Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2018 November 15; 102(4): 775–782. doi:10.1016/j.ijrobp.2018.08.039.

The Importance of Imaging in Radiation Oncology for National Clinical Trials Network Protocols

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Conflict of Interest Statements

Ms. Bishop-Jodoin has nothing to disclose.

Dr. Laurie has nothing to disclose.

Ms. O'Meara has nothing to disclose.

Ms. Davis has nothing to disclose.

Dr. Bogart has nothing to disclose.

Dr. Kalapurakal has nothing to disclose.

Dr. Siegel has nothing to disclose.

Dr. Chakravarthy has nothing to disclose.

Dr. Okunieff has nothing to disclose.

Dr. Haffty has nothing to disclose.

Dr. Michalski has nothing to disclose.

Dr. Ulin has nothing to disclose.

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Dr. Rosen has nothing to disclose.

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Abstract

Imaging is essential in successfully executing radiation therapy (RT) in oncology clinical trials. As technically-sophisticated diagnostic imaging and RT incorporated into trials, quality assurance (QA) within the National Clinical Trials Network groups entered a new era promoting image acquisition and review. Most trials involving RT require pre and post-therapy imaging for target validation and outcome assessment. The increasing real-time (pre/during therapy) imaging and RT object reviews are to ensure compliance with trial objectives. Objects easily transmit digitally for review from anywhere in the world. Physician interpretation of imaging and image application to RT treatment plans are essential for optimal trial execution. Imaging and RT datasets are used to credential RT sites to confirm investigator/institutional ability to meet trial target volume delineation/delivery requirements. Real-time imaging and RT object reviews can be performed multiple times during a trial to assess response to therapy and application of RT objects. This

process has matured into an effective data management mechanism. When necessary, site and study investigators review objects together through web media technologies to ensure the patient is enrolled on the appropriate trial and the intended RT is planned/executed in a trial-compliant manner. Real-time imaging review ensures the patient is 1) entered and eligible for the trial, 2) meets trial-specific adaptive therapy requirements, if applicable and 3) the intended RT is according to trial guidelines. This ensures the study population is uniform and the results are believable and can be applied to clinical practice.

Introduction

In the first generation of cooperative group clinical trials involving radiation therapy (RT), institution-specific approaches using varied computational RT planning algorithms generated inter-institutional discrepancies in dose computation. This created challenges for interpreting radiation dose and relating dose delivered on study to patient outcome. Radiation volumes and fields were defined by anatomical guidelines as imaging tools for target definition were less advanced and hard copy imaging was reviewed centrally in retrospect after study closure due to the extended process involved in data copy and transfer to quality assurance (QA) offices. Computational issues, accelerator output consistency, beam symmetry, machine calibration, and constancy of dose validation were considered the primary essential components to the RT QA program in the initial clinical trials with RT. These elements remain invaluable today for the National Clinical Trials Network (NCTN) RT QA program. Recent publication by colleagues at the Imaging and Radiation Oncology Core (IROC) Houston continue to demonstrate that variances in the application of planning system algorithms directly correlate with the ability to pass phantom tests required for selected clinical trials participation. The role of colleagues in medical physics remains essential to mission for the successful conduct of radiation therapy in clinical trials (1–4).

The role of imaging and the application of imaging to RT target design has become of equal importance for clinical trial conduct with increasing influence for the modern RT QA program. More than 30 years ago, RT QA centers working with the cooperative groups began collecting hard copy imaging to validate targets chosen for RT and review patterns of failure in the analysis of patient outcome. The importance of this became initially visible in Hodgkin lymphoma clinical trials managed by the pediatric groups. Computer tomography (CT) studies were acquired to validate the treatment field and target choice. In these sequential iterative series of clinical trials, all areas of initial disease including pulmonary/visceral parenchymal regions were to be included in the RT treatment fields with response driven targeting only permitted in the mediastinum. The results of Pediatric Oncology Group (POG) protocol 8725 were interesting and established a new paradigm for RT QA with choice of target volume and not radiation dose influencing trial outcome. This study evaluated patients that would have been considered to have intermediate to high risk disease by modern standards. The patients were treated with eight cycles of hybrid chemotherapy including alternating MOPP-ABVD with RT as a point of randomization after completion of chemotherapy. All sites of involvement at presentation required treatment either in sequence or in a single time frame. In the initial primary trial publication (5), it did not appear that the addition of RT after eight cycles of chemotherapy conferred a benefit to patients with the

