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Compliance with Therapeutic Guidelines in Radiation Therapy Oncology Group Prospective Gastrointestinal Clinical Trials

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Abstract

Background—This report analyzes the adherence to radiation therapy protocol guidelines in contemporary Radiation Therapy Oncology Group (RTOG) gastrointestinal trials. We aim to provide insight into current standards and compliance of radiation therapy field design and administration.

Methods—From 1994 to 2006, the Gastrointestinal Cancer Committee of the RTOG initiated and completed 15 phase I-III clinical trials utilizing radiation therapy in the multimodality treatment of gastrointestinal cancers. In each protocol, details for planning and executing radiation therapy were outlined and each protocol contained scoring criteria for these components of radiation therapy, characterized according to per-protocol, variation acceptable and deviation

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unacceptable. Review of treatment planning and implementation was performed in all studies following therapy completion.

Results—Radiation therapy planning and implementation was reviewed in 2,309 of 2,312 (99.9%) patients. The mean rate of compliance over all for the 15 protocols was 65% (total of the 2,309 analyzed patients). The mean variation acceptable rate was 21% whereas the mean deviation unacceptable rate was 5%. The mean “other” rate (no RT given or incomplete RT due to death, progression or refusal) was 8%. Two of the 15 trials (13%) had deviation unacceptable rates > 10%. In four studies incorporating pre-treatment review of radiation therapy planning and treatment, compliance with protocol therapy was enhanced.

Conclusion—The fidelity of radiation planning and execution detailed in protocol to actual therapy is heterogeneous, with a mean per-protocol rate of 65%. As clinical trials evolve, available technology should permit efficient pre-treatment review processes, thus facilitating compliance to protocol therapy. These analyses should also permit prospective analysis of outcome measures by compliance to therapy.

Background

A key factor in the successful outcomes of oncology patients is the quality of therapeutic intervention. In radiation therapy, critical elements in optimizing outcomes include accurate definition of target and normal tissues, radiation field design, technique, dose and proper execution of prescribed treatments. Increasing data is becoming available evaluating the technical quality and administration of radiation therapy which should facilitate objective assessment of practice standards and better define this factor to unsuccessful therapeutic outcomes (1-9).

The National Cancer Institute (NCI)-sponsored cooperative group trials employing radiation therapy provide a unique resource of information by assessing the quality and fidelity of radiation therapy. Specifically, there is strict adherence to protocol guidelines of radiation therapy through evaluation of multiple factors including individual field design, dose, technique, and administration. With increasing integration of radiation therapy in the multimodality management of cancer patients, there is imperative to define the quality measures that are associated with improved patient outcomes. This is especially critical because radiation therapy has become progressively sophisticated, potentially including intensity-modulated radiation therapy, radiosurgery, cranial and extra-cranial stereotactic radiation therapy, image guidance, and particle therapy.

The current report analyzes the adherence to radiation therapy protocol guidelines in recent Radiation Therapy Oncology Group (RTOG) gastrointestinal cancer trials to provide insight into current standards and compliance of radiation therapy field design and administration.

Methods

From 1994 to 2006, the Gastrointestinal Cancer Committee of the RTOG initiated and completed 15 phase I, II or III clinical trials utilizing radiation therapy in the multimodality treatment of gastrointestinal cancers (15-30). In each protocol, details for planning and executing radiation therapy were described in detail, including simulation, use of simulation

films and port film verification, clinical target volume definition, critical normal organ identification, time-dose fraction schemes, acceptable and unacceptable treatment interruptions, treatment beam energy, field arrangement, initial and supplemental field design parameters, criteria for shielding normal organs and tissues, requirements for dosimetric planning, and range of acceptable dose heterogeneity. Each protocol provided criteria for scoring these various components of radiation therapy as per-protocol, variation acceptable and deviation unacceptable (www.rtog.org). In brief, the per protocol prescription is used to encourage institutions to devise treatment plans that are as tight as possible in terms of dose conformality for PTV coverage. The variation acceptable compliance criterion is given to allow leeway for more difficult planning situations. In each protocol, the variation acceptable dose limits should be identified as being less desirable but allowed in situations where per protocol limits could not be met. It is important to point out that the variation acceptable should not be used for misinterpreting the statement of the prescription. If an institution applies the prescription incorrectly, a third category deviation unacceptable is used. This approach provides a mechanism for stating the prescription exactly without variation. Review of treatment planning and its execution were performed in all studies following completion of therapy by the principal investigator or co-investigators in collaboration with the dosimetry/physics group of RTOG.

