Technical Advances of Radiation Therapy for Thymic Malignancies

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Abstract: Radiation therapy often plays a critical role in the treatment of thymic malignancies. However, because of the location of these tumors, historically patients have been at a significant risk for radiation-related toxicity such as pericardial effusions, radiation pneumonitis, long-term pulmonary fibrosis, and occasional long-term esophageal stricture, particularly for unresectable thymoma. Recent advancements in technology have provided the treating radiation oncologist with the ability to more accurately target the region at risk while sparing normal structures. In this review, we provide an overview of key advances in radiation techniques for thymoma over the past two decades. These techniques include 3D conformal therapy, intensity-modulated radiation therapy, 4D treatment planning, adaptive radiation therapy, and proton therapy. Each advancement has brought with it unique advantages in maintaining long-term disease control while improving quality of life in this manageable disease.

Key Words: Thymic malignancies, Radiation therapy, 3D conformal therapy, Intensity-modulated radiation therapy, 4D treatment planning, Adaptive radiation therapy, Proton therapy.

(J Thorac Oncol. 2010;5: S336–S343)

Radiation treatment for thymoma has the potential to carry with it significant toxicity. In addition to the acute damage to the surrounding critical structures such as the heart, lung, and esophagus, the favorable long-term survival in this disease also necessitates that prioritization is given toward preventing chronic adverse events. This issue is further complicated by the fact that there have been publications from several institutions, including our own, that have implemented induction chemotherapy to reduce the rate of pleural recurrences. However, this regimen includes doxorubicin, which is also cardiotoxic. Studies on Hodgkin lymphoma have demonstrated long-term cardiac morbidity with mediastinal radiation and have concluded that this risk is compounded greatly with the addition of doxorubicin. Furthermore, our institution has previously analyzed data from 101 patients with inoperable esophageal cancer treated with definitive chemoradiation and found that a number of dose-volume histogram parameters to the pericardium and heart were associated with a risk of pericardial effusion. Another study demonstrated that with lung cancer, chemotherapy and radiation to centrally located lung tumors cause defects in cardiac perfusion anteriorly, corresponding to those regions that have received higher levels of radiation. Similar conclusions about long-term toxicity have been made with respect to pulmonary side effects such as late radiation fibrosis. It is in this context that the advancement of radiation techniques could have a large impact on reducing serious morbidity, and that this benefit will continue to be witnessed for many years to come.

Radiation therapy has made significant technological strides over the past two decades. The first of these advancements came with the introduction of 3D conformal therapy, which represented a major shift from conventional, “2D” techniques. With this method, physicians were able to select optimal beam angles that could shape the treatment field while minimizing dose to critical normal structures. Then, in the past decade, the field of radiation oncology has witnessed an explosion in intensity-modulated radiation therapy (IMRT) that uses the revolutionary technique of “inverse planning” to optimize doses to the tumor and normal tissue using planning software that delivers a nonuniform radiation dose within the radiation field, further improving dosimetric conformality and thus the therapeutic ratio with radiation delivery. Finally, even more recently there has been a nationwide increase in the application of proton therapy for multiple disease sites. Proton therapy has a theoretical dosimetric advantage over photon techniques such as IMRT through the production of a “Bragg Peak,” which provides a sharp increase in dose at a given depth in tissue that can be modulated by the treating physician. Although initially thought to hold an advantage over IMRT primarily in pediatric and central nervous system malignancies, multiple dosimetric studies published in the past several years have demonstrated that protons could prove to be superior in several other disease sites as well, including prostate, gastrointestinal, and, most pertinent to this review, thoracic malignancies. It is quite possible that future studies will demonstrate that the theoretical dosimetric advantages over photon techniques will ultimately translate into clinical advantages as well, further reducing toxicity in this patient subgroup receiving aggressive treatment in a region surrounded by many sensitive and vital structures.

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Disclosure: The authors declare no conflicts of interest.

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GENERAL PRINCIPLES OF RADIATION THERAPY TECHNIQUES

Proper patient positioning and immobilization are essential to the accurate delivery of radiation therapy in thymoma, regardless of technique. At M. D. Anderson Cancer Center, patients are lied supine for simulation and are strictly immobilized with a customized Vac-Loc cradle. The arms are placed over the head and the hands gently grasp a T-bar. Thin-cut computed tomography (CT) slices are then acquired (2.5 mm), and intravenous contrast is used in select cases. Next, a 4D CT scan is performed to assess for internal motion and to be used for the purposes of treatment planning.