five-year event free survival being identical for both groups. However, a secondary analysis demonstrated that if patients were treated with RT in a protocol compliant manner, five-year survival was improved by 10% and this was statistically significant (Figure 1). Study deviations were exclusively due to excluding initial sites of disease from intended RT treatment fields when compared to the submitted diagnostic imaging. This was one of the first cooperative group studies that assigned deviation in radiation oncology as an image-guided function and not exclusively defined by a computational functional dose error. After committee review of the QA process for radiation oncology, a strategic decision was made in the POG to have the RT fields centrally reviewed pre-therapy (real-time) to improve protocol compliance. This process decreased the deviation rate on study from 30% in 8725 to less than 5% in low risk POG protocol 9426 and intermediate risk protocol 9425. The successful diminution of study deviations was exclusively due to central review of images and intervention by QA centers in real time pre-therapy to ensure that treatment delivery was consistent with trial guidelines. As part of this process, retrospective analysis of response to induction chemotherapy (two cycles) revealed a 50% discordance between site and central imaging review teams on these studies (7). Modern Hodgkin lymphoma trials now perform image response and application of RT fields in real-time. Pre-therapy and the central review adjudicates secondary clinical trial points of randomization for trial management. Children's Oncology Group (COG) protocol AHOD0031 incorporated real-time reviews of all imaging response time points and RT plans in over 1700 intermediate risk patients with longitudinal data sets including outcome imaging. Real-time review of both response and application of RT objects ensured that the intended therapy titration/augmentation (less/more chemotherapy driven by response) and randomization to no RT relative to response could be conducted in a consistent manner (Figure 2). In critique of a paper describing the outcome of the QA process relative to pattern of failure determined by review of outcome imaging, both reviewers commented that the process of QA ensured that the study results were believable and the study outcome could be trusted. Central review of images and RT objects in real time has created a paradigm shift in the conduct of clinical translational studies. Subsets of Hodgkin lymphoma patients with challenges in accrual can now be studied worldwide in a manner not anticipated in the past. Trials are now ongoing for unique Hodgkin populations of very limited disease (surgery only), very young patients, older patients, and those with high risk disease including RT treatment fields based completeness of response and size of disease at presentation. Imaging central review ensures that the patient is on the correct study and care is in alignment with protocol intent in these populations of patients who will face challenges to meet accrual objectives. Robust QA processes including image acquisition and review is essential in these study subsets if are to learn new management strategies.

Imaging reviews are integrated in clinical trials to ensure uniform study population and compliance with trial requirements. Modern clinical trials involving RT require multiple image sets from both diagnostic imaging and RT to confirm the target and validate target treatment delivery. Real time review (pre-therapy/pre-randomization) of imaging ensures that the enrolled patient is 1) entered and eligible for the specific trial and 2) the intended therapy meets clinical trial objectives. Imaging is used to validate outcome including normal tissue injury, disease progression, and site of failure. The importance of imaging in modern

oncology clinical trials cannot be overstated and is equal to the importance of symmetry in dose computational algorithms identified in the early generation of clinical trials. Groups within the NCTN use the timing and quality of imaging and RT planning objects to assign a yearly performance score for protocol compliance. The IROC is directly involved in the development of the protocol, therefore data acquisition standards for imaging and RT are conducted in a group transparent manner consistent with objectives established by CTEP.

