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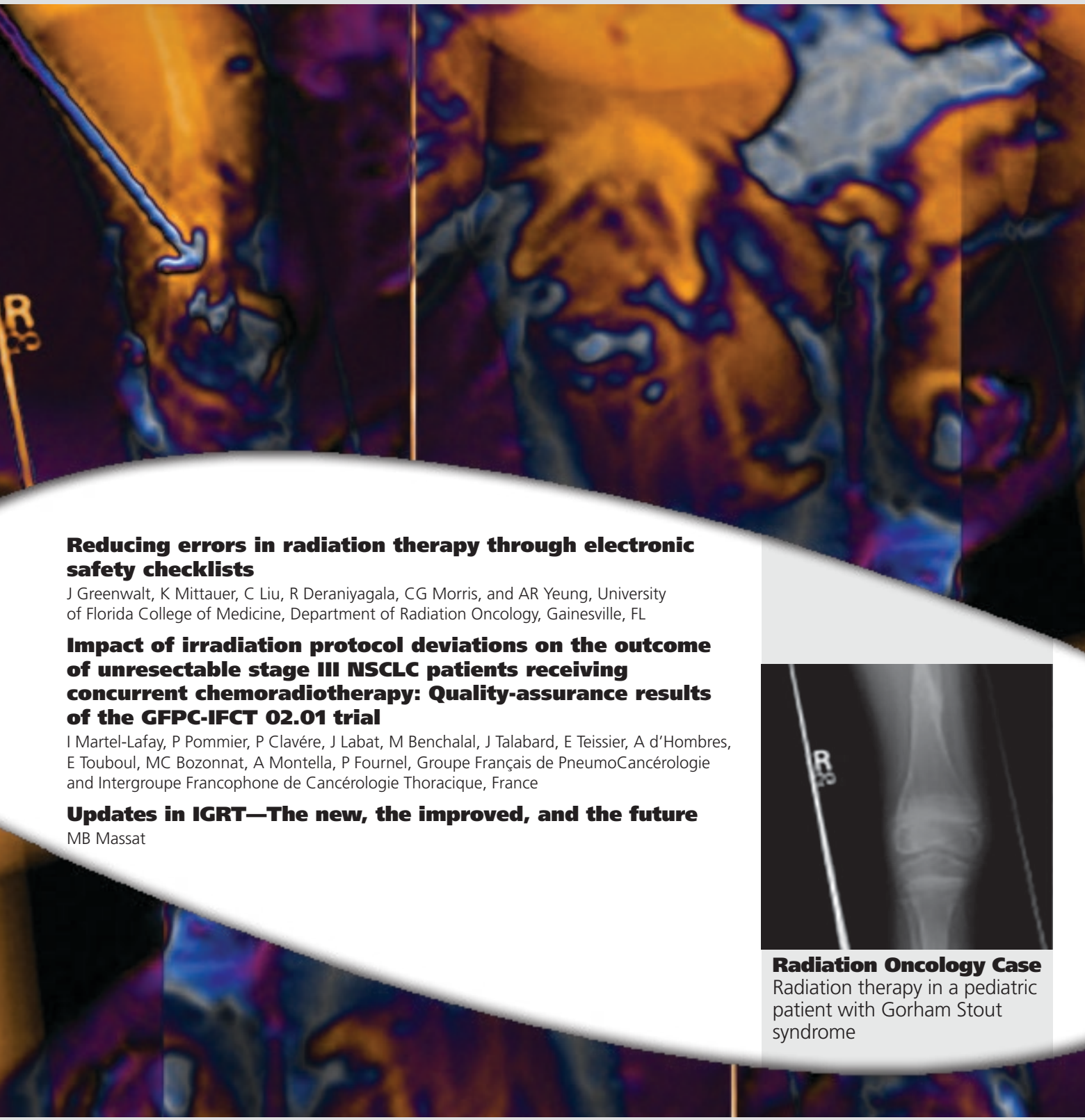

Reducing errors in radiation therapy through electronic safety checklists

J Greenwalt, K Mittauer, C Liu, R Deraniyagala, CG Morris, and AR Yeung, University of Florida College of Medicine, Department of Radiation Oncology, Gainesville, FL

Impact of irradiation protocol deviations on the outcome of unresectable stage III NSCLC patients receiving concurrent chemoradiotherapy: Quality-assurance results of the GFPC-IFCT 02.01 trial

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Updates in IGRT—The new, the improved, and the future

MB Massat

Radiation Oncology Case
Radiation therapy in a pediatric patient with Gorham Stout syndrome

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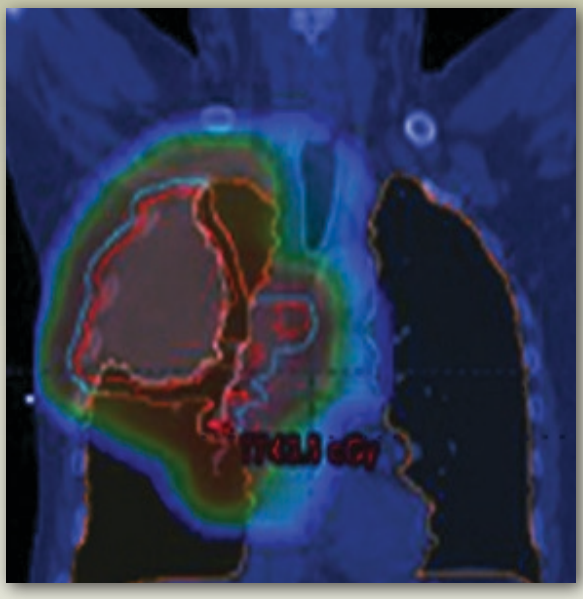

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CLINICAL CASE CONTEST

Applied Radiation Oncology is pleased to renew our monthly clinical case review contest open to all physicians, radiation therapists, and physicists in the field of radiation oncology. Each month we will feature the submitted cases on our website for review by you and your peers.

A rating system at the bottom of each accepted case will allow your peers to rate your case on a scale of 1-5 (5 being the best). The highest rated cases will be submitted for final review by the ARO Advisory Board, which will ultimately choose the "Best Presented and Most Interesting" case that month.

The contest will run through December 31, 2014.

You may enter as many different cases as you wish each month, however, please DO NOT enter the same case more than once.

A winning case will be chosen each month and published in a future issue of ARO. The author of the winning case will receive an American Express Gift Card in the amount of $250.

Click here to see our contest information page!

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Thank you for supporting ARO and we look forward to your participation in our Clinical Case Review Contest! Good Luck!

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VIEW GUIDELINES

EDITORIAL

Innovation showcase: AAPM meeting, electronic safety checklists and RT quality control for lung cancer

John Suh, MD, Editor-in-Chief

Welcome to the July issue of *Applied Radiation Oncology (ARO)*! For many, July ushers in vacation plans and Independence Day celebrations, but it also brings another exciting event: The American Association of Physicists in Medicine (AAPM) 56th Annual Meeting & Exhibition.

The AAPM meeting, which is the largest gathering of medical physicists in the world, will be held July 20-24 in Austin, Texas and will focus on the theme of innovation—from cutting-edge research, to progressive technologies, to continuing education. Among highlights are a joint symposium with the World Molecular Imaging Society and a two-day track on quantitative imaging. For those ready to gamble on fun, the Texas Hold 'em invitational combines poker with adaptive planning for IGRT. And be sure not to miss the Presidential Symposium on disruptive innovation strategies—by a speed-painting artist, no less.

As the AAPM meeting will remind us, innovation needs to be coupled with patient safety to fully impact the care of cancer patients. Julie Greenwalt, MD, and colleagues from the University of Florida College of Medicine in Gainesville, demonstrate this in their review article, *Reducing errors in radiation treatment through electronic safety checklists*. Dr. Greenwalt discusses how erring is indeed human in radiation treatment, since the majority of RT incidents are caused by the transfer of information from one clinician to another. To reduce errors, her team implemented an electronic safety checklist program into the workflow of an academic radiation oncology department. By reading the article, you can learn how the program flagged potentially serious errors, strengthened communication and reaped a host of additional benefits.

This issue also brings you a review article from Isabelle Martel-Lafay, MD, and her colleagues from France, on the need for RT quality control in reducing treatment toxicity and improving tumor control. The article discusses the association between poorer overall survival and prolonged irradiation in a homogenous group of patients with unresectable stage III NSCLC treated with concurrent chemoradiation and conventional fractionation.

Two case studies are featured in this issue, including the most recent Clinical Review Case Contest winner: Joon K. Lee from the University of Illinois-College of Medicine, Rockford. His case describes the successful use of RT for pain management in a pediatric patient with Gorham Stout syndrome, a rare skeletal disorder. The second case examines organ preservation in a 63-year-old patient with locally advanced larynx cancer.

The Clinical Case Review Contest is an excellent way to share treatment experiences and innovations with your colleagues across the globe. Please review the guidelines at http://appliedradiationoncology.com/contest and send in your manuscripts. Remember, knowledge shared is progress gained. Plus, you just may win $250!

Finally, join me in welcoming Sharon Breske to *ARO* as our managing editor. Sharon comes to us with more than 18 years of medical publishing experience, the last 12 of which have spanned imaging and radiation oncology. She will work closely with me and our esteemed advisory board in coordinating and editing manuscripts, and maintaining our home page at www.appliedradiationoncology.com.

Enjoy the issue and summer! If you have ideas on future topics that would be beneficial for our readers, please feel free to contact me at suhj@ccf.org.

Dr. Suh is the Editor-in-Chief of Applied Radiation Oncology, *and Professor and Chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

Reducing errors in radiation therapy through electronic safety checklists

Julie Greenwalt, MD, Kathryn Mittauer, MS, Chihray Liu, PhD, Rohan Deraniyagala, MD, Christopher G. Morris, MS, and Anamaria R. Yeung, MD

For decades, radiotherapy (RT) has been an effective treatment in saving and prolonging life for many cancer patients, but medical errors from radiation treatment can be fatal. For example, overdosing patients through RT has been reported to be lethal.[1] While the error rate in patients treated with RT has been as low as 0.005%, one death is one too many.[2]

The World Health Organization (WHO) in combination with the International Atomic Energy Agency (IAEA) published a review in 2008 titled, "Radiotherapy Risk Profile."[3] In this document they describe that from 1976 to 2007, 3,125 reported patients were affected by RT incidents that led to adverse events. This literature noted that 1% (n=38) of the patients affected by RT incidents eventually died due to radiation toxicity.[3] Per WHO's review, the majority of errors were caused by a communication failure. After classifying where the errors occurred, they discovered that the majority of errors (38%; n=1,732) were related to transfer of information, while 18% (n=844) occurred during actual treatment delivery, and only 9% occurred during the treatment planning stage (n=420). The remaining 35% of the incidents were due to a combination of events during the planning process.

While reducing errors in radiation oncology should be a simple process, the reality is that it is a multistep process.[4] Treatment of a single patient requires contributions from the nurse, physician, computed tomography (CT) simulation staff, dosimetrist, physicist and radiation therapist. Considering the many steps to delivering RT, a single error can be propagated throughout multiple steps of the process. Likewise, there are multiple opportunities to detect an error because of the multistep nature of the process.

While RT errors can be attributed to machine or software errors, the majority of errors are attributable to humans. The United States Nuclear Regulatory Commission (NRC) has recorded that of all reported RT incidents, about 60% or more are due to human error.[5] These data suggest that most errors can be prevented if human errors can be prevented or caught early in the process.

An "incident" is defined by the IAEA safety standards as any unintended event that has consequences that are not negligible from the point of view of protection or safety, whereas a "near miss" is a potential significant event that did not occur owing to the facility conditions prevailing at the time.[6] If "incidents" can be converted to "near misses" or good catches, then patients can be saved from harm.

