Chapter

Modern Clinical Trials in Radiation Oncology

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Abstract

Clinical trials in radiation oncology have improved our translational science and patient care. All patients referred to departments of radiation oncology can be invited to participate in a clinical trial with multiple venues. Study endpoints can include intradepartmental endpoints to improve workflow and patient access as well as interdepartmental clinical translational trials that include the National Clinical Trials Network (NCTN) and industry. The quality of the trial is important to trial outcome and influences interpretation of the results of the study and how the results can be applied to patient care moving forward. Clinical trials in radiation oncology to date have accomplished much, however many important questions remain as patient care matures and systemic therapies become more sophisticated and associated with specific biomarkers and cellular expression products. In this chapter we review the history of clinical trials in radiation oncology and review the current status of the structure of quality assurance in clinical trials. We will review unanswered questions and areas to study in each disease area and how to design strategy for trials to address modern unmet needs in our discipline.

Keywords: quality, clinical trials, oncology

1. Introduction

Clinical trials have become the infrastructure for progress in both translational and clinical science in oncology. Unlike other disciplines, oncology care requires interdigitation of multiple subspecialties, each with influence on patient outcome and toxicity. As part of the National Cancer Institute (NCI) infrastructure, a robust clinical trial mechanism has been established and operational for the past 50 years. This is the National Clinical Trials Network (NCTN). Radiation oncology as a committee and discipline is incorporated into each NCTN member group and plays an important role in the structure and conduct of most trials. Radiation oncology, unlike

medical oncology, can apply dose volume metrics to tumor and normal tissue and assign avoidance strategies to normal tissue. Radiation therapy (RT) is not a drug, yet colleagues in oncology care continue to apply overly simplistic thought processes to RT in the assessment of chemotherapy and RT interactions. Therefore, disease specific normal tissue constraints are written into studies to provide dose uniformity to tumor targets with protocol-specific dose volume limitations to normal tissue. This information can be transferred in digital format from anywhere in the world to a protocol quality assurance center and reviewed on a same day basis to ensure compliance with study objectives. In the next section, we will review the history of clinical trial development in radiation oncology and review the strengths and opportunities of current operational status of the quality assurance process.

2. History of quality assurance in NCTN clinical trials

By the mid 1960's, investigators and early developers of clinical trials processes sought to engage members of different institutions and participate in clinical trials. The NCI saw an advantage in further development of these processes and established a series of cooperative groups to initiate and manage clinical trials in liquid and epithelial adult oncology and pediatric oncology. Over time, this extended into discipline subspecialties including gynecologic oncology. RT began as participants within each group rapidly acquired committee status as the importance of RT in combination with systemic therapy was recognized as an important step in the development of clinical trials. Radiation oncology sections were written into protocols specifying target volume and computational techniques for quantifying dose. As the influence of radiation oncology matured, the Radiation Therapy Oncology Group (RTOG) was established as group charged with developing protocols asking RT specific questions [1–3].

In order to confirm dose was accurately delivered to the target volume intended by the study and calculated by guidelines, investigators including Arvin Glicksman and his colleague Fran Laurie designed a program to collect clinical information, planning documentation, and treatment images. The information was reviewed at the time of study completion and compliance scores were assigned and reviewed by institutional performance committees for each cooperative group [4]. Because there was a significant deviation rate on study, effort was made to move the retrospective review into an on-treatment review ideally performed during the first week on study to confirm compliance to study guidelines. The effort was performed in parallel to colleagues at the former Radiological Physics Center (RPC) who performed work using thermoluminescence dosimetry and phantoms to ensure consistent radiation dose uniformity across institutions participating in clinical trials. These efforts provided the infrastructure need to support the beginning of a quality assurance process in radiation oncology.