A complete review of the patient’s diagnostic imaging studies is crucial to accurately delineate the target volume. It is essential that preoperative imaging is available for review, and that in the postoperative setting, the treatment volumes are discussed with the surgeon. All questionable sites of disease should be reviewed further with a diagnostic radiologist. Standard radiation treatment volumes include the gross tumor volume (GTV) for gross disease, the clinical target volume (CTV) for the GTV plus regions at risk for microscopic spread, the internal target volume (ITV) to include the CTV as well as internal motion, and the planning target volume (PTV) to account for uncertainties in daily patient positioning. In regard to the treatment volumes for thymoma, the region to be included in the CTV has varied by study. Before the introduction of CT planning, the target volume was often defined as the GTV, mediastinal lymph nodes, and bilateral hilar lymph nodes, or the mediastinum without the hilum. At our institution, we define the CTV as the presurgical extent of disease, to include the entire surgical bed, without elective nodal radiation. Acceptable radiation doses for thymoma are as follows: 45 to 50 Gy in the postoperative setting for negative margins, 54 Gy for positive margins, and 60 to 70 Gy in the case of gross residual disease. In general, 1.8 to 2.0 Gy fractions are used.

CONVENTIONAL (2D) RADIATION TECHNIQUES FOR THYMOMA

Before the advent of conformal techniques, patients were treated with two-dimensional methods in which one or two radiation beams were directed at the target region and were shaped using blocks placed at the head of the machine (Figure 1). These blocks were often made of cerrobend, a mixture of bismuth, lead, tin, and cadmium, and were formed using a heating process until reaching the melting point of 158°F. There were many disadvantages to this technique. The target was often identified solely by surface anatomic landmarks or fluoroscopy, the small number of beams limited the amount of conformality that could be achieved on 3D structures, and doses were generally prescribed to a point without corrections for variations in tissue density (most notably lung density). Figure 2 demonstrates different beam arrangements with this technique and the radiation dose distributions that result.

There have been a wide variety of serious toxicities reported with conventional techniques, with 5 to 15% rates of grade 3 to 4 toxicities and 1 to 10% rates of grade 5 toxicities. For example, Mornex et al.8 reported that 7 of 90 patients experienced grade 3 or 4 toxicities after treatment with surgery and postoperative radiation therapy, 3 patients with pericarditis and 4 with lung fibrosis. Nakao et al.9 reported a case of complete ventricular block after radiation therapy, which was attributed to damage to the conduction system. Uematsu et al. reported significant toxicity in 4 of 40 patients receiving postoperative radiation after complete resection in stage II to III thymoma. Three of four complications occurred in patients receiving an extended field including the entire hemithorax at 15 Gy in 15 fractions. Finally, Latz et al.11 reported multiple high-grade toxicities in the setting of surgical resection and postoperative radiation with conventional techniques: pulmonary embolism (grade 5), radiation pneumonitis (two cases, grades 3 and 4), and sternal fistula. However, it should be noted that only two of these complications occurred after the completion of radiation therapy.

Although the radiation treatment field in thymoma is almost always located adjacent to critical structures, high-grade toxicity rates of 10 to 15% are considered unacceptable given that long-term survival in this disease is high and that patients are often otherwise relatively healthy. Therefore, the focus on advances in radiation therapy over the past 10 to 15 years has been on increasing dose conformity and thus increasing the therapeutic ratio. That is, the dose to the target divided by the dose to normal tissue. These aims have been largely achieved through the development of 3D conformal radiation and, subsequently, IMRT.
3D CONFORMAL RADIATION

Three-dimensional conformal radiation differs from historical 2D techniques in that the planning is CT based on “beam’s eye view” technology is used in which the beam is shaped from multiple angles. Figure 3 demonstrates this principle with a radiation treatment field typical of thymoma, directly superior to the heart and surrounded by lung tissue. Rather than cerrobend blocks, multileaf collimators are often used to shape the beam, which are built into the head of the gantry, as are shown in Figure 3C. In addition to increased conformity, 3D conformal radiation allows for evaluation of the treated doses as a function of dose and volume in a representation known as a dose-volume histogram. Radiation toxicity is directly correlated with the volume of tissue receiving a given dose, and as can be seen in Figure 4, with 3D conformal planning, the beam arrangement can be optimized such that the target volumes (GTV/CTV/PTV) receive the prescription dose (70 Gy), whereas the normal structures are constrained to lower doses.