Safety checklists have been implemented in different arenas to reduce human errors through duplication lists or safety timeouts. They have been implemented in the airline industry, NASA engineering, and operating rooms, and have proven successful in reducing human errors.[2] For example, when used in surgery, they have been shown to reduce inpatient complications and deaths. In a study published in the *New England Journal of Medicine* by Haynes et al. titled, "Surgical Safety Checklist to Reduce Morbidity and Mortality in a Global Population,"

***Dr. Greenwalt** is a Radiation Oncology Resident, **Ms. Mittauer** is a PhD Candidate, **Dr. Liu** is a Professor and Chief Physicist, **Dr. Deraniyagala** is Chief Resident, **Mr. Morris** is a Biostatistician, and **Dr. Yeung** is an Assistant Professor at the University of Florida College of Medicine, Department of Radiation Oncology, Gainesville, FL.*

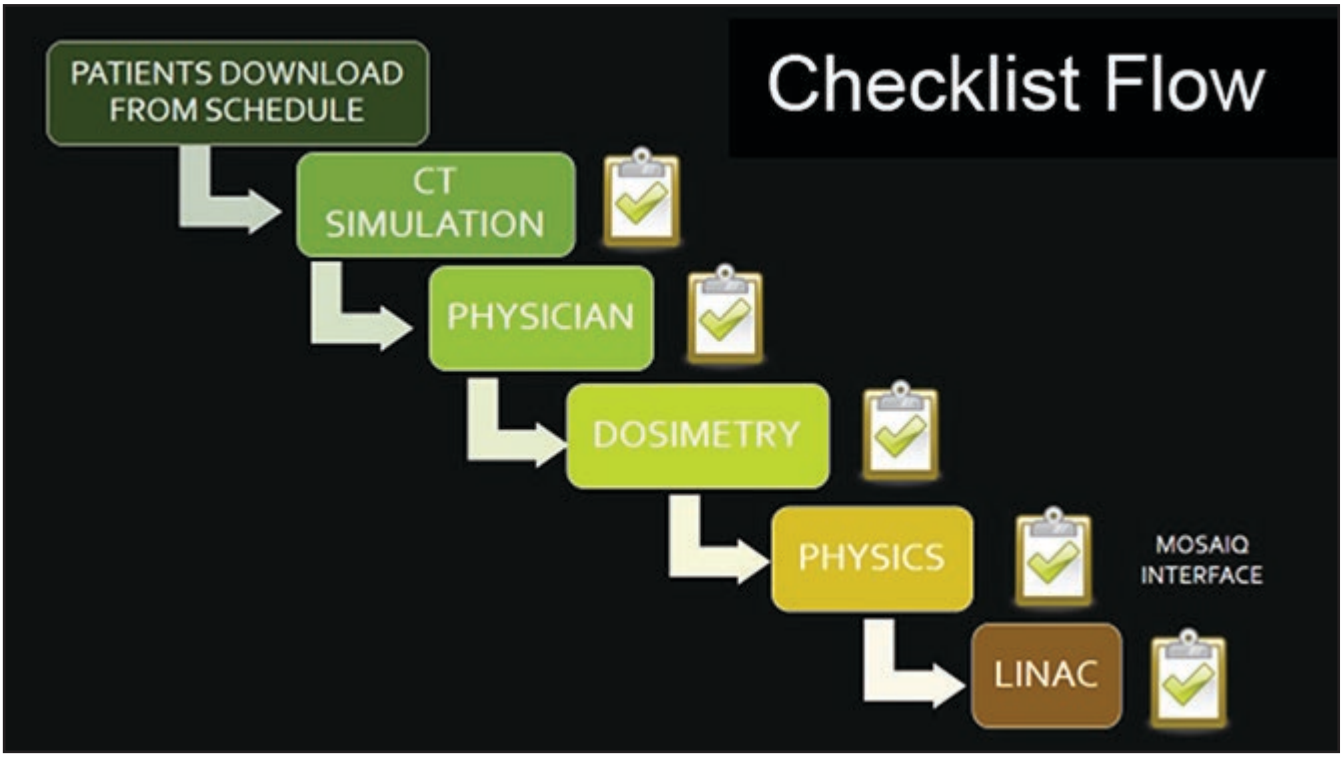

FIGURE 1. *A diagram of the workflow from CT simulation to the start of radiation therapy.*

checklists were enforced in 8 hospitals across 8 different cities. The study investigators demonstrated that checklist implementation reduced the rate of inpatient death after surgery from 1.5% to 0.8% along with the number of inpatient complications from 11% to 7%.[7]

The purpose of this project was to implement an electronic safety checklist program into the workflow of an academic radiation oncology department.

Technology

The implementation of our safety checklist program took about 6 months from origination of the idea to launching the software for department use. We started by forming a team that included a physicist, a therapist, a radiation oncologist, a radiation oncology resident, and a graduate physics student. This team then reviewed all of the errors that had been recorded in our electronic error-reporting system and classified them according to where the error originated. We then created a checklist for each area in our department by including the items that were most commonly missed according to our analysis of the reported errors. Checklists were made for CT simulation, physicians, dosimetrists, physicists and radiation therapists. We reviewed the checklists as a team and reduced the number of checklist items even further with the goal of creating short, powerful checklists for each area to maximize the impact of each checklist.

To determine how to best integrate the checklists into our workflow, we diagramed the workflow from CT simulation to the start of radiation therapy (Figure 1). The ideal checklist program would automatically generate a list of patients scheduled for CT simulation that day. The first checklist to be completed would be the CT simulation checklist. Once completed, the patient's plan would then advance into the queue of the subsequent checklist area, from the physician to dosimetry, physics, and then the therapists at the treatment machine. At each of these steps, the checklist would be completed before the patient's plan could progress to the next step.

To best integrate our plan into practice, we developed software written in VB.NET using a serial workflow based on a checklist philosophy used in vertically integrated manufacturing. The software identified and tracked the completion of tasks appropriate to each patient's treatment, including generation of documentation and multiple/parallel monitoring points. This software was integrated into MOSAIQ (Elekta, Stockholm, Sweden), a common electronic medical system used in radiation

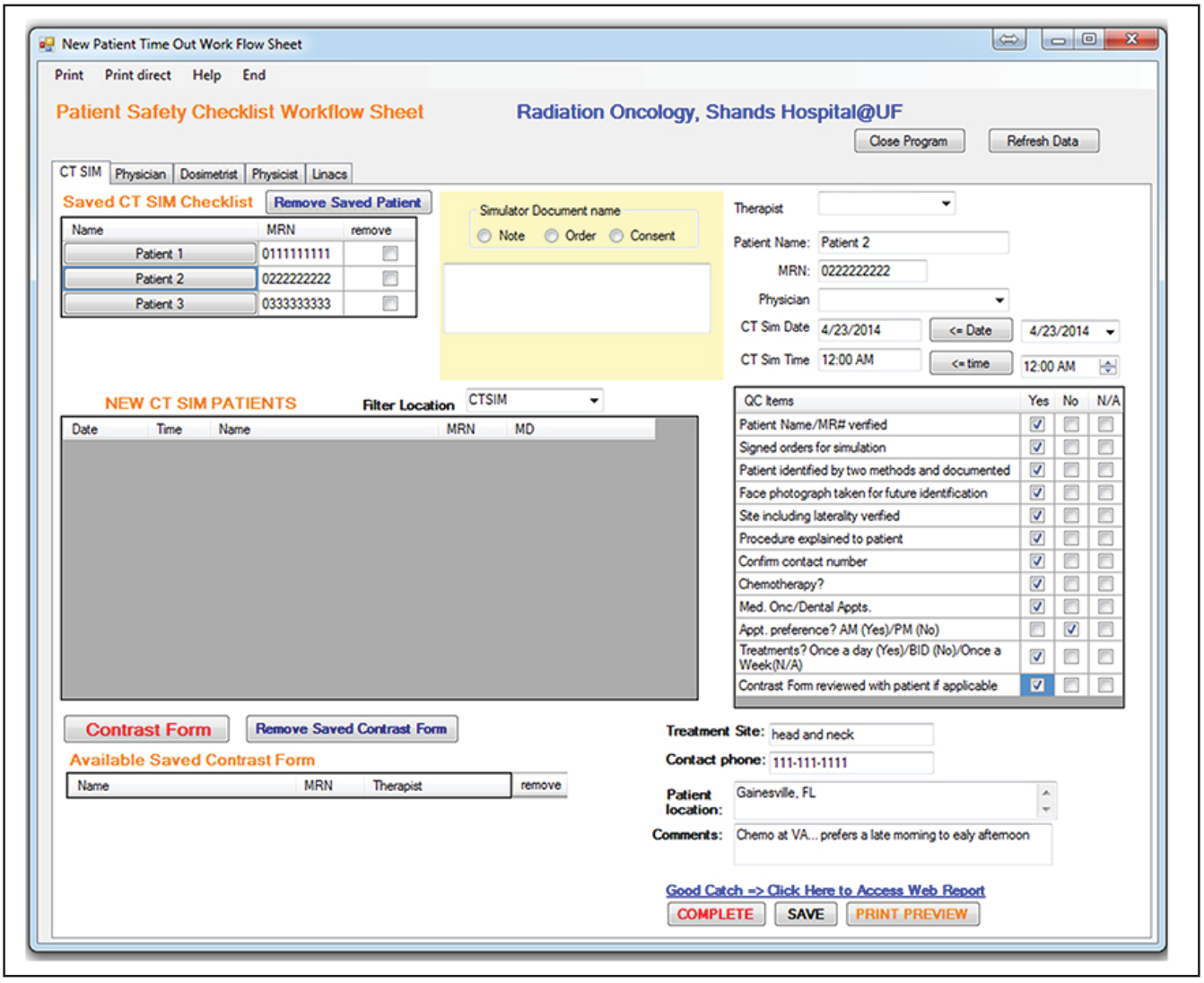

FIGURE 2. *The main view of the checklist software screen when it is first opened.*

oncology, to auto-deposit the generated documents that indicate the listing status of required tasks for each staff member. Microsoft Outlook API (Microsoft Corporation, Redmond, Washington) was used for communication among staff and to coordinate issue resolution through email or text messaging.

The main view of the checklist software screen is shown in Figure 2 demonstrating what the safety checklist software program looks like when it is first opened. The patient list autopopulates from the Mosaiq CT simulation schedule each day, so there is no need to manually enter a patient's name into the system. This patient list is the work queue for the CT simulation technician. Each step of the process from CT simulation to radiation therapy start has a work queue generated by the completion of the checklist at the prior step. For example, once the CT simulation group has completed its patient checklist for Patient 1, this patient will automatically show up on the physician's work queue in the checklist program, notifying the physician that Patient 1 is ready for contouring. Once the physician has completed contouring and written a radiotherapy prescription, he or she can then select Patient 1 from his or her list and complete the checklist on Patient 1.

Once the physician completes the checklist, Patient 1 appears on the dosimetry work queue, notifying dosimetry that Patient 1 is ready for treatment planning. When the radiotherapy plan for Patient 1 has been completed and reviewed by the attending physician, the dosimetrist completes his or her checklist, and Patient 1 appears on the Physics work queue. The physicist then knows that the plan for Patient 1 is ready to be checked.

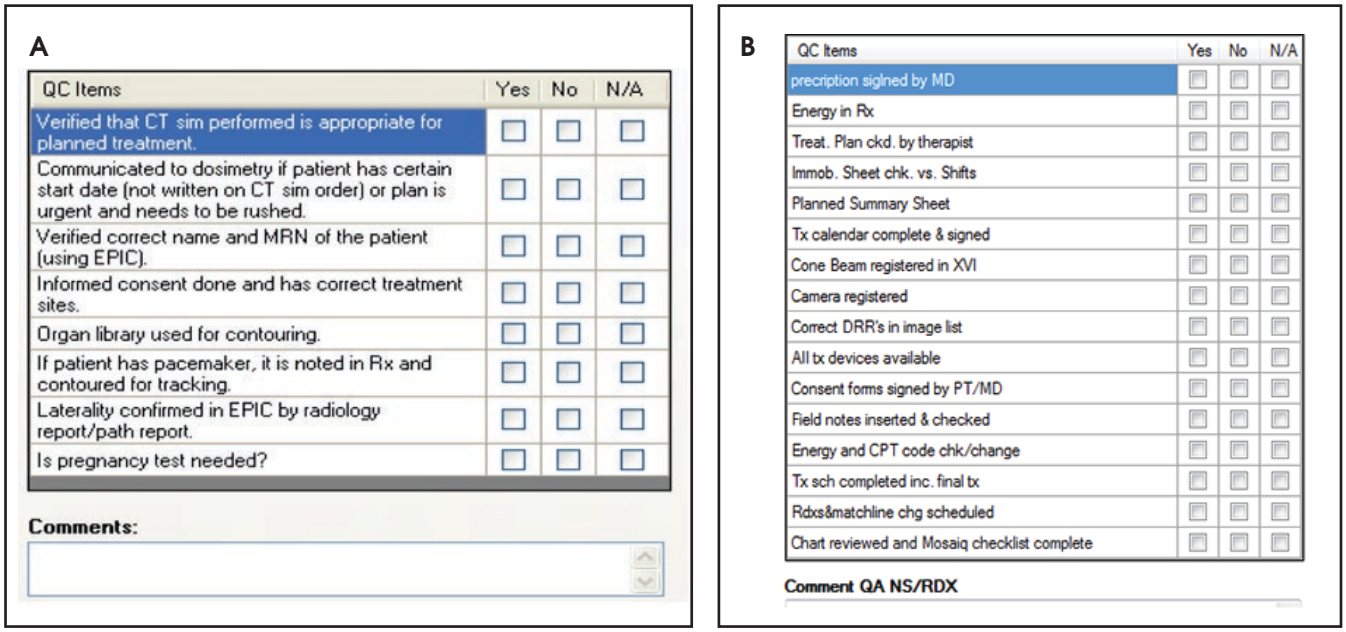

FIGURE 3. *The electronic checklist for (A) physicians and (B) radiation therapists.*

Table 1. Radiation Error Scoring System (RESS)

Severity Level	Level Description
Level I	A solitary event that causes no harm to the patient and does not require a change to the radiation prescription.
Level II	A solitary event requiring a change in the radiation prescription but not felt to pose harm to patients.
Level II	Treatment errors with potential for causing permanent damage or serious injury to the patient, even if the treatment did not result in any harm and was corrected. Treatment errors requiring a change in the radiation prescription and felt to potentially harm patients or substantially missing the tumor volume on any treatment.
Level IV	Errors involving a medical reportable event for radiation, such as wrong individual treated, a > 20% intended dose to the target, or total weekly dose differs from weekly prescribed dose by more than 30% or substantially missing the tumor volume for more than half the number of treatments. The presence of a nonpatient in the treatment room during an exposure regardless of dose received.

Borrowed from Konski A et al.[8]

After the plan is checked, the physicist completes the checklist and Patient 1 then appears on the radiation therapy work queue. This work queue notifies the therapists on each machine that the plan for Patient 1 is ready to be checked.

The checklist program software creates a date and time stamp when each checklist is completed, allowing us to track how long the patient's record has spent in each area of the treatment process. The software includes time analysis functionality to analyze the completion times. Our hope is to eventually use this data to help speed up our treatment planning process.