Imaging as a Modern Vehicle for Credentialing Institutions for Participation in NCTN Clinical Trials

Historically, computational algorithms and strategy for dose calculation varied between institutions. These included, but were not limited to, calculations to specific points and normalization to percent isodose line defined in two dimensions. With the development of three and four-dimensional planning systems, radiation oncologists and physics planning teams gradually adopted volumetric computational treatment planning models with dose being delivered and more importantly prescribed to a volume. Expanded volumetric targets were designed to include potential areas of microscopic disease, inherent target motion, and daily patient set up variability. In a serendipitous manner, volumetric computational programs unintentionally served to both optimize and harmonize dose computational strategies worldwide in the clinical trials process. With alignment of radiation computational algorithms, IROC has incorporated multiple imaging tools into the process of qualifying and credentialing institutions for clinical trial participation including phantoms and planning exercises. One of the initial uses of imaging for credentialing was in clinical trials involving central nervous system stereotactic RT. A credentialing tool was created to evaluate image fusion, target delineation, and definition of coordinates for therapy. A planning CT was made available to institutions and a T1 MR with contrast was also made available. The target lesion was not visible on the planning CT but visible on the MR, therefore the ability to fuse images and report spatial coordinates was evaluated. The plan was created on the fused objects for review. Another important initial image-directed credentialing tool at IROC was the three-dimensional benchmark. In this benchmark a lesion was noted in the right temporal lobe and institutions were asked to develop a RT treatment plan to the target using a vertex field. For this exercise, institutions had to 1) demonstrate the vertex field and 2) create a dose volume histogram to tumor target and normal tissue. These exercises required a CD or materials downloaded from cooperative group websites and were completed on the institution's planning system to demonstrate that institutions could plan to a volume and create a dose volume histogram. While now more commonplace, the exercise facilitated the introduction of volumetric planning into group clinical trials using imaging to credential sites for trial participation. As intensity modulation matured as a treatment vehicle for group clinical trials, guidelines for the use of this tool was published by QA centers (6). It became important to develop a mechanism to credential institutions for this modality of treatment. A benchmark in head and neck oncology was identified at IROC that had a curvilinear target volume near circumferential to the spinal cord best treated with intensity modulated radiation therapy (IMRT) to provide optimal tumor target coverage and normal tissue conformal avoidance. This benchmark complemented the credentialing phantom tool also developed by IROC Houston. It was determined by consensus within the NCTN that if the study had a specific RT clinical endpoint question, then phantom credentialing would be

required for study participation. If intensity modulation was being used as part of RT delivered on a specific study without an intended RT endpoint, then the image guided planning exercise could be used to participate in the study. This was important in the pediatric groups as it is more difficult to ask specific technology driven RT questions in studies relative to technique and dose due to the number of patients on study. The importance of these benchmarks was twofold. IMRT technology was new at the time of the development of the benchmark, therefore planning and treatment execution required validation. As these aspects of care became more familiar and consistent between institutions, the ability to draw objects in a consistent and protocol compliant manner has now become the more visible area of non-uniformity between investigators participating in clinical trials. Additional image associated benchmarks with phantoms currently include lung, spine, prostate and liver. The benchmarks require that objects are imaged, drawn and plans executed and submitted for evaluation. NRG has provided outstanding imaging credentialing processes for hippocampal sparing and PET adaptive management of lung cancer in clinical trials.

For modern trials, the nuance of image interpretation and application of variances in image target interpretation as applied to protocol continues to require management by the QA centers. Even in targets as predictable as prostate, investigators generally agree at mid-gland however vary in interpretation of the apex and base. Image quality often influences drawing of the posterior aspect of the gland as CT often does not easily depict the fat plane posterior to the gland. With motion and positional alignment, even predictable targets can be complex to successfully treat on a daily basis with the precision required for modern patient care including post-operative targets. The informatics tools of modern QA programs ensure that variances in image interpretation and application of imaging to RT treatment objects can be addressed and reconciled in real time (pre-therapy) if managed well. These processes ensure compliance of the patient population to study objectives and provide credibility for trial analysis and interpretation of results.

