncology department to implement. On the basis of responses from

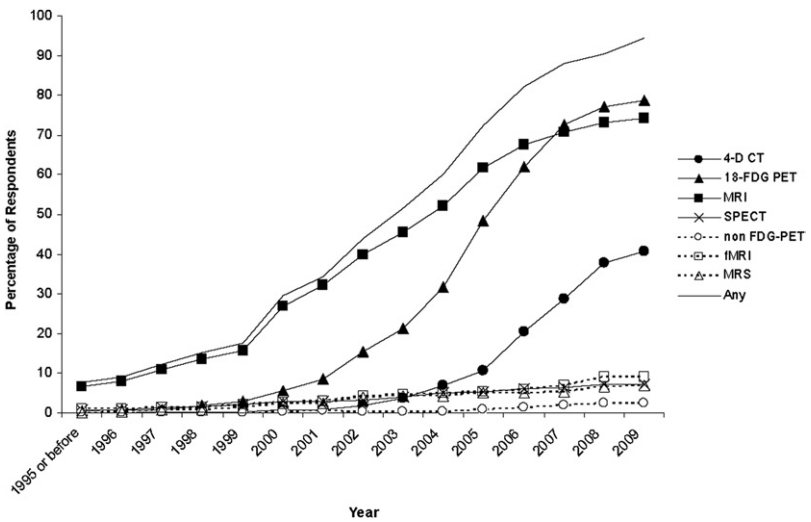

Fig 4. Cumulative utilization of image-guided target delineation, by modality. 18-FDG = 2-[^{18}F]fluoro-2-deoxyglucose; fMRI = functional magnetic resonance imaging; 4-D CT; MRS = MR spectroscopy; SPECT = single-photon emission CT.

physicians regarding past adoption and future plans, the utilization of these technologies seems to have grown rapidly over the past decade, and the frequency of use will likely continue to increase.

There were several limitations to this study. First, the findings are subject to nonresponse bias, because the likelihood of responding to the survey could have been related to physicians' utilization of advanced imaging technologies. However, we did try to address this problem proactively, by specifically emphasizing the importance of responding even for nonusers. We also diligently sought responses by repeatedly sending both e-mails and faxes to physicians who did not reply. Nonetheless, we received a relatively high proportion of responses from academic physicians, who might have greater access to novel technologies than private practice physicians, tending to overestimate the total utilization in the population. Our findings are also subject to self-reporting and recall bias. We plan to conduct a follow-up survey in 2011, which could help characterize nonrespondents and would help assess changes in utilization over time. In the follow-up survey, we will also assess the extent to which physicians are using advanced imaging technologies for normal tissue sparing, as this study was focused solely on tumor targeting.

Our survey provides important information regarding the current state of technology utilization in the radiation oncology community. The utilization of advanced imaging technologies for target delineation seems to have increased significantly in recent years and is expected to increase even further. Although it may seem intuitive that advanced imaging technologies will improve target delineation, their cost/benefit ratio needs to be better evaluated because their utilization is associated with increased time and cost. Moreover, further studies are needed to determine how these technologies should be optimally applied.

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