Clinical application

The clinical utility of the electronic safety checklist program became evident early on. Within the first weeks of going live, we caught several potentially serious errors. These were near misses that were not reported in the error-reporting system because they were caught by the checklist program at the very beginning of the planning process. For example, a physician working on the safety checklist for a female patient of childbearing age noticed she had not taken a pregnancy test. The treating physician ordered a pregnancy test, which revealed that the patient was pregnant even though the patient denied that as a possibility on initial consultation. Reminding

the physician to check the pregnancy status of a woman of childbearing age prevented a serious error. In another example, a radiation prescription was written a few weeks into the implementation of the checklist program. The physician typed the prescription to specify the treatment site as the left neck. While completing the checklist, the physician noticed that the right neck had been contoured as it was the pathologic side of disease. This obligatory double-check that took less than 2 minutes of the physician's time potentially averted a serious error. To review other important items on our safety checklists, see the physician and therapist checklists in Figure 3.

The number of errors caught before reaching the patient (which we call near misses or "good catches") is growing in our department. The severity of errors was graded according to the Radiation Error Scoring System shown in Table 1.[8] In this system, grade 1 and 2 errors are classified as near misses (or events that cause no harm to the patient as defined in the RESS), and grade 3 and 4 errors are those reaching the patient. This is by no means an ideal grading system, but we found that it is better suited for radiation oncology than other error grading systems. We noticed that the number of reported errors increased over time, including after the implementation of the safety checklists; we anticipate that the number of errors actually reaching the patient (grade 3 and 4 errors) is decreasing. Our early experience demonstrates that the number of good catches increased after the safety checklist program was implemented, and the number of serious treatment errors or "incidents," as defined by the IAEA, decreased.

Conclusion

Safety and quality are extremely important to treating cancer patients not only in our radiation oncology department but throughout the nation. It took over 6 months to implement a new electronic safety checklist program. This checklist system has been successfully implemented in our department, identifying and improving clinical and communication issues. Following implementation, we found that the system helped reduce regulatory and treatment documentation compliance events, identify communication problems, and empower staff to submit "good catch" issues to a team working to improve workflow, improve treatment quality, and improve safety. The program also enabled us, through time analysis, to easily identify and improve treatment-related bottlenecks.

Not only did the electronic checklist system benefit the overall clinical workflow in regard to treatment planning, it also resulted in an increase in reported errors (good catches). There was a trend toward reducing the severity of errors (more reported "near misses," fewer errors reaching the patient), although more time is needed to determine if the safety checklists actually reduce the number of errors reaching patients.

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Impact of irradiation protocol deviations on the outcome of unresectable stage III NSCLC patients receiving concurrent chemoradiotherapy: Quality-assurance results of the GFPC-IFCT 02.01 trial

Isabelle Martel-Lafay, MD, Pascal Pommier, MD, Pierre Clavére, MD, PhD, Jean-Paul Labat, MD, PhD, Mohamed Benchalal, MD, Jean-Noél Talabard, MD, Eric Teissier, MD, Anne d'Hombres, MD, Emmanuel Touboul, MD, PhD, Marie Cécile Bozonnat, MD, Anthony Montella, MsC, Pierre Fournel, MD, and the GFPC IFCT 02.01 Team

A dose-effect relationship of exclusive radiotherapy (RT) is likely to exist in non-small cell lung cancer (NSCLC) with lower doses providing poorer local control.[1,2] However, high doses result in more severe toxicity. Based on 3D conformal RT, thresholds have been established for pulmonary dose-volume histograms (DVH), with the aim of avoiding severe radio-induced pneumonitis.[3] In selected patients with unresectable stage III NSCLC, concomitant chemoradiation has proven superior to sequential combination therapy,[4,5] but causes more frequent acute esophagitis.[6-9] Therefore, RT quality control is useful for reducing treatment toxicity and improving tumor control.

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In some other malignancies, both toxicity and overall survival (OS) correlate with the quality of RT.[10] Very few data on RT quality are available for NSCLC, as quality assurance usually focuses on technical and physical assessment of linear accelerators.[11-12]

We analyzed RT quality in a phase II randomized trial of concurrent chemoradiation for unresectable stage III NSCLC. The main objectives were to assess compliance with the trial's protocol and the impact of observed deviations on survival and toxicity.

Materials and methods

The GLOT-IFCT-GFPC 02.01 (Groupe Lyon-Saint-Etienne d'Oncologie Thoracique, Intergroupe Francophone de Cancérologie Thoracique, Groupe Français de Pneumo-Cancérologie), study was a multicenter randomized phase II trial

Table 1. Definition of major and minor deviations from radiotherapy protocol guidelines

	Planned	Minor deviation	Major deviation
Immobilization device	Personalized	T-bar device	none
Dose per fraction (Gy)	2	1.8	<1.8
Total dose (Gy)	66	60 to 63 and >69	< 60
Elective node irradiation	not allowed	----	done
Beam number	≥6	5	<5
Portal imaging before RT	done	-----	not done
Portal imaging during RT	Weekly > 6	<6	< 3
RT duration (days)	45	>48	> 55
Treatment interruption (days)	0	< 7	> 7
Pulmonary DVH	V20 ≤30 V30 ≤20	30%<V20 ≤ 40% 20%<V30 ≤ 30%	V20 > 40% V30 > 30% DVH not done missing data

of concurrent chemoradiation either preceded (arm A) or followed (arm B) by chemotherapy for unresectable stage III NSCLC. The chemotherapy regimen was cisplatin 80 mg/m^2 and paclitaxel 200 mg/m^2 every 21 days for two cycles, cisplatin 80 mg/m^2 every 21 days, and vinorelbine 15 mg/m^2 weekly concurrently. Standard inclusion criteria applied.

The trial's RT protocol conformed to European Organisation for Research and Treatment of Cancer (EORTC) guidelines.[13] The gross tumor volume (GTV) included the primary tumor and enlarged mediastinal lymph nodes (smallest diameter ≥ 1 cm). Prophylactic node irradiation was not authorized. The planning treatment volume (PTV) was defined as GTV + 15 mm without field reduction. A personalized immobilization device was required for CT scanning in the treatment position. The total dose was 66 Gy in 33 fractions. Three-dimensional conformal irradiation was mandatory. Maximum spinal cord dose was 46 Gy. Pulmonary DVH were required, with the following recommended values: V20 ≤ 30% and V30 ≤ 20%. Six beams or more had to be used. All fields were verified before starting treatment, and weekly thereafter. All patients were examined weekly by the radiation oncologist, who scored acute toxicity according to the CTCAE v3 scale. The following items were collected and reviewed twice a year by the GFPC radiation oncologists panel: immobilization device, total dose, dose per fraction, prophylactic nodal irradiation (supraclavicular or mediastinal), number of beams, control imaging before and during irradiation, treatment duration, treatment interruption (number of days, reasons), and pulmonary DVH.

As the aim of this study was to assess the quality of RT, the analysis included only patients who completed the concurrent chemoradiation. Major (MD) and minor (md) deviations were defined for 11 criteria (Table 1). Four clinically most relevant MDs were grouped together for analysis: the total dose, the pulmonary V20 DVH (V20), treatment interruption and elective node irradiation.

Statistical analysis

Comparisons were made using the chi-2 or Wilcoxon test. The survival time was calculated from the date of cancer diagnosis to the date of death, or censored at the date of last follow-up for survivors, based on Kaplan-Meier estimates.[14] Progression-free survival was calculated from the date of cancer diagnosis to the date of progression. Cox proportional hazards models were used to test the effect of each deviation, with adjustment for the treatment arm.

Results

Between May 2002 and March 2005, 132 patients were irradiated in 28 centers. Median follow up was 44.9 months (95% CI: 42.3-47.4). Five patients were ineligible, 18 patients were excluded before concomitant treatment, and 8 patients did not receive the entire irradiation. The remaining 101 patients completed the concurrent chemoradiation and constituted the study population (Figure 1). The characteristics of the patients were well-balanced between the two arms, except for the histological type (Table 2).

Grade 1-2 pulmonary toxicity affected 24% and 25% of the patients, respectively, in arm A and arm B; one case of grade 5 pulmonary toxicity occurred

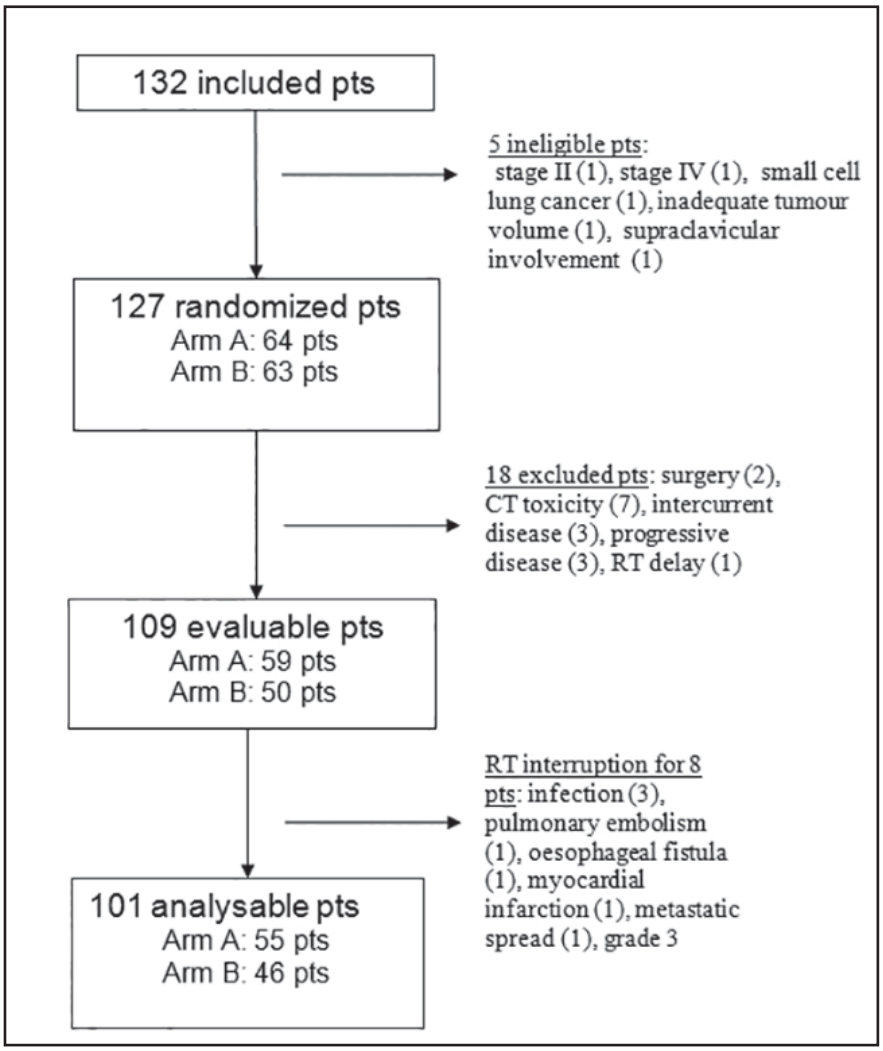

FIGURE 1. *FLOW CHART Arm A: Induction chemotherapy; Arm B: Consolidation chemotherapy.*

in arm B. Grade 3-4 esophageal toxicity affected 15.8% of patients overall (6 patients in arm A, 10 patients in arm B). The 2-year OS rates were 47% and 43% in arms A and B, respectively, and the objective response rates were 55% and 48%.

Full data on RT were provided by all but 3 of the radiotherapy centers (6 patients). All patients received an adequate photon energy, and most patients received 2-Gy fractions. Twelve patients (13%) had a treatment interruption of one week or more.

Among the 101 assessable patients, 69 (68.3%) had at least one MD, 27 (26.7%) had at least one md, and 5 (5%) had no deviation (Table 3).

The most frequent MDs were an inappropriate number of beams in 27 (27.6%) cases, and inadequate values for pulmonary DVH, respectively, in 26 patients (25.7%) for V20, and 29 patients (28.7%) for V30. Other MDs were prophylactic nodal irradiation and treatment interruption lasting >1 week. The total dose was that recommended, except in 7 patients. There was a strong correlation between the total dose and treatment interruption ($p < 0.0001$). Age, gender, weight loss, histological type and tumor stage were not predictive of MD risk.

There was a significant difference between the 2 treatment arms with respect to V20 MDs (17.4% in the induction arm versus 32.7% in the consolidation arm, $p = 0.04$). The reduction in tumor volume after 2 cycles of induction chemotherapy may explain this difference. There was no difference between the treatment arms with respect to the total dose, RT duration or elective nodal irradiation.

Consequences of the deviations

The 2-year OS tended to be lower in patients with at least one MD (40%, 95% CI: 28.1; 51.9) than in patients with no MD (53.1%, 95% CI: 35.8; 70.4), as well as the median OS (19 versus 25.3 months, $p = 0.31$), but the difference was not statistically significant. When considering only the 4 clinically relevant MDs (total dose, V20, treatment interruption, elective nodal irradiation), outcome tended to be poorer among patients with MDs than in patients without MD: The median OS times were respectively 13.3 and 19 months, and the 2-year OS rates were respectively 31% (95% CI: 17.8; 45) and 54.5% (95% CI: 10.6; 66.6) ($p = 0.077$, Figure 2). OS was significantly affected by deviations from the total dose ($p = 0.0001$) and by treatment interruption ($p = 0.0003$), but not by V20 or elective nodal irradiation (Figure 3). Patients with MD from the total dose had a median OS of 4.8 months, compared to 23 months in other patients, and the difference in the 2-year OS rate was huge (0% versus 47.8%, 95% CI: 37.2; 57.6). Patients with MDs due to treatment interruption received a lower total dose (54.7 Gy vs 66 Gy), which likely influenced their OS. In multivariate analysis, the only factor predictive for a lower OS was TI.