Benchmarks and RT credentialing vehicles are managed and applied in a group transparent manner by IROC, thus available to all investigators and protocols in each of the five cooperative groups. There is no redundancy in the effort and institutions do not need to complete separate benchmarks for individual group participation. A benchmark in image guidance for use by all NCTN members is also available. Although image guided adjustments are made daily at institutions pre-therapy, the benchmark evaluates the process of adjustment when the planned field is not aligned to preliminary pre-therapy imaging.

Imaging and Clinical Trial Outcome: Problems and Pitfalls

Clinical trials remain our primary vehicle to evaluate and improve the delivery of clinical care in oncology. The outcome of the clinical trial is greater than the sum of the parts in trial design because outcome will influence patient care long after the trial is completed. The trials should be well designed and anticipate the information to be acquired for data management and successful trial conduct including imaging and tissue for biomarkers. In the HeadSTART phase III clinical trial evaluating the role of Tirapazamine in Head/Neck cancer with the experimental agent (Tirapazamine/hypoxic cell sensitizer) being the point of

randomization. Diagnostic imaging was acquired to determine the accuracy of the field design of RT and make certain that areas requiring full dose RT were receiving the correct protocol dose. In this protocol with international participation, the clinical trial committee did not want to have a real-time pre-treatment review of objects as there was concern about timely submission of objects in both digital and hard copy format during that era. Objects instead were required to be submitted within the first three days of RT to accommodate perceived delays in the process of data transmission. This study accrued nearly 900 patients worldwide. Two hundred and eleven (211) plans were asked for revisions to meet study objectives for volume coverage. In each patient requiring an adjustment, gross tumor in either or both the primary lesion and neck were not fully contoured/treated. Ninety-five (95) made the requested adjustments and 116 did not. RT treatment quality became the most visible driver to study outcome with a 30% difference in patient survival between compliant and non-compliant RT plans (Figure 3). It was interesting to note that plans that made required adjustments or non-compliant plans that were not deemed clinically significant on secondary re-review 1) each had equal outcome and 2) patient survival was both equally inferior (8%) than compliant plans at the time of initial data submission. The deviations on study were exclusively related to image interpretation of disease and application of imaging to target definition. This protocol established the importance of RT QA and the application of imaging to target definition in radiation oncology. RT was not the study endpoint, however the quality of RT directly influenced trial analysis and overrode trial randomization. Years of effort in drug development and preliminary clinical trial programs were quickly lateralized due to RT quality on study (9). IROC Rhode Island currently manages five active NCTN and industry trials in head/neck cancer examining multiple questions including the use of robotic surgery and the addition of immunotherapy to patients treated with radiation therapy. The current trials are managed with real-time review. There has been a decrease in requests from IROC for adjustments in RT treatment fields for contouring gross tumor, however there has been an increase in requests for adjusting fields for coverage of microscopic disease for protocol compliance. For studies with immunotherapy, objectives often are related to outcome with non-inferiority toxicity objectives. For assessment of toxicity, it is important for uniform nodal coverage and mucosa dose. This has been an interesting shift in quality of head and neck treatment plans over the past decade.

Real Time Review of Imaging Objects for Clinical Trials

All groups within the NCTN use real time review of imaging and RT objects in most of the studies involving RT. Seventy-seven percent (77%) of all clinical trials monitored by IROC Rhode Island for COG, ECOG-ACRIN, Alliance, and SWOG have real time (pre-therapy) review built into the study charter. IROC Philadelphia and NRG have many excellent examples of clinical trials evaluating the role of imaging and image application in multiple disease sites including thoracic, hepatic, head/neck, and gynecologic malignancies including selected trials for pre-treatment review. COG and NRG are collaborating on a non-rhabdomyosarcoma soft tissue sarcoma trial in which both adult and pediatric patients undergo image acquisition and real-time pre-treatment review of study objects. This study includes chemotherapy for selected patients independent of age. COG and NRG each have radiation principal investigators who work together for review of objects for protocol compliance. Electronic data submission has facilitated this process and QA databases house