The former Pediatric Oncology Group (POG) established a protocol for what today would be called intermediate and early advanced stage patients with Hodgkin lymphoma, POG 8725. This study treated patients with eight cycles of hybrid chemotherapy (MOPP-ABVD alternate) with RT post chemotherapy as the point of randomization. RT was intended to be delivered to all sites of disease at presentation with dose titration permitted to areas of normal tissue tolerance including cardiac and pulmonary structures. The results of the study revealed no statistical advantage to patients receiving RT. However, a subset analysis revealed that patients treated with RT in a protocol compliant manner had a statistically significant improvement in

survival at 5 years. There was a significant number of study deviations on study. Most were associated with volume of tissue treated with areas of involvement at presentation at times excluded from management due to concerns of late effects. An example of this approach would be the exclusion of involved axilla at presentation to titrate the perceived risk of a secondary event such as breast cancer in this patient study population. The overall survival in patients with study deviations was equivalent to chemotherapy alone. The survival in patients with chemotherapy and study compliant RT was 10% greater than chemotherapy alone [1–3, 5].

This study established the fact that the process of quality assurance required adjustment if radiation oncology was going to have a meaningful impact on clinical trial function and improve the conduct of clinical trials. A decision was made to have RT treatment objects, including imaging, reviewed for quality assurance purposes in order to make certain clinical trial volumes for treatment were consistent with study objectives. The protocols were Children's Oncology Group (COG) 9425 and 9426. COG 9425 was an intermediate risk study permitting mediastinal volume reduction after chemotherapy to limit dose applied to pulmonary parenchyma after five cycles of chemotherapy. COG 9426 was an early-stage protocol designed to titrate therapy based on response to induction chemotherapy. If patients were considered a rapid early responder to two cycles of chemotherapy, chemotherapy was discontinued, and the patient received 21 Gy of RT to sites of original involvement. Although at that time all materials were forwarded to quality assurance offices as hard copy, the pre-treatment review of objects considerably improved protocol compliance to RT guidelines with a statistically significant improvement in study compliance. Investigators demonstrated that the process of quality review pre-therapy could be accomplished in an enterprise manner across a clinical trial. However, the process uncovered another issue which required process improvement. COG 9426 required a response assessment after two cycles of chemotherapy. Review of response assessment was performed as a retrospective central review and what was identified was that response assessment between radiologists at the site of treatment and the central radiology reviewer was not aligned in 50% of cases. This implied that a similar process for intervention was required for radiology building upon the success for pre-treatment review for radiation oncology. The challenge became how to manage this effort in a nimble and time effective manner in order not to delay care for on-site investigators. A different approach was going to be required for data transfer in order to achieve these objectives as an enterprise function [1–3, 6].

In parallel with the effort to review objects in hard copy, colleagues in the RTOG initiated a process for digital transfer of treatment objects directly through the planning system. Jim Purdy was responsible for this fundamental change in data exchange and this process became efficient and timely for management of RT protocols [7]. The American College of Radiology Imaging Network (ACRIN) was developed and strategies for digital transfer of imaging objects directly from site investigator imaging systems to central archiving supported by the American College of Radiology (ACR) [8]. Keith White developed an internal system used by the COG based on a program he developed for digital transfer of imaging objects at his home institution to review images for tumor board. These efforts created the infrastructure required to re-visit models for data transfer and set in motion mechanisms for protocol management that remain in use today [1–3, 9–11].

The strategy for simultaneous review of imaging and RT treatment objects using digital media was applied extensively in the COG intermediate risk Hodgkin lymphoma protocol AHOD0031. In this study, adaptive therapy strategies were deployed

to identify patients who had a rapid/delayed response to two cycles of chemotherapy which prompted a secondary randomization to a more titrated approach to care with rapid response and augmented care in those with a delayed response. A tertiary randomization occurred for patient with rapid early response to therapy and a complete response by imaging definition after four cycles of chemotherapy was imbedded in the study as these patients were randomized to either RT or observation. The quality assurance process for this study was extensive as more than 1700 patients were enrolled in the study requiring real time imaging response assessment at two time points in the study and pre-review of radiation oncology treatment objects. In this study metabolic and anatomic response imaging was acquired for outcome analysis. The dataset is invaluable and has been used for many publications on secondary study endpoints including but not limited to response to pleural effusions, response in bone, etc. The protocol demonstrated that these tasks assigned for managing protocols could be accomplished due in large part to the development of modern digital transfer tools and re-purposing them for management of group studies [12, 13].