There was no difference in progression-free survival or the time to local progression according to the MDs. Metastasis-free survival was significantly shorter in patients with MDs for treatment duration ($p = 0.004$).

Table 2. Characteristics of the patients in the two treatment arms. Arm A: induction chemotherapy, Arm B: consolidation chemotherapy; (* = p < 0.05)

	Arm A N = 46	%	Arm B N = 55	%	All N =101	%
Age (min-max)	56.5	(40-69)	58.7	(42-70)	57.7	(40-70)
Gender						
Male	43	93.5%	47	85.4%	90	89.1%
PS						
0	30	68.2%	42	77.8%	72	71.3%
1	14	31.8%	12	22.2%	26	25.7%
Weight loss >5%						
No	35	77.8%	40	74.1%	75	74.3%
Histology*						
AdenoCa	14	31.1%	16	32.0%	30	29.7%
Squamous cell Ca	18	40.0%	30	60.0%	48	47.5%
Large cell Ca	13	28.9%	4	8.0%	17	16.8%
Stage						
IIIA N2	10	21.7%	16	29.1%	26	25.7%
IIIB	36	78.3%	39	70.9%	75	74.3%
Local progression						
No	36	78.3%	49	90.7%	85	85.0%
Yes	10	21.7%	5	9.3%	15	15.0%
Distant progression						
No	24	52.2%	27	50.0%	51	51.0%
Yes	22	47.8%	27	50.0%	49	49.0%
Death						
No	11	25.0%	17	32.1%	28	28.9%

Discussion

The study's aim was to assess the quality of RT and its impact on patient outcome. In published trials of concurrent chemoradiation, information on the RT is restricted to the total dose, fractionation and recommended volumes.[8] Data on the treatment actually administered are rarely provided.[6,7,9] In definitive radiotherapy, the volumes, total dose and toxicity are strongly related. As radiotherapy plays a major role in the local control of unresectable NSCLC, the question arises as to whether the quality of radiotherapy is related to patient outcome. Despite protocol requirements concerning centralized review of the radiotherapy data, some centers failed to provide their patients' records, or provided only very sketchy information with many missing data.

The OS time in the entire study population was slightly longer than in other series of concurrent chemoradiation for NSCLC, with a median of 20.2 months, compared to 15 months in the French GFPC 95.01 study,[7] 17.1 months in the Radiation Therapy Oncology Group (RTOG) 94.10 study,[15] and 16.5 months in the Japanese trial[16] and the EORTC study.[6] OS was significantly influenced by the total dose (4.8 months if < 60 Gy vs 21.9 months if ≥ 60 Gy, p < 0.0001), as in previous studies that showed that the total dose must be > 60 Gy for curative purposes.[1,2]

OS was also negatively affected by treatment interruption and by a longer radiotherapy duration (p = 0.005 and p = 0.0001, respectively), as was metastasis-free survival (p = 0.047 and p = 0.002, respectively). Treatment interruption is a well-known prognostic factor in patients with head-and-neck tumors or cervical cancer.[17,18] Fowler suggested that clonogens proliferated within the tumor after 3 or 4 weeks of radiotherapy.[19] Machtay et al.[20] pooled patient data from 3 RTOG trials, including concurrent chemoradiation for unresectable NSCLC, with most patients receiving hyperfractionated radiotherapy. Altogether, 18% of the patients had treatment interruption lasting more than 5 days. The median OS was not significantly better among patients who completed their treatment on time (19.5 versus 14.8 months, p = 0.15).

In multivariate analysis, prolonged treatment time was associated with poorer OS (hazard ratio 1.02, CI: 1.003-1.03, p = 0.01) and a lower total dose (p = 0.03). In the present study, there was also a strong correlation between treatment interruption and total dose. In the 12 patients who had MD for treatment interruption, the mean total dose was 54.7 Gy, compared to 66 Gy among patients with no delay (p < 0.0001). Progression-free survival and locoregional progression-free survival were not affected by the occurrence of MDs, suggesting that the impaired survival reported in the deviation group was not related to an increased rate of locoregional recurrence. Treatment interruption (p = 0.047) and longer RT duration (p = 0.002) were associated with a poorer metastasis-free survival. The small size of this study probably explains the lack of any significant difference in OS according to the occurrence

Table 3. Observed major and minor deviations (* = p < 0.05)

	All		Arm A		Arm B	
	N = 101	%	N = 46	%	N = 55	%
All deviations						
MD	69	68.3	34	73.9	35	63.6
Md	27	26.7	10	21.7	17	30.9
No deviation	5	5.0	2	4.3	3	5.5
Total dose (Gy)						
MD	7	7.0%	3	6.5%	4	7.4%
Md	6	6.0%	2	4.4%	4	7.4%
no deviation	87	87.0%	41	89.1%	46	85.2%
Pulmonary DVH V20Gy						
MD*	26	25.7%	8	17.4%	18	32.7%
Md	30	29.7%	12	26.1%	18	32.7%
No deviation	45	44.6%	26	56.5%	19	34.5%
Pulmonary DVH V30Gy						
MD	29	28.7%	12	26.1%	17	30.9%
Md	35	34.7%	15	32.6%	20	36.4%
No deviation	37	36.6%	19	41.3%	18	32.7%
Treatment Interruption (days)						
MD	12	13.0%	5	11.4%	7	14.6%
Md	13	14.1%	4	9.1%	9	18.7%
No deviation	67	72.8%	35	79.5%	32	66.7%
RT duration (days)						
MD	10	10.3%	4	8.9%	6	11.5%
Md	47	48.5%	20	44.4%	27	51.9%
No deviation	40	41.2%	21	46.7%	19	36.5%
Elective node irradiation						
MD	17	16.8%	7	15.2%	10	18.2%
No deviation	84	83.2%	39	84.8%	45	81.8%
Immobilization device						
MD	7	7.7%	4	9.5%	3	6.1%
Md	20	22.0%	9	21.4%	11	22.4%
No deviation	64	70.3%	29	69.1%	35	71.4%
CT scan						
No deviation	101	100.0%	46	100.0%	55	100.0%
Dose per fraction						
Md	9	9.0%	2	4.3%	7	13.0%
No deviation	91	91.0%	44	95.7%	47	87.0%
Beam number						
MD*	27	27.6%	19	41.3%	8	15.4%
Md	5	5.1%	0	0.0%	5	9.6%
No deviation	66	67.3%	27	58.7%	39	75.0%
Imaging before RT						
MD	11	11.6%	6	13.6%	5	9.8%
No deviation	84	88.4%	38	86.4%	46	90.2%
Imaging during RT						
MD	20	33.3%	8	25.8%	12	41.4%
Md	10	16.7%	6	19.4%	4	13.8%
No deviation	30	50.0%	17	54.8%	13	44.8%

of any MD or any of the 4 clinically relevant MDs.

Prophylactic nodal irradiation was delivered to 17 (16.8%) patients, either to uninvolved mediastinal areas or to the supraclavicular fossae. Some studies have shown no improvement in local control or survival with elective node irradiation.[21,22] In the present study, patients receiving prophylactic node irradiation did not have worse pulmonary DVH values, and were not at a greater risk of receiving an inadequate total radiation dose. This could be explained by the use of field reduction techniques to avoid excessive irradiated volumes, and by the central location of the node areas in the chest. Pulmonary DVH values for V20 and V30 were extremely variable, ranging from 9% to 64% and from 3% to 61%, respectively. For V20, the median value was 31.4% and the mean value was 30.5%. According to the protocol, the percentage of lung receiving more than 20 Gy should not have exceeded 30%, which is a stricter cut-off than the 35% accepted in most recent studies. Nevertheless, MD from V20 was defined as V20 > 40%, which is well above the maximal value recommended. After excluding missing values (11 patients), 24 (23.8%) patients had V20 > 35% and 15 (16.7%) patients had V20 > 40%. The rates of MD for the total dose (7%) and pulmonary DVH (25.7%) seem to show that radiation oncologists preferred to stick to the recommended dose while accepting inadequate pulmonary DVH values.

The question of whether the PTV, the GTV, or neither should be subtracted from the total lung volume when calculating DVH values is controversial, and practices vary across published studies.[13] The protocol guidelines required the PTV to be subtracted from the total volume of the two lungs. Despite the large number of patients with DVH values outside the recommended range, this deviation did not correlate with increased toxicity. The incidence of acute

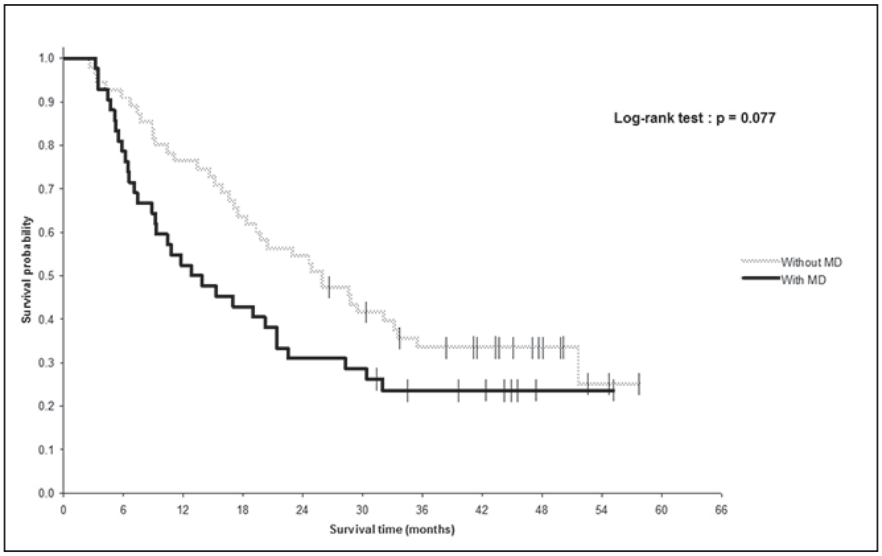

FIGURE 2. *Overall Survival for patients having at least one of the 4 major deviations (Total Dose, V20, TI, Elective Nodal Irradiation).*

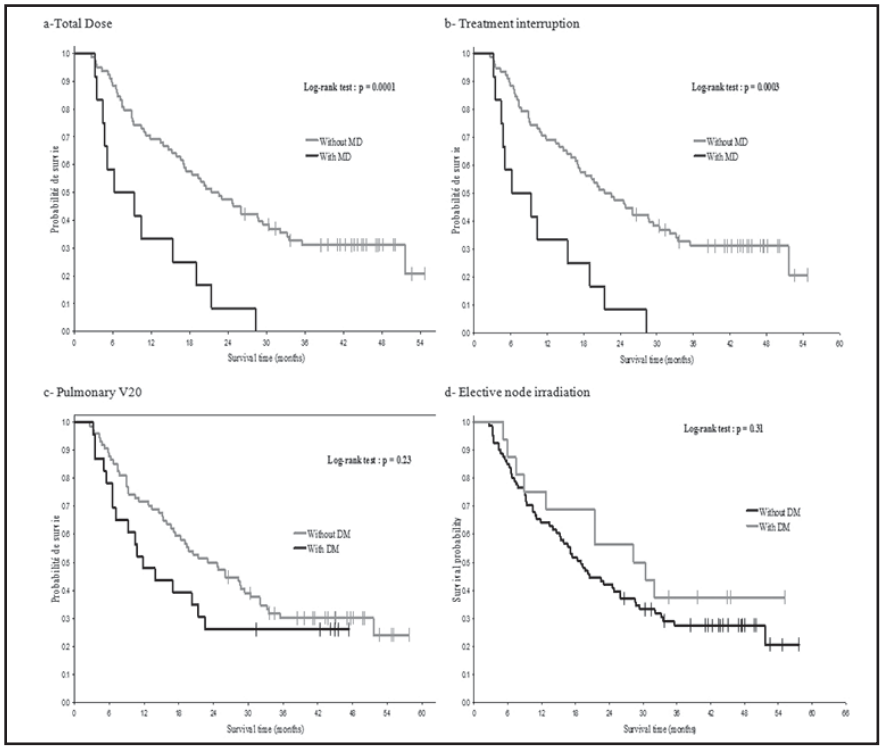

FIGURE 3. *(A to D) Overall survival according the four major deviations (Total Dose, V20, treatment interruptions, Elective Nodal Irradiation); black lines correspond to patients with deviations and grey lines to patients without deviations.*

pulmonary toxicity was low and similar to that reported in randomized trials of concurrent chemoradiation and in the Cochrane review[5,7,15,16] A Japanese study focusing on radio-induced pneumonitis following concurrent chemoradiation showed a 28% crude incidence of grade 2 or higher pneumonitis. Severe toxicity (grade ≥ 3) affected 4.2% of patients.[23] This confirms that radiation pneumonitis may be overlooked unless specifically sought.