During the time period of these studies, treatment planning became increasingly complex, evolving from two-dimensional techniques (relying primarily on bony anatomy on orthogonal films) to CT-based three-dimensional conformational techniques, and more recently, to intensity-modulated radiation therapy (IMRT) techniques. For all 15 trials, the radiation planning and dosimetry data were reviewed and scored after all treatment was completed. Because of application of radiation therapy in new disease settings such as gastric cancer or implementation of new techniques, four studies incorporated a prospective review of treatment planning prior to initiation of therapy (RTOG 0114, RTOG 0438, RTOG 0529, and RTOG 0822). In these studies, images and treatment planning details were prospectively reviewed and feedback provided to the treating radiation oncologists prior to initiation of therapy. In the IMRT studies (RTOG 0529 and RTOG 0822), institutional credentialing of IMRT was also required before patient registration. One trial (RTOG 9704) requested pre-treatment imaging and treatment planning information for prospective review. However, this was generally not performed because materials required for review did not arrive within the time frame of scheduled therapy.

Results

Review of radiation therapy planning and its implementation was carried out for 2,309 of 2,312 (99.9%) eligible patients for 15 phase I to III RTOG gastrointestinal cancer protocols (Table 1). Overall, the mean per-protocol rate of the 2,309 analyzed patients was 65%. The mean variation acceptable and deviation unacceptable rates were 21% and 5%, respectively. The mean “other” rate (no RT given or incomplete RT due to death, progression or refusal) was 8%. Across the 15 protocols, the per-protocol rate ranged from 37% to 88%, the variation acceptable rate ranged from 0% to 39%, and the deviation unacceptable rate varied from 0% to 42%. Two of the 15 (13%) trials had deviation unacceptable rates > 10%. In

malignancies for which the RTOG has conducted numerous studies, such as esophageal and pancreatic cancer, the deviation unacceptable rates were usually 5%.

Four trials (RTOG 0114, RTOG 0438, RTOG 0529 and RTOG 0822) included a preliminary review of radiation field design prior to initiation of therapy. In contrast to an earlier gastric trial (RTOG 9904) where the deviation unacceptable rate was 42%, this figure was 2% and 4% in RTOG 0114 (Table 1). In a study evaluating radiation dose escalation and hypofractionation using highly conformal radiation therapy in the treatment of hepatic metastases (RTOG 0438), the per-protocol rate was 87% (Table 1). In a trial assessing the feasibility of intensity modulated radiation therapy in anal cancer (RTOG 0529) 81% of 52 patients required revisions prior to treatment on initial submission and 46% required multiple resubmissions. Ultimately, there was a 6% deviation unacceptable rate in PTV small bowel scores in this trial and 0% in nodal scores. An 85% per-protocol rate was observed in another trial employing IMRT in the neoadjuvant treatment of rectal cancer patients (RTOG 0822).

On review of the three phase III trials (RTOG 9405, RTOG 9704, and RTOG 9811) and the most recent IMRT trial in anal cancer (RTOG 0529), unacceptable deviations were usually attributed to incorrect gross target volume (GTV) contouring or incorrect field design. Unacceptable deviations in dose or fractionation were uncommon.

Discussion

The results of this analysis demonstrate that a centralized review of radiation therapy techniques is feasible in multimodality gastrointestinal cancer cooperative group clinical trials. The fidelity of described protocol treatment to actual therapy is heterogeneous, with a mean per-protocol compliance rate of 65%. Two of 15 trials (13%) had deviation unacceptable rates > 10% (detailed above).