Modern digital transfer tools have greatly facilitated protocol management and have brought quality assurance centers and study/site investigators together in real time on a same day basis for protocol management. Often protocols may be written in language which can be interpreted through a different prism by site investigators. The purpose of quality assurance and pre-review of objects is to ensure that the correct objects have been obtained for review in a protocol compliant format and the intended treatment plan is consistent with study objectives. The process ensures that all necessary data required for study interpretation is complete. In this manner, the dataset acquired and managed for the study is harmonized and the study results can be trusted.

The tools have also permitted expansion of clinical trial complexity including modern studies on therapy titration. These studies included surgery only for young Hodgkin lymphoma patients with highly favorable features and titration of the intended fields of RT in high-risk Hodgkin lymphoma patients to areas of less than complete response or areas that residual disease measures greater than 2.5 cm. Modern head and neck adult trials are asking titration questions for both RT target volumes and dose with patient functional endpoints to adjudicate the trial. Protocols such as this can only be successfully managed by integrative efforts of diagnostic radiology and radiation oncology as part of a central protocol review process in support of site investigators. These are important questions to answer and can only be successfully addressed in a protocol setting in order to accrue enough patients to study to answer the study question. These strategies are now applied at an enterprise level in all disease areas.

Digital transfer tools have altered the paradigm about clinical trials and how trials are managed. They have permitted real time interactions to ensure study compliance and archives for the next generation of investigators to review and ask better questions for subsequent clinical studies. The tools have also made data transfer process more nimble and given study investigators the opportunity to review all relevant imaging and RT treatment information as part of the review process. In the next section we will review pitfalls and problems associated with incomplete data acquisition.

3. Data management and problems generated by incomplete datasets

The tools today for data acquisition and management are outstanding and provide opportunity to manage protocols on a worldwide basis with real time response

assessment. Other sponsor partnerships have brought quality assurance centers to standard consistent with industry needs for data compliance, security, and anonymization. These are important steps and have generated significant process improvements at quality assurance centers. This is important as many clinical trials centered in the NCTN have other sponsor partnerships imbedded into the study. The cost associated with management is largely centered in the development of the program. Once the program is established and operational, maintenance costs associated with data acquisition/management are more predictable and study driven. There is a perception, however, that cost savings is secured by data titration with ceiling imposed in the study charter to limit the amount and volume of information acquired for each study. This is an unfortunate perception and has led to limitations in the interpretation of study outcome due in part to limitations in the dataset and lack of pre-review of objects before the patient is treated on study. In the HeadSTART study of patients with locally advanced primary head and neck carcinoma evaluating in a phase III format the utility of the hypoxic cell sensitizer Tirapazamine, on-treatment review of imaging and RT treatment objects was applied for protocol management with objects to be reviewed within the first 3 days of patient treatment. Even in patients where adjustment in therapy fields were requested and adjusted for compliance, there was a statistically significant decrease in patient survival compared to patients where no adjustment was required. This would imply that every treatment mattered and created an argument that pre-treatment review of objects would be an important component to clinical trials in head and neck cancer to ensure optimal study performance [14]. The former American College of Surgeons Oncology Group Protocol Z0011intended to study the role of surgical and RT volume titration to the axilla in selected patients undergoing breast lumpectomy and post-operative RT intended to be directed to the breast only without axillary staging. It is understood that approximately 60% of the axilla including level 1 are included in the tangential RT treatment field by default as these tissues are synergistic with breast tissue. The strategy was clinically attractive as the goal was to demonstrate efficacy for more limited therapy for what was perceived as low risk patients. Targets and RT fields were not collected and completion notes describing the fields were collected for validation of what was treated to what dose. In retrospective review, however, it was found that a large number of patients with high-risk features were treated to more comprehensive regional nodal volumes than intended by the study, therefore challenging the study objectives, and making interpretation of study results more difficult as a significant number of high-risk patients were treated to extended nodal volumes. This could have been adjusted with pre-review of protocol treatment objects and conversations generated between site and study investigators ad hoc to ensure compliance objectives on study [15–17]. RTOG study 0617 became a signature study for radiation oncology as the study demonstrated non-inferiority to 60 Gy to target in comparison to 74 Gy to target. This has had significant influence in the oncology community suggesting that "less is better". What is less well known is that patient-specific diagnostic imaging defining the target was not collected as part of the quality assurance process and the plans were reviewed for quality based on submitted RT treatment objects. Although this followed more traditional quality assurance processes, for the first 3 years on study the high dose arm had statistically inferior local control compared to the low dose arm, possible implying that in the early phase of the study, tumor may have unintentionally received less dose. This may/may not have influenced trial outcome. Investigators on study accurately point out that the local control rates balanced between the two arms over time, but one has to wonder if the separation in local control did not occur in the early phase of the trial,