In a recent retrospective study focusing on dosimetric factors associated with treatment-related pneumonitis in patients with NSCLC receiving concurrent chemoradiation, the cumulative rate of severe pneumonitis was 22% at 6 months and 32% at 12 months, which is higher than the rates usually reported. The authors found that V5 (the percentage of lung volume receiving 5 Gy) was the most relevant factor for predicting pulmonary toxicity, with pneumonitis incidence rates of 3% and 38% for V5 ≤ 42% and > 42%, respectively. The influence of the mean lung dose was confirmed, with a threshold of 16.5 Gy. Interestingly, the patients analyzed had mainly received platinum-taxane or platinum-etoposide combinations and, occasionally, irinotecan, gemcitabin or doxorubicin-based regimens, which are known to be highly radiosensitizing and could explain the high rates of severe pulmonary toxicity.[24] Concurrent chemoradiation with cisplatin and vinorelbine is usually better tolerated than other chemotherapy regimens,[8] as confirmed in this trial. In a literature-based review of clinically relevant radiation pneumonitis following concurrent chemoradiation for lung carcinoma, the rate of severe radiation pneumonitis was 7.8% and the only factor associated with an increased incidence of toxicity was a fraction size larger than 2.67 Gy.[25]

In a more recent retrospective study, the incidence of severe radiation pneumonitis was similar (8.3%), and the only factors associated with a higher incidence were performance status (1 versus 0) and female gender.[26] The number of events suggestive of severe radiation pneumonitis was insufficient to test these hypotheses. Unfortunately, the protocol was not designed to collect treatment planning volumes, and it was not therefore possible to study correlations between these volumes and toxicity, survival or loco-regional control.

Conclusion

This study shows an association between poorer overall survival and prolonged irradiation in a homogenous group of patients treated with concurrent chemoradiation and conventional fractionation. This calls for procedures to obtain treatment planning data before randomization, in order to include only patients whose V20 pulmonary DVH is no more than 35%. The next step will be to organize a centralized review of radiotherapy quality criteria and protocol compliance before participating radiation oncologists are allowed to enroll patients, as is already the case in some multicenter studies.

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TECHNOLOGY TRENDS

Updates in IGRT: The new, the improved, and the future outlook

Mary Beth Massat

When a 56-year-old liver transplant patient came to Henry Ford Health System, Detroit, Michigan, with a metastatic focus recurrence from hepatocellular cancer nestled between the porta hepatis, duodenum, stomach, and large colon, M. Salim Siddiqui, MD, PhD, had a plan. Rather than refer the patient for palliative care, the director of the Stereotactic Radiation Program opted for treatment.

"The soft tissue mass was surrounded by organs that move and expand at different rates relative to each other, so we couldn't rely on just cone-beam computed tomography (CBCT) because the mass could move," explains Dr. Siddiqui. Fortunately, Henry Ford Hospital had recently installed the Edge (Varian Medical Systems, Palo Alto, California), a new dedicated radiosurgery suite that offers real-time tumor tracking and motion management technologies, along with triggered imaging with beam-hold ability for planning and delivering radiosurgery treatments.

Three fiducial markers were implanted in the mass. Dr. Siddiqui and his team performed a 4D-CBCT simulation to create an internal target volume (ITV) motion envelope for tumor movement and for each fiducial. With this information they had a plane reference to capture any rolls, pitches, yaws and translations of the mass. With the integrated 6 degrees of freedom treatment couch, Dr. Siddiqui could quickly and easily adjust for those as well. The plan called for 5 fractions of 7 Gy, with only 2 mm expansion from the ITV to the planning target volume (PTV).

"We used 4D-CBCT to capture and image the tumor within its motion envelope and precisely align to the planned soft tissue tumor, then used kV imaging to see if the fiducials fell within the corresponding ITV," he explains. "Then we used triggered kV imaging to track in real time the fiducials, delivering the treatment beam only when the fiducials were within the ITV and PTV expansion."

Without this technology, the patient could not have been treated. "This was just remarkable," says Dr. Siddiqui. "This was his only soft-tissue recurrence, and we gave the patient tremendous hope."

Advanced image-guided therapy systems are changing external-beam radiation treatment (EBRT) plans, enabling radiation oncologists to prescribe radiation therapy in areas of the body that were previously difficult to treat.

For Paul J. Kim, MD, medical director at Skyline Radiation Oncology, Tustin, California, the use of 4D imaging with Clarity (Elekta, Atlanta, Georgia) is improving certainty of the prostate gland's location during radiotherapy. By applying the ultrasound to the perineum, he can visualize and track the prostate's position continuously during each radiation treatment.

"If the prostate moves away from the beam, we can stop, adjust and resume," says Dr. Kim. "Because real-time tracking has improved our certainty of the prostate's location during the treatment, we have the opportunity to reduce our treatment planning margins. It's non-invasive and does not require placement of any fiducial markers, thereby improving patient acceptance of the treatment."

While the length of treatment remains the same, the treatment delivery is of a higher quality. "We are hitting the target with less volume of surrounding tissues, such as the rectum or bladder, receiving high doses of radiotherapy," he adds. "This is where real-time imaging technology is helping, to track moving targets and enable us to more safely deliver treatment."

Certainly, image guidance in EBRT has come a long way, adds Sandra Zaky, MD, DABR, from Palo Verde Cancer Center-Scottsdale in Scottsdale, Arizona. One advantage is the ability to deliver higher dose levels to the tumor, which can result in better disease control, while at the same time reducing margins around the tumor to protect

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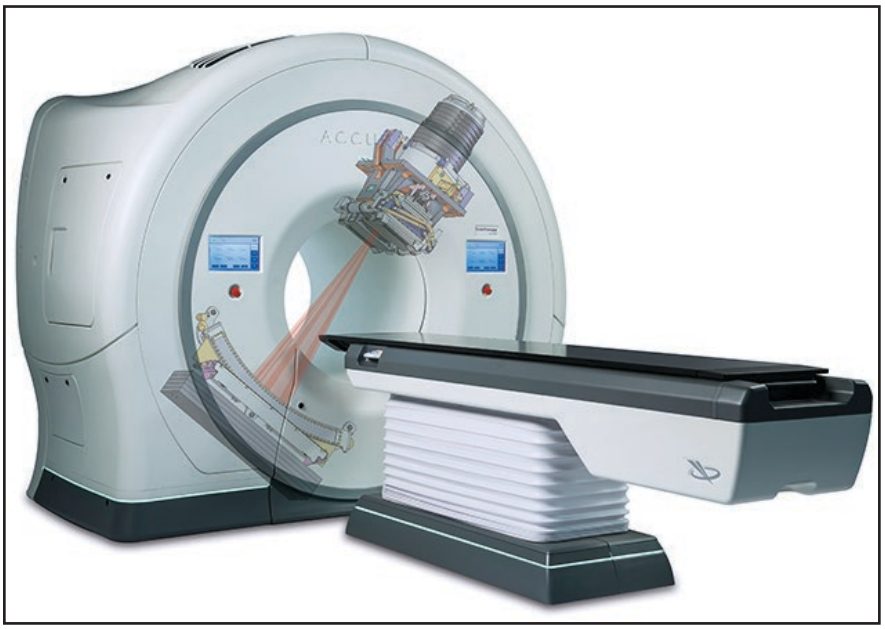
Hybrid imaging is achieved by acquiring Elekta's Clarity images at the same time as the CT acquisition procedure with the patient in the same RT setup position. This allows CT and Clarity images to be automatically fused for seamless integration into simulation and planning workflows. Clarity's software-assisted segmentation technology supports clinicians in rapidly contouring 3D soft-tissue targets and anatomy prior to treatment planning.



Accuray's TomoHDA™ System is the latest innovation in the TomoTherapy product portfolio and is equipped to deliver helical and direct-angle IMRT. With a unique combination of features including daily CT image guidance, VoLO Treatment Planning and TomoEDGE Dynamic Jaws, the system offers radiation oncologists fast, accurate and flexible treatment planning and delivery for patients, regardless of location, size and complexity of the tumor.

critical structures and reduce side effects. She sees a tremendous difference in the quality of treatment from a reduction in margins, particularly in head and neck cancers.

"Many patients receive chemotherapy concurrent with radiation, and it can be very toxic for the patient," Dr. Zaky explains. "Before we had the ability to acquire CT images throughout the course of treatment, we used larger margins so that we weren't missing the disease. Now, because we can use these daily images for more precise patient positioning and monitoring of treatment progress, we can reduce our margins. As a result, the dry mouth, skin changes, oral ulcers and other irritation in the mouth is reduced. With smaller margins, there are fewer side effects for the patients."

Dr. Zaky and her colleagues use the TomoHDA System (Accuray, Sunnyvale, California) with VoLO Planning to create treatment plans with tighter margins that spare healthy tissue and organs. The system's integrated imaging and flexible radiation delivery modes help keep treatments on track, and allow for more aggressive approaches, such as stereotactic procedures, that can be completed in fewer treatment sessions.

"Image guidance has changed stereotactic radiotherapy," she says. "We can confidently pinpoint the tumor with accuracy and deliver high doses at each treatment."

With the system's CT scanner-like design, Dr. Zaky can seamlessly image and treat larger fields compared to conventional linacs with smaller set size image fields, she explains. For example, she can image the entire leg with the CT while the patient is in the treatment position, and then deliver the therapy.

Intra-operative imaging

Advanced image guidance is also being used for brachytherapy in an intra-operative environment. At the University of Virginia School of Medicine

TECHNOLOGY TRENDS

The Siemens SOMATOM Sensation Open sliding gantry can be used for in-room imaging within an intra-operative setting. It enables clinicians to slide the CT to the anesthetized patient to capture imaging during a surgical procedure, such as brachytherapy treatments.

During treatment, the ViewRay system continuously monitors the patient's anatomy and adjusts for motion in real time, delivering the dose only when the tumor is located exactly where it should be. Continuous MRI and soft-tissue targeting assure accurate treatment delivery and minimize the dose to critical structures and surrounding healthy tissues.

in Charlottesville, Timothy Showalter, MD, assistant professor in the Department of Radiation Oncology, and Bruce Libby, PhD, associate professor, Radiological Physics, and chief of Clinical Brachytherapy Physics, are using a SOMATOM Sensation Open CT sliding gantry in a brachytherapy suite.

"To do brachytherapy in the intra-operative setting, you need several components all in one room," explains Dr. Showalter. "This includes shielding for [high-dose-rate] HDR brachytherapy, as well as in-room imaging, and the ability to perform a lumpectomy or surgical procedure. It's a unique arrangement, and having the CT scanner in the room enables us to slide the CT across the floor toward the anesthetized patient who has just received a lumpectomy—without moving the patient—which is really critical."

In any setting, moving a patient comes with a risk. Dr. Libby shares a story of a patient who had applicators and needles placed in the OR, only to have one of the applicators perforate the uterus when she was moved to the brachytherapy treatment room. Bringing the scanner to the patient, he adds, is safer for the patient and provides added flexibility.

"The whole combination of equipment ensures maximum flexibility, not just for breast patients, but also for our gynecological patients," Dr. Libby says. "If we are not happy with how the applicator is placed, we can take the applicator out and place it properly without moving the patient to a different room for placement. So the image guidance part of it is really important."

Plus, there's an added advantage of a more efficient workflow. According to Dr. Showalter, an ambulatory brachytherapy procedure for cervical cancer is extremely efficient in the image-guided brachytherapy suite.

"We can complete a tandem and ovoid case in less than an hour and a half," Dr. Showalter says. "That's in contrast to care delivered at radiation oncology centers without an integrated suite, [where] each step has to be completed in a different room or location. This might take 3 to 5 hours for a tandem and ovoid brachytherapy treatment.

"The rapid workflow allows us to offer new programs like the breast intraoperative radiation therapy, something that is innovative and not available elsewhere," he adds. "This alone will not necessarily improve cure rates, but it certainly will improve patient satisfaction."

MRI image guidance

For years, radiologists have realized the superiority of MRI for imaging soft tissues in the body, including the brain, spine and joints. In radiation therapy, using MRI for image guidance in treatment planning is no longer a vision—it's reality.

The Siteman Cancer Center, part of the Washington University School of

Varian's EDGE Radiosurgery Suite is a fully integrated, dedicated system for performing advanced radiosurgery using new real-time tumor-tracking technology and motion management capabilities.

Medicine in St. Louis, Missouri, is the first site to implement the ViewRay (Oakwood Village, Ohio), the only commercially available MRI-guided radiation therapy system. With it, Jeffrey R. Olsen, MD, assistant professor of radiation oncology, can image soft tissue anatomy in real-time to keep the radiation beam on target when the target moves during treatment. Dr. Olsen is performing research to apply this technology to cancer situations—including pancreatic cancer—to reduce treatment side effects.

Radiation alignment is traditionally performed using 2D X-ray images or CT imaging. Although such techniques allow visualization of bony anatomy, the use of MRI allows alignment based on the soft tissue tumor and critical structures not visible with traditional localization techniques such as X-ray imaging. The ability to capture real-time MR images means that as the position of critical structures move, or the shape of the tumor changes, the radiation beam can be adjusted to allow a more targeted treatment field. These changes allow treatment modification, called adaptive radiotherapy, based on a patient's individual anatomy. However, adaptive treatment presents a new logistics issue that the treatment team at Washington University is working to resolve—the quality assurance (QA) process. To reduce side effects, that's a problem Dr. Olsen doesn't mind having.

With traditional radiation therapy plans, the patient is imaged one day, and then treated the following day based on the QA process. The challenge is to implement a QA process so the patient can be imaged, planned and treated on the same day. It's a process where the patient receives repeat MR scans to make adjustments based on changes in anatomy. Allowing daily adaptation and planning revision can reduce the amount of normal tissue receiving radiation dose.

"We have seen increased motion and variability in some tumors, and we've been able to act on that information," says Dr. Olsen. "MRI changes the information we have and provides the initial foundation for moving forward with image-guided adaptive treatments. This is something that has the potential to improve outcomes and reduce toxicity."