Not only did the sophistication and multimodality character of the clinical trials evolve over the time period of this study but the treatment planning and administration of radiation therapy became increasingly complex as well. Early clinical trials were based on simple and reproducible 2-D treatment planning techniques and orthogonal x-rays. With time, radiation therapy planning utilized CT-based three-dimensional conformal techniques and more recent trials have employed IMRT methods. Without confidence that the actual radiation therapy planning and delivery is accurate and successfully implemented, results of contemporary and future studies will be potentially skewed. Thus, it is imperative that measures are taken to facilitate the accurate translation of protocol therapy into daily clinical practice.

First, clinical trials need to be written clearly, simply and succinctly to ensure understanding of complex treatments and techniques by caregivers with diverse background of treatment familiarity and sophistication.

As the data from this study has demonstrated, another method to maximize compliance to protocol therapy is pre-treatment review. In this analysis, the 4 studies including pre-treatment review had high levels of compliance. This finding is consistent with the results of Intergroup study 0116, an adjuvant trial for gastric cancer, where modification of pre-

treatment radiation therapy fields enhanced compliance to protocol therapy (29). For many ongoing and future studies, the RTOG has introduced the use of a rapid and efficient prospective method of review via the RTOG Head Quarter's Radiation Therapy Quality Assurance, Image-Guided Therapy Quality Assurance Center (ITC) and the Radiological Physics Center (RPC) (www.rtog.org).

Other steps that would be expected to facilitate treatment compliance include enhanced education of residents and other post-graduates, standardized atlases of critical radiologic anatomy tailored for radiation therapy and case examples. Some first reports recently demonstrated the benefit of using guidelines for target volume delineation in decreasing inter-observer variability, especially in breast cancer (10). One limitation of the current analysis is that it does not provide information on important clinical outcomes (e.g. toxicity or efficacy). It is reasonable to assume that non-compliant therapy results in poorer outcomes; however, there is scant evidence to support this relationship (1-9). In a secondary analysis of patients with advanced head and neck cancer treated in a large international phase III trial evaluating radiation therapy with concurrent cis-platin plus tirapazamine, radiation therapy quality was critically important on outcome of these patients (8). In head and neck patients who received at least 60 Gy, those with major deficiencies in their treatment plans (n = 87) had a markedly inferior outcome compared with those whose treatment was initially protocol compliant (n = 502): -2 years overall survival, 50% v 70%; hazard ratio (HR), 1.99; P < .001; and 2 years freedom from locoregional failure, 54% v 78%; HR, 2.37; P < .001, respectively. In gastrointestinal cancer, a recent analysis supports the notion that protocol compliance is associated with treatment outcomes. A secondary analysis of RTOG 9704 (a phase III trial adjuvant trial evaluating maintenance 5-fluorouracil or gemcitabine in resected pancreatic cancer patients receiving chemoradiation) demonstrated an effect of protocol compliance on patient outcomes (31). Specifically, the median survival for resected patients receiving postoperative chemoradiation per-protocol was 1.74 years versus 1.46 years (p=0.008) for patients treated with chemoradiation with variation acceptable or deviations unacceptable. In a multivariate analysis of factors of 359 patients with pancreatic head cancer correlating with survival, treatment arm, nodal status, and radiation therapy quality assurance (per-protocol versus variation acceptable and deviation unacceptable) were all found to be significant factors (Table 2). It is important to recognize that this is a secondary analysis and thus by definition is hypothesis-generating.

The heterogeneity of protocol compliance observed in this analysis is concerning. To enhance compliance, the EORTC compared the influence of a “dummy run” performed before the start of a trial with “the individual case review” done during the course of the trial in a breast cancer trial as well as the comparison between two “individual case reviews”, one done early and late of another breast trial (2,4). Both showed an improvement of the quality assurance measurements over time likely due to the quality assurance measures undertaken.