would trial outcome have been different. The trial has become important for multiple reasons beyond target dose as the trial called attention to the importance of cardiac dose relative to long term outcome as well as provide insight into pulmonary normal tissue metrics. It is an important question to re-visit as it remains counter intuitive that a decrease in RT dose below what is applied to early-stage larynx cancer would be an advantage. The argument is toxicity, however planning techniques have improved since the initial phase of that study and it may be the right time to ask the same question with the process improvements identified in biomarker driven therapy including immunotherapy [18–22].

The data and digital objects from these trials are important and can be repurposed for multiple uses for secondary trial analysis and intercomparison of data between studies. However, each carries a flaw based on trial charter with each titrating data collection and management at different levels. The titration was well intended in order to support data management at the institutional level however titration of data can lead to unanticipated downstream consequence in outcome analysis which can shape outcome interpretation.

Therefore, trials need to be comprehensive in the data acquisition process in order to be fully confident in outcome review and use the data to answer unanticipated questions not recognized at the time of trial design. Outcome imaging is likewise crucial for study interpretation as there can be altered impressions between site and study radiology interpretation not easily recognized when we review reports. The more comprehensive we become in data acquisition, the more we can move forward in clinical trial structure. It is the responsibility of quality assurance centers, however, to ensure that the data acquisition process is not so cumbersome that it cannot be successfully managed.

4. Next steps in clinical trials

In this section progress in disease specific clinical areas is discussed and opportunities for clinical improvement in RT associated protocols is identified.

4.1 Central nervous system (CNS)

This remains an important area for clinical improvement in both adult and pediatric oncology. There is no other disease site that can affect the status of the individual afflicted with the disease from a constitutional and neuro-cognitive perspective. Brain tumors comprise 25% of childhood malignancies and primary brain tumors have a relatively equal incidence per decade in adult life, often affecting individuals during work life and family growth years. For adults with glioblastoma, recent progress has been made in the identification of biomarker expression with adjustments to care in selected patients based on genetic expression and presence of biomarkers. Studies to date have not shown a clear benefit to RT dose escalation. This may be due in part to asymmetry among radiation oncologists relative to target contours. With modern magnetic resonance (MR) imaging and sequence series, each series gives a different picture of what a target could resemble including fluid-attenuated inversion recovery (FLAIR) and single positron emission computer tomography (SPECT) imaging. Historically, most radiation oncologists generated contours from T1 images with contrast. This would identify areas of breakdown of the blood brain barrier however would not necessarily define areas of tumor deoxyribonucleic acid (DNA) synthesis

which today may be defined by positron emission tomography with amino acids. There is tumor in FLAIR and when tumor is involving central structures including the corpus, SPECT may better define disease extension across the corpus which may explain failure in the contralateral hemisphere in patients with central disease when this volume is untreated. There are protocols currently active evaluating dose painting to separate target volumes using targets derived from multiple MR sequences. Establishing uniformity among radiation oncologists in this regard with agreement on dose to target will optimize the evaluation of the benefit of biomarker driven therapy moving forward as neuro-oncology is dependent on the development of therapies for the next generation of CNS clinical trials in concert with RT.