and harmonize imaging and RT objects into a single platform which further promotes nimble review of objects by study investigators. Objects can be evaluated concurrently for imaging and RT trial endpoints by all investigators and the necessary applied imaging objects can be reviewed to determine the appropriateness of the plan intent for trial objectives including response to therapy and outcome evaluation. The real-time pre-treatment review serves multiple purposes which strengthen the quality of the trial. Real time review ensures that the correct patient is placed on the correct study. Standard risk medulloblastoma requires no evidence of metastatic disease on imaging as well as post-operative imaging demonstrating less than 1.5 cm residual disease at the primary site. Retrospective review of imaging in completed previous low risk and high risk clinical trials has demonstrated that 10% of patients entered on these trials are entered on the inappropriate trial due to differences in interpretation of imaging between site and central review (10). Interestingly, this number has not significantly improved in recent active medulloblastoma clinical trials, indicating that image quality and image interpretation have not yet reached a point of equilibrium in current trials and we simply cannot assume that imaging interpretation without central review can be a protocol standard in this disease. Moving forward, the COG has discussed establishing pre-protocol entry review of medulloblastoma imaging to ensure that each patient is enrolled on the correct study. The areas of most common controversy are in the interpretation of gross residual disease in the posterior fossa and the presence/absence of leptomeningeal disease. Motion complicates interpretation of spine imaging in the pediatric population. From the RT perspective, all RT treatment plans on associated central nervous system protocols in COG are evaluated pre-treatment to ensure appropriateness of study entry and treatment delivery. When high risk patients are unintentionally entered on low risk studies, high risk patient outcome is compromised (10). With object transfer made facile through modern digital media, today any protocol requiring pre-treatment review can be easily managed with immediate communications between site and study investigators from anywhere in the world.

Real time reviews can have a positive impact on specific disease sites. Pediatric rhabdomyosarcoma is a challenging disease to treat as the sites of origin of tumor are ubiquitous in anatomic distribution and sites of treatment. Furthermore, RT target doses are adjusted to both response, anticipated normal tissue tolerance, and intervention by surgery. Therefore, study guidelines are complex and greatly influenced by multiple factors including patient age and the anticipated impact of therapy on development. With the advent of digital media data transfer vehicles, RT compliance for modern studies has improved from the historical level of 70% to >95%. This is important as study compliance is one of the few vehicles available to make a meaningful contribution and optimize our role in this disease due to the limited patient numbers available to empower a study and the varied sites of disease origin. (11). Fairchild and colleagues evaluated the role of quality in clinical trials involving RT and found that 50% of clinical trials using RT were directly influenced by the quality of the RT. Real time pre-treatment review of planning objects facilitates compliance to study. Real time review including imaging objects and their application to the RT treatment plan can ensure that the correct imaging has been obtained and it is completed in a study compliant manner including contrast and sequence as indicated. Real time review ensures that the imaging objects are applied to the RT treatment plan and that normal tissue

constraints as defined by the study are achieved. As technologies mature and become more complex, real time review ensures that radiation technology is applied in a protocol compliant manner (12).

Imaging and Study Outcome

Obtaining outcome imaging is essential to validate treatment response, disease progression, and identify therapy injury. In a recent high risk medulloblastoma protocol, several patients were evaluated as showing disease progression in the brain stem on institutional review of serial follow-up imaging and scored as treatment failures in the COG database. Because outcome MR imaging had been acquired at IROC in sequence as part of the protocol objectives, central radiology review performed in retrospect suggested that necrosis, not disease, may be the primary diagnosis in several patients (10). In this patient population, the entire brain stem receives a uniform radiation dose and the brain stem is an unintended component of the target. The site of potential injury was uniformly in the basilar artery region of the pons and upper medulla on initial evaluation. Therefore, having outcome imaging in the database may permit more enhanced detailed analysis of features potentially predictive of necrosis and not disease progression.