Furthermore, as radiation oncologists use imaging such as MR or positron emission tomography/CT (PET/CT) to monitor patient progress earlier in the treatment cycle, adaptive treatments may allow for changes based on early response. If the patient is responding favorably to treatment, the oncologist can reduce dose or stay the course; if there is an unfavorable response, the dose might be escalated or the patient can be moved to another type of therapy. The key is that treatment can be tailored to the individual patient.

Three trends resonate across different sites: 1) treating cancers once considered untreatable; 2) providing new options that enhance quality of life post-treatment by reducing toxicity to healthy tissues and critical structures; and 3) using advanced imaging to personalize treatments based on patient response to treatment and the individual nature of the specific cancer. Even in the same body area, no two cancers are necessarily alike.

Hypofractionation, quantitative imaging, radiomics and more

Real-time imaging and adapting therapy to changes in motion, anatomy and tumor shape/size—these are today's innovations. But what does the future hold?

"There is a clear movement toward hypofractionation," says Corey Lawson, senior director, TomoTherapy Brand Management, Accuray. "Most importantly, it appears that shorter treatment courses can have a positive impact on outcomes for a variety of disease types…there are obvious quality-of-life benefits for patients as well, including reduced travel time and time spent in the treatment room." He also believes

TECHNOLOGY TRENDS

that with shorter treatment courses, hypofractionation can help increase capacity on a radiation therapy system, providing opportunities for centers to use the technology more effectively and efficiently.

"The key to hypofractionation is the ability to deliver dose aggressively to the tumor to achieve better control, without incurring increased toxicities or side effects," Lawson adds.

For Mike Saracen, senior director of marketing at ViewRay, now that MRI is used in conjunction with treatment, the next step is making personalized treatments a reality. "There is an untapped opportunity to leverage MRI technology, whether that is through the use of different sequences, contrast enhancement, or even functional MRI," he says. "I can see a future where, instead of looking at 4 frames per second, it becomes faster, maybe even 12 frames per second. Or instead of slices, the clinician is looking at a whole 3D volume. MRI offers that possibility."

At Elekta, Kevin Brown, global vice president of scientific research, says that the company is also pursuing the integration of high-field MRI with state-of-the-art radiotherapy. "The goal is to sharpen soft-tissue visualization to the extent we can—to maximize dose to the target and minimize the dose to surrounding tissues—and to improve the ability to image moving targets, such as those in the lung."

Brown also believes that quantitative imaging can help oncologists assess the tumor's response during the patient's radiation course. By extracting quantifiable features from medical imaging, such as PET or other functional imaging, oncologists can more precisely assess response based on functional or cellular changes rather than qualitative changes in the tumor shape or size.

Corey Zankowski, Varian Medical System's vice president of product management, envisions the emergence of radiomics, or the extraction of more information from medical imaging for further analysis, as an emerging frontier in image-guided radiation therapy. Looking at the characteristics of a tumor, such as size, shape and texture, as well as complex wavelet transformation, can help stratify patients into categories to help predict treatment response.

"Enabling clinicians to see the texture of the tumor and where it is invading can help characterize aggressiveness of the tumor," Zankowski says. "This can help guide and personalize the treatment, and I think that will drive a lot of what we will be doing in the future."

He also believes that optical monitoring (e.g., multiple cameras in different positions that look at the patient's surface and detect small shifts) will give clinicians added confidence in patient positioning and the delivery of treatment near organs that move.

One thing is certain for Cecile Mohr, PhD, director of global product marketing at Siemens Radiation Oncology, Malvern, Pennsylvania: Multi-modality imaging is becoming more important for devising the treatment strategy. Specifically, the use of advanced imaging, such as MRI and PET, helps significantly in many cases, including stereotactic radiosurgery and stereotactic body radiosurgery. It also further advances therapy planning beyond these specialties. "In brachytherapy, clearly CT and MRI are significantly helping with local control," says Dr. Mohr. "These modalities provide more precision in the treatment homogeneity, and the whole treatment pathway is changing."

Siemens is also exploring PET/MR. "With PET/MR, clinicians can access multi-parametric images and look at the biology of the tumor for planning and treatment response. This is a promising and active area of research," says Dr. Mohr, noting that many questions remain.

With the extent that CT is used today in conjunction with treatment planning, Aenne Guenther, vice presient of Marketing & Sales, Siemens Radiation Oncology, anticipates that dual-energy CT will be utilized in the near future. Dual-energy CT takes images at different energy levels, providing information on tissue composition.

"Dual-energy provides more diverse information from the CT scanner," Guenther explains. "It could potentially improve contrast-to-noise ratio for more reliable contouring, provide patient-specific electron density and atomic number, and improve dose calculations in both proton and brachytherapy procedures."

There is no question that imaging in radiation therapy treatment planning continues to play an essential role. New technologies and techniques are quickly evolving, providing the ability for clinicians to view the organs, structures and tumor in real time for more accurate planning that spares healthy tissue and better targets the disease. Imaging can also help determine the response to treatment earlier in the cycle, so clinicians can better personalize therapy to the individual patient—an inspiring goal in the fight against cancer.

Congratulations to our Clinical Case Contest winner for July 2014!

RADIATION ONCOLOGY CASE

Radiation therapy in a pediatric patient with Gorham Stout syndrome

Joon K. Lee, MS4, Joel L. Grow, MD, and Baldassarre Stea, MD, PhD, FASTRO

CASE SUMMARY

A 14 year-old female presented to the University of Arizona Cancer Center, Tucson, 8 years ago with a pathologic fracture in the right distal femur secondary to a diagnosis of Gorham Stout syndrome (GSS) established since infancy (Figure 1). She was successfully treated with radiation therapy (RT) and had a complete pain response.

She returned to the clinic several months ago with severe pain in the right hip, requiring hospitalization. A magnetic resonance image (MRI) of the pelvis revealed cortical destruction of the anterior aspect of the proximal right femur at the intertrochanteric region secondary to lymphatic malformation consistent with GSS. She was treated with 3-dimensional conformal radiation therapy (3D-CRT) using 15 MV photons to the right femoral head to 3,000 cGy in 200 cGy fractions. The previous radiation fields were reviewed to avoid overlapping treatment fields.

Prepared by Mr. Lee, a fourth year medical student at the University of Illinois-College of Medicine, Rockford, IL; by Dr. Grow, a third-year radiation oncology resident at the University of Arizona, Tucson; and Dr. Stea, professor and chairman of the Department of Radiation Oncology at the University of Arizona, Tucson.

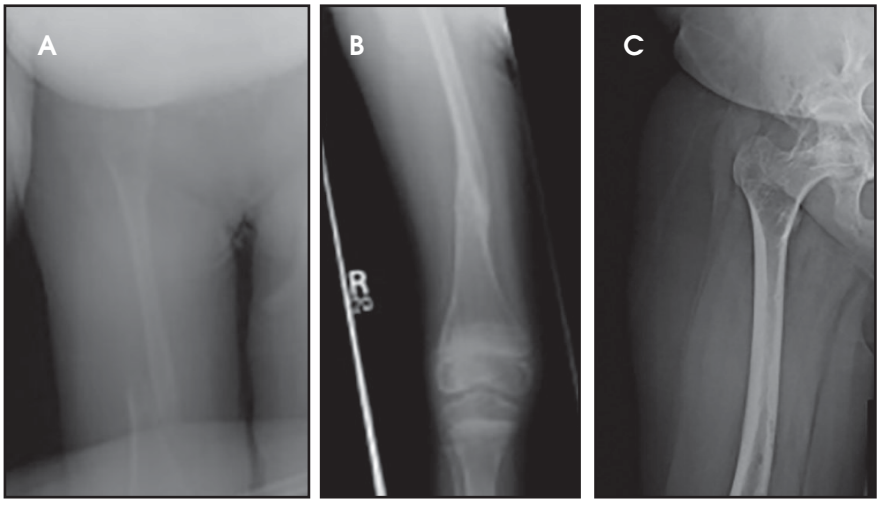


FIGURE 1. *(A) Pathologic fracture of the distal right femur at age 6 secondary to the patient's Gorham Stout syndrome. (B) The same lesion shows abnormal healing 6 months later. (C) Osteolytic lesions in the right femoral head and neck represent new disease. Note that the previous lesion to the distal femur has completely healed.*

The patient had excellent pain response to treatment and continues to be pain free 6 months later without the need for pain medications. Furthermore, she remains pain free in the previously treated distal right femur 8 years after treatment.

IMAGING FINDINGS

At age 6, the patient experienced a pathological fracture of the distal right femur related to her GSS (Figure 1). The lesion was treated successfully

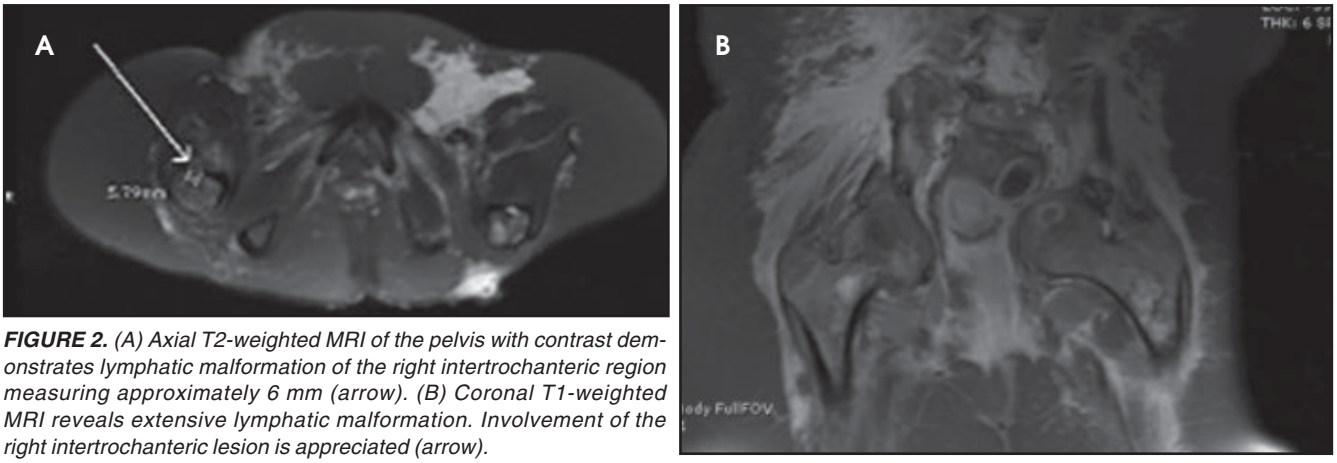


FIGURE 2. *(A) Axial T2-weighted MRI of the pelvis with contrast demonstrates lymphatic malformation of the right intertrochanteric region measuring approximately 6 mm (arrow). (B) Coronal T1-weighted MRI reveals extensive lymphatic malformation. Involvement of the right intertrochanteric lesion is appreciated (arrow).*

with 3,000 cGy in 300 cGy fractions with a complete pain response. A more recent radiograph revealed new osteolytic lesions in the right femoral head and neck.

An MRI of the pelvis demonstrated lymphatic malformation involving the anterior aspect of the right intertrochanteric region measuring approximately 6 mm (Figure 2). There was associated disruption of the cortex and extension of the lymphatic malformation into the adjacent musculature, as well as a small effusion in the right hip joint.

DIAGNOSIS

The patient's presentation and radiographic evidence are consistent with a diagnosis of GSS. The differential diagnosis includes angiosarcoma, osteolytic metastases, juvenile Paget's disease, Langerhans cell histiocytosis, and mastocytosis.

DISCUSSION

Prior to radiation therapy, the patient's right hip lesion was managed with oral and IV pain medications, femoral nerve block, bisphosphonates, calcitonin, and immobilization with a pelvic girdle brace. Despite these efforts, the patient continued to complain of excruciating pain. She ultimately required conscious sedation during her CT simulation. The lesion was identified in the right femoral head and neck, and the images were reviewed and transferred to the Pinnacle planning system (Philips Healthcare, Andover, Massachusetts) for treatment planning.

Treatment with a standard anterior-posterior posterior-anterior (AP PA) field was initially planned. However, the patient's pelvic girdle brace blocked a small portion of the treatment field and an additional right posterior oblique (RPO) field was required. As mentioned, the patient had a pathological fracture secondary to GSS located at the distal right femur 8 years ago. This was successfully treated to 3,000 cGy in 300 cGy fractions. Upon review, it was decided that the patient's current lesion was situated reasonably outside of the old treatment field and could be safely treated.

The patient was treated with 3D-CRT using 15 MV photons to the right femoral head to 3,000 cGy in 200 cGy fractions. The mean dose to the femur and femoral head were 3,074.3 and 3,110.9 cGy, respectively (Figure 3).

It is worth noting that the patient also required conscious sedation for each treatment visit. She could not tolerate being transferred from her hospital bed to the treatment table without anesthesia due to excruciating pain in her right hip. This did not cause any complications with her treatments, and she reported doing well at each on-treatment visit. Her pain began to improve significantly as the treatment dose approached the prescribed dose. She had a complete pain response after 2 weeks of treatment.

The patient completed her radiation therapy to the prescribed dose without interruptions or complications. She denied any adverse radiation effects, including skin erythema and desquamation. Six months after treatment, she reported improved mobility in her right leg, and continues to be pain free, while remaining off of all pain medications. Furthermore, the patient's lesion in the right distal femur remains asymptomatic 8 years following radiation treatment.

GSS is a rare skeletal disorder characterized by unregulated interosseous lymphovascular proliferation leading to progressive bone resorption and/or destruction. It was initially described by Gorham et al[1] in 1954, but its cause remains idiopathic with no evidence of infection, malignancy, or other etiology being described in the literature. Other names used to describe this disease include massive osteolysis, vanishing bone disease and phantom bone disease.[2]

In a recent case series by Hu et al.[3], the mean age at diagnosis was 28 years.