If expanded target volumes using multiple MR sequences proves to be of benefit to patients, it becomes important to the radiation oncology community to study our use of expanded targets and how they can be applied with modern image guidance moving forward. Historically, our volumetric planning language included dose to gross tumor (GTV), clinical target volume (CTV), and a planning target volume (PTV) to provide for daily patient set up variability. In selected areas an image target volume (ITV or internal gross tumor volume (IGTV)) is applied for internal motion associated with respiration. The language of expanded targets pre-dated modern image guidance. The tools of today include auto-registration of kilovoltage imaging, cone beam computer tomography, and optical tracking for positioning with motion management, therefore with more security that targets can be reproduced on a daily basis in the CNS, PTVs likely can be titrated to one-two millimeters in a manner similar to stereotactic management. This can be studied both from an intra-institutional perspective and a cooperative group perspective with online imaging and outcome imaging used to confirm the success or difficulties associated with titration of PTVs. This is important as the objective is to minimize dose to normal tissue in as safe a manner as possible and feasible. This will be important for adults and children [23].

Sub-total volume CNS directed therapy for primary and metastatic disease will become increasingly important moving forward and the radiation oncology community is assuming more responsibility for follow up in this patient population. Targeting and outcome imaging will help optimize the appropriate dose to target in selected disease areas as well as better define dose volume limitations to normal tissue.

4.2 Head and neck

Head and neck malignancies have been an important disease area for radiation oncology. With more than 30 sites of origin, significant expertise on the part of the radiation oncologist and planning team are important for optimal patient outcome. Improvements in both anatomic and metabolic imaging have improved targeting and contours for the radiation oncologist. Although contouring objects was challenging during the HeadSTART trial, metabolic imaging with PET has help to optimize the size and extent of what would be referred to as a GTV.

During the past two decades there has been an increase in the incidence of head and neck malignancies as the disease now includes viral origin as well as pre-existing environmental habits. A subset of patients with viral origin appears to have rapid early response to therapy and this cohort merits increasing attention for studies for both radiation dose and volume titration. This concept will require rigor in quality assurance to make certain that titration, especially for RT volumes, is accomplished in a uniform format. Outcome imaging is essential to perform pattern of failure analysis in order to see if radiation dose and volume can be successfully decreased in selected

patients with favorable biomarkers for outcome and this should be imbedded for acquisition in clinical trials moving forward. There is evidence that immunotherapy coupled with RT can provide outcomes similar to chemotherapy and RT with a goal maintaining optimal tumor control and reduce toxicity associated with therapy. Optimizing therapy and decreasing toxicity remains important objectives moving forward, therefore clinical trials of the future will include strategies for both dose and volume titration for selected patients with more favorable features and biomarkers for a durable treatment outcome [24–29].

4.3 Thoracic oncology

Lung cancer has evolved in the past two decades. In the past, the disease was exclusively associated with environmental exposure, however recent history has demonstrated that the disease has changed both with respect to pathology and biomarker expression and targeted therapies have been approved for use with multiple subsets of patients. Immunotherapy has also become important in lung cancer and has shifted the paradigm and thought process with this disease including re-introduction of maintenance therapy.

This is important as RT remains an important co-partner to systemic therapy in this disease Because of known toxicity to pulmonary parenchyma with immunotherapy, there have been efforts in clinical trials involving thoracic RT to limit the volume of pulmonary parenchyma receiving 20 and 5 Gy as well as limit cardiac dose. Often lung tumors are located in regions vulnerable to exceeding normal tissue constraints and considerable planning skill is required to optimally treat the disease and limit dose to critical structures. Although tools for artificial intelligence used in radiation oncology strive to provide uniform dose homogeneity through the disease target, at times this is at the expense of delivering more dose to normal tissue than desired. In this circumstance, it is considered reasonable to accept more non-uniform dose distribution is less critical areas (soft tissues of the chest wall, etc.) in order to limit dose to cardio-pulmonary parenchyma. This has changed the treatment of patients on study. In order to meet cardio-pulmonary constraints defined on modern protocols, RT treatment plans are generated without elective areas to treatment which can require discontinuous planning volumes intentionally omitting areas that appear uninvolved despite target volumes contoured both inferior and superior to the volume omitted in generating the plan. The goal is to provide control of gross tumor without intentionally treating tissues as we had done on previous studies before immunotherapy and targeted therapy became available for patient care.