Pre-operative and sequential post-therapy imaging coupled with biomarker availability may provide the infrastructure to establish radiomic/pathomic features predictive of outcome and injury. Imaging is an important vehicle available to investigators to establish patterns of failure essential for validating the success or failure of primary RT. This has been invaluable in Hodgkin lymphoma. Outcome imaging has provided us the opportunity to study many aspects of follow up that otherwise would not have been available for review. For example, we recently have completed analysis on outcome of patients with large pleural effusions at presentation relative to patterns of failure (13). We have been able to develop metrics for evaluating response in bone disease for these patients. Having the ability to fuse outcome imaging and therapy objects will help support research evaluating injury and response assessment in all anatomical regions. We are treating image-driven disease in patients with lung cancer with less emphasis on treating areas of potential disease, therefore target volumes of treatment on study often appear smaller than historical trials. Outcome imaging is the only vehicle to define whether this is a reasonable adjustment in patient care. Collecting outcome imaging will be important for modern trials moving forward and this needs to be imbedded into the trial at the time the trial charter is developed to be successful. Our experience in trying to collect imaging and objects after completion of the study has been less successful as many institutional review boards require a separate consent from patients to acquire this information in retrospect if it was not written into the original protocol. Therefore, anticipation of the data needed for secondary trial objectives is important moving forward to make certain we have the information needed for analysis of unanticipated events. Imaging plays an invaluable role in this regard and its importance as part of the data acquisition process cannot be over stated.

Next Steps

Imaging has evolved to be essential in defining target volumes, evaluating outcome, and define normal tissue toxicity for nearly all clinical trials involving RT. Our technologies have

evolved to the point where nearly all radiation oncology associated clinical trials are volume driven for targeting requiring volumetric dose computation for successful protocol execution.

The modern resident is exclusively taught volumetric image driven RT planning. Clinical trials with radiation oncology are now image-centered and the QA programs have adjusted to fully embrace this change. RT QA in clinical trials developed historically as a physics driven process; however, imaging has increased the importance of the radiation oncologist's image interpretation in successful conduct of clinical trials. There is no algorithm that can correct dose to volume if the volume is not drawn per protocol. QA programs need to optimize the management of image acquisition and apply imaging appropriately for the execution of radiation oncology in clinical trials. It cannot be assumed that images and RT objects will be applied in a uniform manner without central review of images and targets. Real time review has matured into a nimble, uncomplicated, and highly effective mechanism to ensure study compliance. Imaging and RT objects can be transmitted through one of many digital media for review from anywhere in the world. Site and study investigators can review objects together in real time to ensure that the patient is assigned to the appropriate protocol and that the objects for intended therapy are applied in a study compliant manner. This ensures that the patient population under study is uniform and the results of the study are believable.

The arguments against QA and data acquisition are growing weaker with the continued cost-effective development and improvement of tools for digital transfer of data. Historically, the argument was that deviation in studies are "the norm" and will be equally distributed between the study arms. The deviations in the HeadSTART trial overrode the study randomization and sadly lateralized years of work in trial development and execution.

In the previous standard risk medulloblastoma trial COG A9961, 173 institutions with international partners were needed to meet an accrual objective of 420 patients. Ten percent (10%) of patients were deemed ineligible due to evidence of metastatic disease on pre-therapy imaging or imaging that was viewed as unevaluable. Each patient has value to each study, therefore there is value to making each patient study evaluable and enrolled on the correct study (10). Many investigators and administrators use cost as a narrative to limit and truncate data capture. This approach will create permanent injury to the importance of clinical trials and limit important data acquisition. The cost associated in the quality assurance process with digital object capture is in the development of the program. Once in situ, the informatics infrastructure can function at an enterprise level with remarkable cost efficiency. We need to collect outcome imaging for routine patient care and this imaging should be part of data capture for the clinical trial. The advantage to the clinical trial is that we have a uniform study population to help us learn and make improvements in our patient care moving forward. There is no defined limitation on what we do as clinicians in patient care and data management for trial patients should be equally robust. The brain stem necrosis question as an example can only be answered through data acquisition in the clinical trials. If there was a ceiling on object capture, this information would remain undiscovered and lost in single institution imaging archives. We are now treating potentially smaller volumes in patients with lung cancer as we move to image only disease sites for