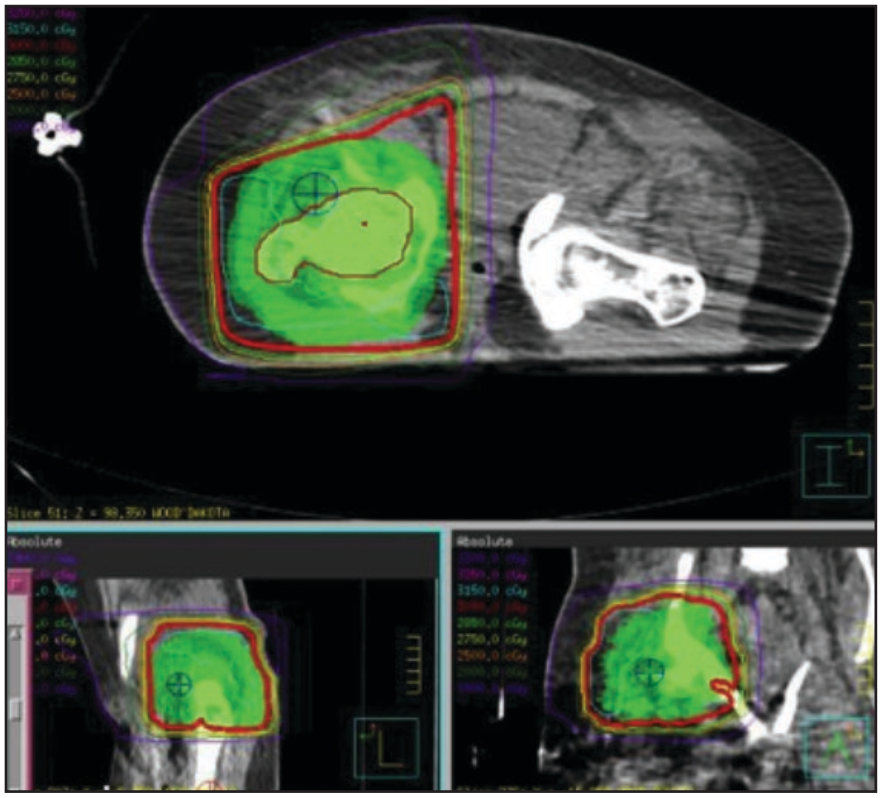


FIGURE 3. *Treatment fields for the right femoral head. The mean dose to the femur and femoral head were 3,074.3 and 3,110.9 cGy, respectively.*

However, the proper diagnosis is often delayed months to years due to the rarity of this condition, and a high index of suspicion is required to arrive at an early diagnosis. Any part of the skeletal system can be involved and the most common sites are the shoulders, skull and pelvic girdle. A handful of cases have been described in the humerus.[4] Most patients present with a progressive dull aching pain and the disease is rarely fatal. Other signs and symptoms include weakness and pathologic fracture.

Treatment options include surgical intervention, bisphosphonates, alpha 2B interferon and radiation therapy. Recently, Nir et al.[5] reported that propranolol may be a therapeutic option for GSS. Hu et al. reported the results of a literature review consisting of 67 patients of GSS treated with different modalities.[3] Surgery alone was the most popular treatment modality, with 27 patients. Only 6 patients were treated with radiation therapy alone, 4 of whom experienced symptom control with a mean follow-up of 14 months. The efficacy of one modality over another was not established in this study due to the limited number of cases.

Heyd et al.[6] reported a retrospective series of 10 patients treated with radiation therapy for the management of GSS and found that 3,000 to 4,500 cGy conferred local control in 8 patients with a median follow-up of 42 months. Radiation was well-tolerated with no patient developing grade 2 or higher toxicity. Four patients developed grade 1 toxicity, including erythema and dysuria.

The mechanism by which radiation therapy controls disease progression and provides pain relief is unknown. We hypothesize that it causes lymphovascular involution similar to the effect of radiation therapy in lymphangiomatous malformations.

CONCLUSION

We report a pediatric patient with a painful intertrochanteric lesion secondary to GSS who responded well to radiation therapy. She had complete pain remission after treatment, and continues to be pain free 6 months after treatment without the need for pain medications. She was previously treated with radiation therapy to the distal femur for a separate lesion, which has remained pain free 8 years after treatment.

The diagnosis of GSS requires a high clinical suspicion, and it should be considered in the differential diagnosis in all children and adolescents presenting with extensive osteolysis. There are limited reports of GSS in the literature with no consensus on standard of care. In our experience, radiation therapy appears to be a well-tolerated and viable therapeutic option for symptomatic patients.

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RADIATION ONCOLOGY CASE

Organ preservation in patients with locally advanced larynx cancer: Important principles and treatment considerations

Rupesh Kotecha MD, Matthew C. Ward MD, Shlomo A. Koyfman MD

CASE SUMMARY

A 63-year-old male with a 20 pack-year smoking history and a hard liquor intake of 12-16 drinks per week presented with a 5-month history of hoarseness and a sore throat. He also had a 1-month history of progressive stridor on exertion. Flexible laryngoscopy revealed a bulky, submucosally infiltrative mass with the epicenter at the right false cord with involvement of the right true cord, the right arytenoid and a fixed larynx. The superior aryepiglottic fold on the right appeared to be spared, as did the epiglottis, but the airway was significantly narrowed.

The patient underwent local and systemic imaging studies, as well as a direct laryngoscopy with biopsy and tracheostomy. Intraoperative findings included significant narrowing of the airway from extensive subglottic extension of the tumor, obliteration of the right false and true cords, and extension of the tumor to the anterior commissure. Biopsy of the right hemilarynx revealed an invasive moderately differentiated squamous cell carcinoma.

Prepared by Dr. Kotecha, Resident Physician, and Dr. Ward, Resident Physician, both at the Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH; and Dr. Koyfman, Associate Staff, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH.

IMAGING FINDINGS

Computed tomography (CT) of the neck revealed fullness in the right true vocal fold extending across the anterior commissure, with obliteration of periglottic fat plane, and asymmetric sclerosis and lytic change in the thyroid lamina (Figure 1). There was asymmetric sclerosis of the right arytenoid cartilage and mild asymmetric fullness of the strap muscles overlying the larynx on the right concerning for extralaryngeal spread. There was no obvious radiographic evidence for gross subglottic extension, and the subglottic airway was patent. There was no bulky adenopathy in the neck.

A positron emission tomography/CT (PET/CT) scan revealed a 3.5 x 3.0-cm soft tissue thickening of the right vocal cord with moderately increased fluorodeoxyglucose (FDG) uptake (Max SUV 16) consistent with neoplasm (Figure 2A). The tumor crossed midline and extended across the anterior commissure, obliterating the periglottic fat plane. It encased and eroded the right thyroid lamina. There was a 1.7 x 0.8-cm mildly FDG avid lymph node in the right level IIa (Max SUV 3.7) (Figure 2B).

DIAGNOSIS

Stage IVA T4aN1M0 locally advanced squamous cell carcinoma of the larynx.

DISCUSSION

Prior to the publication of the Veterans Affairs (VA) Laryngeal Cancer Study, the standard treatment for patients with locally advanced laryngeal cancer consisted of a total laryngectomy with postoperative radiation therapy recommended for patients with certain high-risk pathological features. The results of the VA study demonstrated that a strategy of induction chemotherapy followed

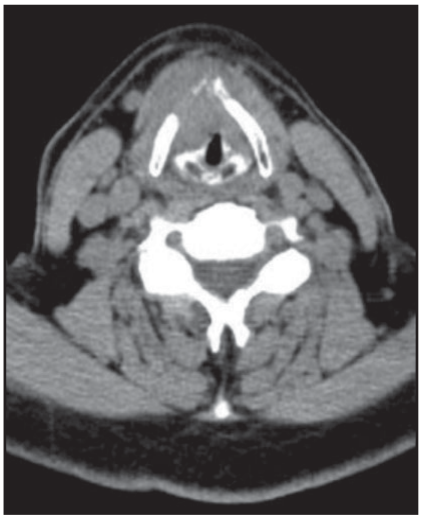

FIGURE 1. *Axial CT image demonstrating thickening of the right true vocal fold and adjacent changes in the right arytenoid cartilage and thyroid lamina, as well as mild prominence of the extra-laryngeal strap musculature on the right.*

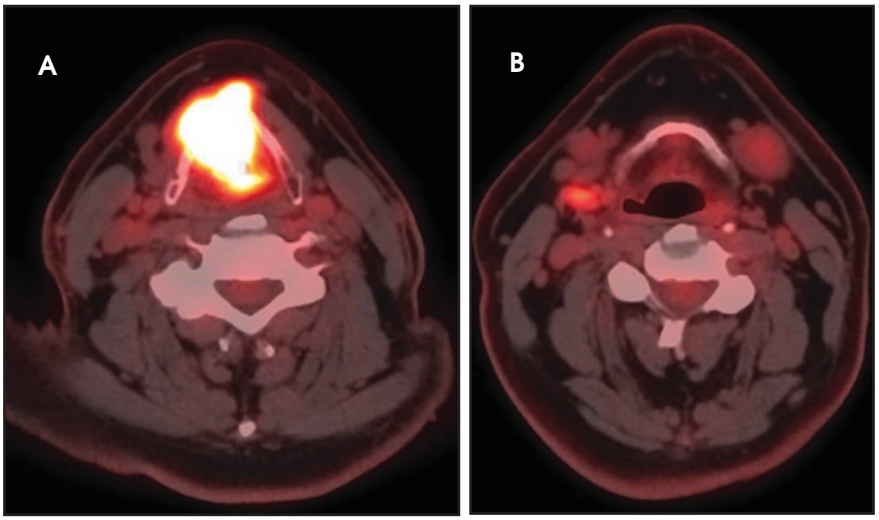

FIGURE 2. *Axial PET/CT images demonstrating a 3.5-cm laryngeal neoplasm centered in the right vocal cord but crossing the midline (A), and a right level IIa mildly FDG avid lymph node, suspicious for metastasis (B).*

by definitive radiation therapy was an effective approach for larynx preservation without compromising a patient's overall survival compared to total laryngectomy. Despite these promising general results, 56% of patients with T4 cancers required salvage laryngectomy, compared to 26% of patients with smaller primary tumors, p=0.001.[1]

Consequently, patients with high-volume T4 primaries (invasion > 1 cm into the base of tongue or penetration through cartilage) were excluded in the subsequent RTOG 91-11 trial evaluating the benefit of concurrent chemoradiotherapy compared to induction chemotherapy followed by definitive radiotherapy or definitive radiation therapy alone.[2] Since the publication of the VA Larynx Study and RTOG 91-11, the inclusion of this cohort of patients into randomized studies investigating voice-preserving treatment alternatives has been limited.

In addition to the requirement of a permanent tracheostomy and the morbidity of the surgical procedure, total laryngectomy is also associated with a significant detriment to a patient's vocal communication, reducing quality of life.[3] Moreover, in a survey of volunteers given the treatment option of either total laryngectomy or a laryngeal preservation protocol using chemotherapy and radiotherapy, only 24.6% of patients rated survival their main consideration (versus quality of life) if faced with advanced-stage laryngeal cancer.[4] This philosophy has led to a reduction in laryngectomies in the United States by 48% over the past 10 years.[5]

For patients with T4 larynx cancer who decline surgery, the National Comprehensive Cancer Network guidelines recommend concurrent chemoradiotherapy, induction chemotherapy followed by response assessment, or enrollment in a clinical trial.[6] Multiple institutional experiences have demonstrated modest outcomes in patients with T4 primary cancers treated with larynx-preserving approaches (Table 1).[7-15] Even in these series, however, patients with thyroid cartilage invasion are underrepresented. A review of 25 patients with thyroid or cricoid cartilage invasion treated with chemoradiotherapy demonstrated that patients with cartilage invasion involving both cortices had an inferior local control compared to patients with no or minor cartilage invasion (2-year rate: 55% versus 81%, p<0.05), but no significant reduction in survival with a functional larynx or overall survival.[16]

When using CT imaging to determine the optimal patient management approach for patients with advanced larynx cancer, it is also important to understand the limitations of imaging accuracy in detecting thyroid cartilage penetration or extralaryngeal spread. For example, in one series of 107 laryngectomy specimens, CT imaging identified 59% and 49% of cases of pathologically documented thyroid cartilage penetration and extralaryngeal spread, respectively, with corresponding positive predictive values of 74% and 81%.[17]

At our institution, only select patients who are healthy enough to tolerate combined modality treatment, compliant enough for close follow-up,

Table 1. Selected institutional studies of organ preservation for T4 locally advanced laryngeal carcinomas.