Not unexpectedly, the protocols in the current study with the highest compliance rates included a pre-treatment review process. Presently available technology should aid in efficient processes of pre-treatment review, thus facilitating compliance to protocol specific therapy as well as permit formal analyses of protocol compliance to treatment-related outcomes, including toxicity and disease-related outcomes.

However, although pre-treatment review can improve protocol compliance, it has not been demonstrated that this is the best way to achieve this result. Pre-treatment review is labor-intensive and the suggestion given above to first investigate methods for improving the clarity of the instructions contained in the protocol might also improve compliance. Another approach used for some RTOG protocols tries to reduce the overall case review effort with a two-step approach that uses a combination of pre-treatment review for a limited number of the initial patients registered by each institution and the timely review of all other patients. This approach can be used to amend, if necessary, the protocol based on lessons learned from the review process. The advantage of this approach is the development of a final protocol that is more universally applicable as it is implemented by a broad range of institutions around the world.

Conclusions

In gastrointestinal cancer clinical trials, the fidelity of radiation planning and implementation detailed in the protocol to actual therapy is heterogeneous, with a mean per-protocol rate of 65%. The mean variation acceptable and deviation unacceptable rates were 21% and 5%, respectively. Two of 15 trials (13%) demonstrated deviation unacceptable rates > 10%. As clinical trials evolve, available technology should aid efficient pre-treatment review processes, thus facilitating compliance to protocol specific therapy. These analyses should also permit prospective and timely analysis of outcome measures by compliance to therapy.

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Table 1

Radiation Therapy Compliance

Disease Site	RTOG Trial(reference #)	Study Design	Pt. #	Cases Reviewed #	Per-Protocol (%)	Variation Acceptable (%)	Deviation Unacceptable (%)	Other † (%)
Esophageal Trials	9405 (15)	Phase III Trial of Combined Modality Therapy for Esophageal Cancer: High-Dose (A) vs. Standard-Dose RT (B)	218	A: 109 B: 108	A: 61 B: 79	A: 11 B: 8	A: 4 B: 5	A: 24 B: 8
	0113 (16)	Phase II Randomized Trial of Two Nonoperative Regimens (A, B) of Induction Chemo Followed by ChemoRT with Localized Carcinoma of the Esophagus	76	A: 39 B: 37	A: 46 B: 70	A: 35 B: 11	A: 3 B: 0	A: 15 B: 19
	0246 (17)	Phase II Study of a Paclitaxel-Based ChemoRT Regimen With Selective Surgical Salvage for Resectable Locoregionally Advanced Esophageal Cancer	41	39	87	0	0	13
Gastric Trials	9904 (18)	Phase II Trial of Preoperative ChemoRT in Patients with Localized Gastric Adenocarcinoma	43	43	37	7	42	14
	0114# (19)	Randomized Phase II Trial Evaluating Two Paclitaxel and Cisplatin-Containing	73	A: 28 B: 45	A: 64 B: 53	A: 11 B: 11	A: 4 B: 2	A: 21 B: 33

Disease Site	RTOG Trial(reference #)	Study Design	Pt. #	Cases Reviewed #	Per-Protocol (%)	Variation Acceptable (%)	Deviation Unacceptable (%)	Other [†] (%)
		ChemoRT Regimens (A, B) as Adjuvant Therapy in Resected Gastric Cancer ChemoRT Regimens (A, B) as Adjuvant Therapy in Resected Gastric Cancer ChemoRT Regimens (A, B) as Adjuvant Therapy in Resected Gastric Cancer ChemoRT Regimens (A, B) as Adjuvant Therapy in Resected Gastric Cancer ChemoRT Regimens (A, B) as Adjuvant Therapy in Resected Gastric Cancer						
Liver Trial	0438# (20)	Phase I Study of Tightly Conformal RT for Liver Metastases	23	23	87 [†]	13	0	0
	9704 (21)	Phase III Study of Pre and Post ChemoRT 5-FU (A) vs. Pre and Post ChemoRT Gemcitabine (B) for Postoperative Adjuvant Treatment of Resected Pancreatic Adenocarcinoma	451	A: 230 B: 221	A: 51 B: 45	A: 36 B: 43	A: 5 B: 5	A: 8 B: 7
Pancreas Trials	9812 (22)	Phase II Trial of External RT (50.4 Gy) and Weekly Paclitaxel (Taxol) for Non-Metastatic, Unresectable Pancreatic Cancer	109	109	88	5	2	6
	0020 (23)	Randomized Phase II Trial of Weekly Gemcitabine, Paclitaxel and External RT (50.4 Gy) Followed by the Farnesyl Transferase Inhibitor R115777(A, B) (NSC #702818) for Locally Advanced Pancreatic Cancer	185	A: 91 B: 94	A: 60 B: 57	A: 33 B: 30	A: 0 B: 3	A: 7 B: 10