This is an area where motion management will play an important role moving forward. Because motion needs to be managed on-site at the participating institution in real time, it may be optimal to have institutions submit a questionnaire listing on-site equipment and complete a benchmark test demonstrating competence in contouring objects in four dimensions and making an adjustment between online imaging and planned treatment execution. Lymphoma often involves the thorax and volume modulated arc therapy provides an opportunity to be curvilinear around cardiac structures providing conformal avoidance to important structures. Cardiac avoidance may also play an important role in innate immunity for patients on study. If a significant volume of cardiac chambers is included in the treatment field, the blood pool will be exposed to therapy during the time on treatment. Lymphocytes die an intermitotic death from RT, therefore if the blood pool is exposed to radiation, a significant volume of lymphocytes will be depleted with each treatment. Clinical

trials of the future will likely not contour the heart as a single structure, however tools including artificial intelligence will help contour chambers, valves, coronary arteries, and the electrical conduction system. Different disease types will influence the importance of each structure. For example, the anterior descending artery and anterior left ventricle will be important for breast cancer patients while the left atrium and electrical conduction system will be important for esophageal patients [30–38].

As outcomes improve, clinical trials will provide an opportunity to support and improve normal tissue outcome that can be quantified with RT dose volume metrics and normal tissue function.

4.4 Liver

Hepatocellular carcinoma and metastatic disease are becoming of increasing importance for patient management. The number of patients afflicted with disease in the liver is increasing and we are learning how to apply modern therapy technology to primary and secondary liver disease. One of the many challenges in modern patient care is that multiple therapies have efficacy for patients afflicted with disease including surgery, chemotherapy, stereotactic RT, and radiopharmacy. Each, however, competes for normal tissue tolerance and the benefits of multiple therapies may not be additive and may unintentionally serve to limit additional therapy due to additive toxicities. To complicate matters, at the time of diagnosis there is often pre-existing normal tissue compromise with image associated injury potentially influencing both choice and intensity of therapy. Primary hepatocellular carcinoma therapy is often optimally treated by transplant and therapies are often designed to bridge patients until transplant can be performed. Often, however, patients are not candidates for transplant, and they need to be managed medically with either stereotactic RT or radiopharmacy including modern targeted therapy. The choice of therapy can be nuanced and driven by the heath of the patient and liver function including Child-Pugh status. Therapies, although available for patient care, need to be studied in more detail to know how to apply them and limit risk of injury. Although radiopharmacy with Yttrium-90 (Y-90) can deliver dose to target, there are clinical challenges associated with the delivery of therapy. Although intrahepatic catheters can be accurately placed, tumor vascularity is irregular with areas of limited vascular access, therefore shunt and movement of particles/dose away from the intended target can result in dose delivery to unintended target and limited dose to the intended target. Because of the previous lack of computational software for post therapy dosimetry, quality assurance metrics have been limited to the activity of the isotope. Today, computational dosimetry software is now available to assess dose to tumor target and normal tissue using SPECT as an imaging tool to perform voxel dosimetry. This will help move the care of these patients to a more optimal assessment of dose to volume and assess, especially with Y-90, in defining areas receiving less than tumor specific dose and which areas require additional dose augmentation. Although Y-90 is thought to be specific to target, there can be unintended consequence to uninvolved segments of hepatic parenchyma through migration and dose can extend to organs abutting hepatic parenchyma including renal parenchyma and bowel. Modern radiosurgery can place limitations and dose gradients in a secure manner across targets with motion management and image validation [39–45].

There is a paucity of studies comparing therapies which serves to limit advancing the discussion concerning safety and efficacy of each approach. Often patient care is driven by the specific expertise of providers on-site. Each case will have tumor

specific vascularity, location, and size, therefore, randomized clinical trials will be difficult to perform in this area. A registry with clinical information, therapy imaging/dosimetry, and outcome imaging may be the best initial approach to developing a definition of dose volume metrics for patient safety.