Series author	Year	N (% node +)	Treatment	Median FUP (m)	LC	LRC	LP	LFS	% salvage laryngectomy	Successful salvage	DSS	OS
Harwood[7]	1981	56 (0%)	RT alone	—	56%	—	—	71%	—	—	—	64%
Haugen[8]	2005	32 (21.9%	RT (84%) or Chemo RT (16%)	15.3	75%	75%	—	—	9%	67%	—	39%
Nishimura[9]	2007	8 (62.5%)	Chemo RT	44.8	50%	—	55%	—	—	—	71%	—
Hinerman[10]	2007	22 (22.7%)	RT alone	68.4	82%	78%	—	—	18%	25%	87%	67%
Worden[11]	2009	36 (52.8%)	ChemoRT	69.0	—	—	73%	58%	—	100%	—	78%
Patel[12]	2010	21 (62%)	ChemoRT	12.0	71%	—	—	—	—	—	—	—
Stenson[13]	2011	80 (36%)	ChemoRT	49.2	—	—	88%	—	—	—	71%	49%
Mucha-Malaka[14]	2013	114 (52%)	RT alone	—	42%*	—	—	—	20%*	—	—	40%*
Karatzanis[15]	2014	28 (51%)	ChemoRT	56.4	95%	—	—	—	—	—	29%	23%
Kotecha et al	*2014*	*15 (80%)*	*ChemoRT*	*42.4*	*92%**	*92%**	*100%**	—	*0%**	—	—	*70%**

Abbreviations: FUP = follow-up period, LC = local control, LRC = locoregional control, LP = larynx preservation, LFS = laryngectomy-free survival, DSS = disease-specific survival, OS = overall survival. 5-year outcomes are reported, except when indicated with an *, which represents 3-year outcomes.

and motivated enough for larynx preservation are treated with concurrent chemoradiotherapy. Upon review of an institutional review board (IRB)-approved tumor registry, 15 patients with T4 disease were treated at the Cleveland Clinic from 1993-2011 with combined chemoradiotherapy. For this cohort, the local control, locoregional control, and larynx preservation rates have been 92%, 92% and 100%, respectively at 3 years (Table 1). Note, however, that one patient with a local failure was recommended to undergo laryngectomy and declined, putting the recommended larynx preservation rate at 92% as well (95% CI 77.8%-100%). While it remains uncommon for our institution to treat these patients with a non-surgical approach, these results demonstrate favorable outcomes in a carefully selected subset of patients.

Evaluation of the response to induction chemotherapy is one proposed method to better select patients with locally advanced larynx cancer for organ preservation. For example, Urba and colleagues reported a favorable larynx preservation rate of 70%, and a 3-year overall survival rate of 85%, in a population of patients selected for larynx preservation based on >50% response to induction cisplatin and fluorouracil.[18] This, however, may not be the optimal method to appropriately select patients. In the Radiation Therapy Oncology Group (RTOG) 91-11 trial, of the 11 patients who had less than a partial response to induction chemotherapy but continued with additional chemotherapy or radiation therapy, all 11 had a complete response, and only one patient eventually required a laryngectomy.[19] Therefore, it is important to note that the response to chemotherapy alone does not always correlate with a patient's response to concurrent chemoradiotherapy.

When embarking on a larynx-preservation approach in patients with locally advanced primary cancers, it is important to evaluate the need for a tracheostomy before therapy (and its coverage during treatment planning), design nodal volumes to include the at-risk nodal drainage pathways during target delineation, make use of an adaptive re-plan to reduce the treatment volume as the tumor volume shrinks, and follow the patient closely after therapy completion. One should also consider pre-treatment placement of a tracheostomy in patients with bulky tumors causing a narrowed airway that could become occluded by radiation-induced edema. For routine intensity-modulated radiation therapy (IMRT) treatment planning, the bilateral cervical nodal levels II-IV are included in all patients with supraglottic primaries or stage III/IV glottic primaries (Figure 3).[20]

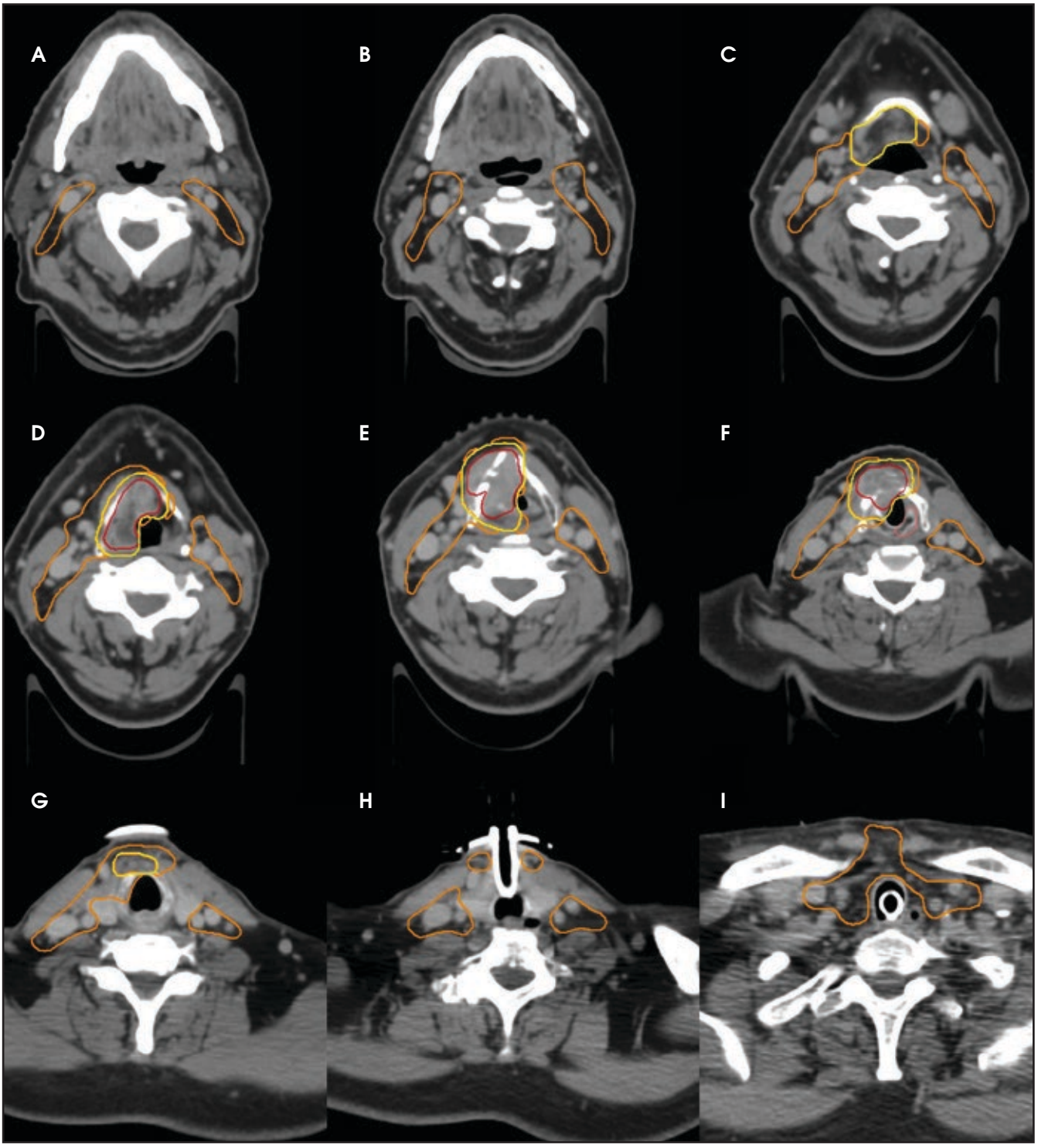

FIGURE 3. *Axial CT treatment planning images of the GTV70 (red), CTV70 (yellow), and CTV56 (orange) are shown for a patient with locally advanced larynx cancer. Outlined in pink is a larynx avoidance structure used for IMRT planning to reduce the dose to the contralateral side (F). In addition to levels II-IV bilaterally, level VI was also included in the CTV56 volume (I), given the anterior disease extent. The GTV70 to CTV70 expansion was 3 mm, and the PTV expansion was 2.5 mm. The patient was treated with daily cone-beam computed tomography (CBCT) IGRT. Please note these are representative slices and not all slices are included.*

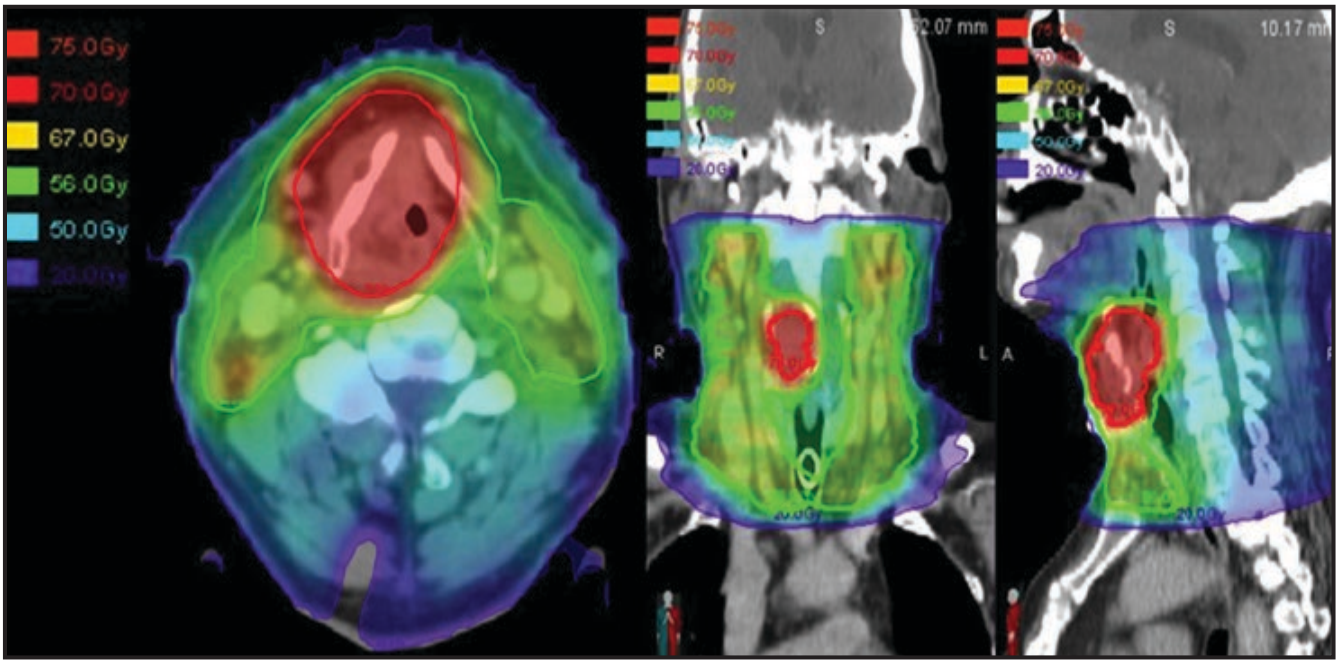

FIGURE 4. *Axial, coronal and sagittal CT images with an overlying dose-grid demonstrate the treatment plan used for this patient. The red outline represents the 70 Gy isodose line, and the green outline represents the 56 Gy isodose line. Other dose levels are indicated on the color legend.*

For patients with more advanced local disease, especially with anterior extension of disease through the cartilage or subglottic extension, the level VI nodes should also be included (Figure 3I). As defined in the 2013 update of the consensus guidelines, adequate coverage of the level VI nodes includes the anterior jugular, pre-laryngeal, pre-tracheal and paratracheal (recurrent laryngeal nerve) nodes, as well as the deep previsceral space.[21] Thus, the level VI contour volume should extend from the caudal edge of the hyoid bone to the cranial edge of the sternal manubrium, limited anteriorly by the platysma and posteriorly by the anterior surface of the infrahyoid muscles. Adaptive radiotherapy has been proposed as a method of decreasing late toxicity and possibly preventing a geographical miss in patients who experience significant tumor shrinkage or weight loss during therapy. While the dosimetric benefit of adaptive re-planning is clear, whether this dosimetric benefit correlates to improved control and reduced toxicity remains to be demonstrated.[22-23]

Finally, in bulky T4 patients who decline laryngectomy, the importance of close follow-up with laryngoscopy cannot be overstated. The randomized data showed no survival benefit to laryngectomy, but this depends on effective salvage, which may be compromised if the patient is lost to follow-up.

To recapitulate, the patient in this report was diagnosed with a Stage IVA (T4 secondary to thyroid cartilage penetration) locally advanced laryngeal cancer. He declined surgery and was enrolled onto the RTOG 35-01 randomized trial (a phase II randomized study investigating the use of lapatinib, a tyrosine kinase inhibitor with dual action against Her-2/neu and EGFR pathways, in conjunction with standard chemoradiotherapy) and underwent concurrent chemoradiotherapy to a total dose of 70 Gy in 35 fractions, accelerated over 6 weeks, using 6 MV photons via 9-field IMRT (Figure 4). He received 44 Gy in 22 fractions with an initial IMRT plan, and the remainder 26 Gy was delivered using an adaptive re-plan due to significant tumor response as observed on flexible laryngoscopy during his OTR visit. He received two cycles of bolus cisplatin (100 mg/m^2) and was also randomized to receive Lapatinib. He tolerated the treatment well with (CTCAE criteria v4.0) grade 1 dysphagia, mucositis, xerostomia, and taste changes. He experienced grade 2 fatigue, nausea, vomiting, and weight loss. He had a grade 3 voice change (whispered speech) upon therapy completion.

CONCLUSION

A total laryngectomy followed by adjuvant radiation therapy remains the conventional treatment for patients with locally advanced laryngeal cancer, especially in those with extension of disease through the thyroid cartilage. For select motivated patients who desire organ preservation, this

approach can lead to modest local control without sacrificing the chance of long-term survival. Important principles in selecting these patients for a non-surgical approach include assessment for the need for upfront tracheostomy, ability to tolerate concurrent chemotherapy, and reliability for close follow-up. To optimize radiotherapy management, accurate target volume delineation should include coverage of the gross tumor volume and adequate coverage of the at-risk lymph node levels.

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