Disease Site	RTOG Trial(reference #)	Study Design	Pt. #	Cases Reviewed #	Per-Protocol (%)	Variation Acceptable (%)	Deviation Unacceptable (%)	Other [†] (%)
	0411 (24)	Phase II Study of Bevacizumab with Concurrent Capecitabine and RT Followed by Maintenance Gemcitabine and Bevacizumab for Locally Advanced Pancreatic Cancer	82	82	73	7	13	6
	0012 (25)	Randomized Phase II Trial of Preoperative Combined Modality ChemoRT (A, B) for Distal Rectal Cancer	103	A:50 B:53	A: 72 B: 77	A:16 B: 21	A: 4 B: 2	A: 8 B: 0
Rectal Cancer Trials	0247 (26)	Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy (A, B) for Locally Advanced Rectal Cancer	139	A: 70 B: 69	A: 70 B: 67	A: 17 B: 26	A: 1 B: 1	A: 11 B: 6
	0822# (27)	Phase II Evaluation of Preoperative ChemoRT utilizing IMRT in Combination with Capecitabine and Oxaliplatin for Patients with Locally Advanced Rectal Cancer	68	68	85	7	7	0
Anal Cancer Trials	9811 (28)	Phase III Trial of Fluorouracil, Mitomycin and RT (A) vs. Fluorouracil, Cisplatin and RT(B) for	649	A: 325 B: 324	A: 68 B: 69	A: 22 B: 18	A: 6 B: 8	A: 3 B: 6

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Disease Site	RTOG Trial(reference #)	Study Design	Pt. #	Cases Reviewed #	Per-Protocol (%)	Variation Acceptable (%)	Deviation Unacceptable (%)	Other [†] (%)
		Carcinoma of the Anal Canal						
	0529# (29)	Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal	52	52	85*	13	0	2
		TOTAL	2312	2309	65	21	5	8

Abbreviations: RT, radiation therapy; chemo, chemotherapy; chemoRT, chemoradiation; IMRT, Intensity Modulated Radiation Therapy.

[†] Other - no RT given or incomplete RT; death, progression or refusal

[‡] Tumor volume contouring score

* Planning Target Volume (PTV) anal score

: Trials undergoing pre-treatment review

Table 2
Multivariate analysis for overall survival: head of pancreas patients only (n = 359) (31)

Adjustment Variables	Comparison	Adjusted HR	p-value [‡]
Treatment	Gemcitabine vs. 5-FU	0.79 (0.62-0.99)	0.043
Nodal Involvement	No vs. Yes	1.47 (1.13-1.91)	0.0036
Tumor Diameter	<3 vs. 3cm	1.25 (0.98-1.59)	0.070
Surgical Margin Status	Negative	Ref level	--
	Positive	1.07 (0.82-1.40)	0.64
	Unknown	0.94 (0.69-1.27)	0.68
RT QA Score	< PP vs. PP	0.75 (0.60-0.95)	0.016

Abbreviations: 5-FU = fluorouracil; HR = hazard ratio; CI = confidence interval.

[‡] p value from chi-square test using the Cox proportional hazards model.