4.5 Gastrointestinal

Gastrointestinal (GI) disease encompasses many important areas for radiation oncology. Esophageal cancer is highly responsive to chemoradiotherapy, and preoperative therapy has rapidly become the standard of care. The targets for RT are driven in large part by imaging generated from positron emission tomography and endoscopy. Initial studies using image-guided definitions for targeting applied generous superior and inferior margins, however extended volume therapy into uninvolved nodal regions can make planning difficult to meet dose volume constraints especially for cardiac and pulmonary parenchyma. This merits further investigation as can targets be titrated considering cardiac and pulmonary parenchyma as "natural barriers" even though they abut tumor targets. In other words, can the gross tumor volume and the CTV be synergistic in this location with the image-guided target symbiotic with the PTV. Outcome metrics relative to cardiac and pulmonary parenchyma balanced with outcome imaging to identify local regional failure could be part of radiation oncology study objectives challenging traditional computational metrics and tumor target definition balanced with normal tissue tolerance metrics [46, 47].

A similar approach can be applied for pancreatic cancer. Although RT has been lateralized in clinical protocol development, meta-analysis continues to suggest an important role for RT in this disease. Protracted chemotherapy protocols with RT applied at the time of disease progression limits the perceived effectiveness of RT given as either definitive therapy or post-operative therapy. However, therapy must be balanced with normal tissue tolerance as hepatic, renal, and bowel volumes must be respected including important anastomoses in post-operative patients. RT will eventually be seen again as an asset in this disease and radiation committees will be cognizant of the responsibility we need to apply to this situation particularly in patients with borderline resectable disease [48].

There is increasing information that compressed fractionation strategies can be applied to patients with rectal cancer. Short term data suggests that compressed schedules are non-inferior with respect to surgical intervention with variability in contouring structures including the mesorectum. More long-term data is needed to determine if compressed schedules are non-inferior to local control and normal tissue function. This is an area where tissue is available both pre and post therapy and biomarkers may play a role in outcome assessment [49, 50].

Anal cancers remain of increasing importance in the treatment community. Protocols have often applied a uniform strategy to patients with varied stage and tumor burden. Moving forward, stratification of patients in clinical trials by stage/tumor burden including RT alone trials in selected favorable patients will be an important next step in management. Likewise, we need to define as best as possible what target volumes should resemble for modern patient care. For example, can the mesorectum be considered a CTV at risk with the tumor defined on positron emission tomography as the CTV of high risk? If so, dose painting can be applied including optimal definition of what nodal volumes are at risk. Only clinical trials with shared data information can answer these important questions [51].

4.6 Genitourinary

Genitourinary (GU) oncology remains an important area of research for radiation oncology. Prostate cancer is exceptionally well treated with modern radiation oncology. With image guidance and intensity modulation, outcomes have been exceptional and continue to improve. Because in large part to limited dose to normal tissue including bladder and rectum, compressed fractionation schedules have become more popular in clinical care. It is important to couple these changes with patient symptoms at presentation in order to optimize dose and fractionation schemes to pre-existing genitourinary health. Clinical trials will help us segregate which patients are more optimally served with traditional fractionation likely including those with high-risk features including the need for regional therapy. Oligometastasis therapy is moving forward at a rapid pace as outcome appears to be improved with more aggressive management upfront in patients with limited metastatic disease. The nature of treatment in this situation coupled with emerging technologies including radiopharmacy hold promise to improve survival in this patient cohort. It will be important to include modern anatomic and metabolic imaging as part of staging. This will help optimize targets of therapy and identify patients in need of extended volume therapy due to oligometastatic disease [52–55].

One potential area for clinical trials is to think of the prostate differently with respect to target technology. Today we think of the prostate gland as a uniform structure for target definition, often independent of disease identified on imaging including MR. As imaging improves, can we consider the gland as a target volume of intermediate risk and dose paint image associated areas of concern as targets of high risk. This would potentially further serve to titrate dose across critical structures including bladder, urethra, nerve bundles, and rectum potentially improving normal tissue outcome and not sacrifice local control.

Bladder preservation technology is improving. Often these patients are medically vulnerable, therefore therapy choices are often influenced by medical co-morbidities. Likewise, the choice for systemic therapy in combination with RT has to recognize the potential for toxicity, therefore choices are balanced. Immunotherapy coupled with RT remains under investigation and appears well tolerate. These pathways will need further exploration [56].