treatment targeting. Outcome imaging is the only vehicle to ensure this is a correct approach. Collecting outcome imaging is important moving forward. This can be applied with reason; however, this imaging is one of our best opportunities to improve our processes for the future.

Medical physics colleagues have played an essential role in partnership for RT QA and will continue to play a more important role as our technologies mature. However, radiation oncologists now play an equally important role in ensuring that imaging and imaging objects are appropriately applied to study patients in all trials involving RT, both with and without RT specific study endpoints. Today, the quality of RT treatment plan is driven by the volumes drawn including normal tissue structures. Uniform application of imaging to RT protocols coupled with developing associated biomarker analysis are the primary vehicles to ensure our success in the future.

Acknowledgement:

NCI Grant CA 180803

Dr. Followill reports grants from NCI Grant CA 180803, during the conduct of the study.

Dr. FitzGerald reports grants from NCI Grant CA 180803, during the conduct of the study.

Dr. Kry reports grants from NCI, during the conduct of the study.

Dr. Rosen reports grants from NCI Grant CA 180803, during the conduct of the study.

Dr. Xiao reports grants from NCI Grant CA 180803, during the conduct of the study.

Dr. Knopp reports grants from NCI Grant CA 180803, during the conduct of the study.

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Deviation Adjustment

Survival According to Treatment* (POG 8725)

Treatment	5 Year Relapse Free Survival (%)
Arm 1: Chemotherapy Alone	85
Arm 2: Chemotherapy + RT:	
Appropriate volume	96
Major & Minor Deviations	86

* Only patients who were in complete remission at the end of chemotherapy

Figure 1.

Survival According to Treatment (POG 8725). Reprinted from International Journal of Radiation Oncology* Biology*Physics, 71/1, FitzGerald T. J., Urie M., Ulin K., Laurie F., Yorty J., Hanusik R., et al., Processes for quality improvements in radiation oncology clinical trials. S76-S79. Doi: <http://dx.doi.org/10.1016/j.ijrobp.2007.07.2387>. Copyright (2008), with permission from Elsevier. (6).

Figure 2.

Adapted from COG Protocol, AHOD0031 schema displaying the real time review assessment points. Reprinted from *Frontiers in Oncology*, Future vision for the quality assurance of oncology clinical trials. 3:31, FitzGerald T. J., Bishop-Jodoin M., Bosch W. R., Curran W. J., Followill D. S., Galvin J. M., Hanusik R., King S. R., Knopp M. V., Laurie F., O'Meara W., Michalski J. M., Saltz J. H., Schnall M. D., Schwartz L., Ulin K., Xiao Y., Urie M. doi: [10.3389/fonc.2013.00031](https://doi.org/10.3389/fonc.2013.00031). Copyright (2013), This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in other forums, provided the original authors and source are credited and subject to any copyright notices concerning any third-party graphics etc. (8).

Figure 3.

Overall survival by deviation status: (1) compliant from the outset ($n = 502$), (2) made compliant following a review by the Quality Assurance Review Center ($n = 86$), (3) noncompliant but without predicted major adverse impact on tumor control ($n = 105$), and (4) noncompliant with predicted major adverse impact on tumor control ($n = 87$). Overall $P < .001$. Pair-wise tests: not statistically significant except for cohort 1 versus cohort 4 ($P < .001$), cohort 2 versus cohort 4 ($P = .041$), and cohort 3 versus cohort 4 ($P = .006$). TCP, tumor control probability; RT, radiotherapy. Pending permissions. (9).