Aggressive RT management upfront of renal metastasis will also be important to study moving forward as this may make response to targeted and immunotherapies more durable and not interrupt systemic therapy treatment schedule.

4.7 Gynecologic

This remains an important area to study as gynecologic malignancies remain an important worldwide public health issue. The incidence of cervix cancer worldwide including medically underserved populations continues to grow and often patients with limited access to care present with advanced stage disease. Modern imaging including positron emission tomography has demonstrated an increase incidence of nodal involvement at presentation than was previously acknowledged. Treatment programs with RT coupled with brachytherapy remain important and essential to patient care, however improving outcome will require optimal application of new and novel systemic therapy. Biomarker-driven clinical trials including immunotherapy will be important to see if outcome can be improved in these patients [55–61].

Although endometrial cancers are often found early in the disease process because of clinical symptoms, selected patients do not uniformly have optimal outcomes and these patients become candidates for chemotherapy and biomarker-driven therapy coupled with surgery and RT to optimize tumor control. These can include carcinosarcoma and papillary serous histology [62–64]. Current protocols seek to define improvements in systemic care. With biomarker-driven care and immunotherapy, protocols for therapy are evaluating these issues. Medically inoperable patients are increasing in frequency as society ages, therefore protocols optimizing care for these patients is likewise important moving forward. Ovarian carcinoma remains a clinical challenge as to date, imaging of disease has not been optimal however improvements in imaging are anticipated. Biomarker-driven therapeutic options are important moving forward to optimize care for this cohort and well as those with primary peritoneal disease.

4.8 Musculoskeletal

For both adults and pediatric patients, this is an area of increasing importance. For adults, patients are often treated with pre-operative RT in order to facilitate surgical resection. This provides opportunities to use pre and post therapy imaging to determine if radiomics predicts for response and outcome. Tissue is available both pre and post therapy, therefore elements of tumor microenvironment and tumor related biomarkers are available for study. Tumor specific biomarkers identified in post therapy specimens may provide insight into resistance molecules and mechanisms for the next generation of studies and identify additional agents and biomarker driven therapy could be applied on a pre-operative basis [65, 66].

For childhood sarcoma, these diseases affect both bone and soft tissue. Pediatric tumors are less likely to be influenced by epigenetics. In the NCI pediatric Molecular Analysis for Therapy Choice (MATCH) trial, a significant percentage of pediatric tumors have an actionable mutation. These diseases have remarkable responses to systemic therapy and often local control can be achieved with surgical and RT titration of resection and RT dose. These have been studied by outstanding investigators in the past within cooperative group disease specific committees. The structure provided by the committees will be an excellent resource moving forward as systemic therapy and personalized application of targeted therapy moves forward. There will be an increasing use of particle therapy for these diseases in order to exclude normal tissue from the RT treatment field and decrease sequelae from management [67].

4.9 Pediatrics

Process improvements in the technology of RT will significantly benefit pediatric radiation oncology. The increasing use of particles and intensity modulation coupled with image guidance will limit dose to unintended structures and serve to further improve outcome relative to tumor control and normal tissue. This will be important in all areas of pediatric oncology including the aforementioned sarcoma subgroups but also for pediatric brain tumors and all additional disease areas. Because of the security provided in treatment reproducibility, PTVs can be titrated to institutional tolerance. These is especially important in younger children as an additional 1–2 mm of expansion can significantly influence the volume of normal tissue receiving full dose, therefore when feasible, titrating high dose and low dose volumes can have a measurable impact on outcome. This is true in all disease areas [68–74].

5. Conclusions

RT has matured as a discipline with tools now readily available to generate metrics to assess both tumor control and normal tissue outcome. Databases are available to house information in a format to re-purpose the data generated from RT treatment objects and imaging to perform accurate and believable outcome assessment. The Cancer Imaging Archive (TCIA) has been developed to house data in a format available for clinical/translational research. Data acquisition and management processes are robust and prepared to function at an enterprise level to move us forward [20, 75].

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