INTENSITY-MODULATED RADIATION THERAPY

Although 3D conformal radiation offers a significant improvement over 2D techniques, IMRT offers yet another advance in terms of improving dose conformity and limiting the dose to the surrounding critical structures of the heart, esophagus, lung, and spinal cord. The physician and physicist involved in planning the radiation are able to optimize the dose to the tumor and normal tissues by using a “cost-benefit” algorithm in which the planner specifies the priorities of treatment (tumor coverage, heart dose, lung dose, etc.) and the treatment planning system then designs an optimal plan based on these prespecified priorities, a process termed “inverse planning.” The physician and physicist then work to modify and fine-tune this plan through techniques such as adding avoidance structures and altering the cost-benefit ratios. IMRT also achieves a higher level of conformity than 3D conformal treatment by using a delivery system that modulates the intensity of each beam during radiation delivery with dynamic multileaf collimators. The technique and indications of IMRT have been well described in

FIGURE 2. Isodose distributions with various beam arrangements in 2D treatment planning to a prescription dose of 5000 cGy. A, Single anterior to posterior (AP) beam with a significant hot spot anteriorly. B, Anterior and posterior beams (AP/PA) beams weighted 2:1 anteriorly because of the anterior location of the tumor. It is evident that amount of tissue receiving a dose >120% of the prescription level (6600 cGy) is greatly reduced, although the amount of conformality is limited. C, Wedged pair technique using oblique beams, which improves conformity as compared with the former two techniques but still contains large significant hot spots in the region of normal tissue.
many publications, including recent consensus guidelines by the American Society for Therapeutic Radiology and Oncology and the American College of Radiology. Figure 5 depicts an example of the differences in planning and treatment of an intrathoracic tumor in an individual patient. It is evident that the isodose lines extend to the surface both anteriorly and laterally in the case of 3D conformal planning, whereas IMRT offers a more conformal distribution. Figure 6 demonstrates IMRT in the postoperative treatment of an invasive thymoma, with significant sparing of the posterior structures and the heart.

Because of the rarity of invasive thymomas, the majority of published studies are retrospective reviews spanning several decades. As a result, there have been no dedicated studies examining the toxicity of radiation in the setting of thymoma with 3D conformal radiation or IMRT as compared with conventional techniques. However, until the results of patients treated with modern techniques mature, toxicity outcomes can be extrapolated from those patients with other thoracic tumors, such as lymphoma and non-small cell lung cancer (NSCLC).

Nieder et al. compared the dose distribution of three different mediastinal radiotherapy techniques in female patients: 2D AP/PA opposed fields, four-field 3D conformal techniques, and a seven-field IMRT technique. Better heart sparing was achieved with conformal techniques, particularly IMRT as compared with the 2D technique. There was also a decrease in the maximum dose to the breasts with IMRT. Komaki and coworkers compared outcomes for patients with medically inoperable stage I NSCLC treated with 2D versus 3D radiation and found that overall survival, disease-free survival, and locoregional control rates were superior with 3D conformal treatment. Wilson et al. performed a dosimetric comparison with these same two techniques in locally advanced NSCLC and found that spinal cord and lung doses were significantly lower and tumor control higher with 2D techniques. Finally, Liao et al. compared IMRT with 3D conformal techniques with concomitant chemotherapy for the treatment of NSCLC. The authors found that the toxicity
rate was significantly lower in the IMRT group, and that the rates of freedom from locoregional progression and distant metastasis were at least as good with IMRT.16

4D TREATMENT PLANNING

In addition to using highly conformal techniques to target thymic tumors and other thoracic malignancies, an advance in technology that has further improved target localization and in the process reduced the dose to normal structures is the development of 4D treatment planning, i.e., quantitating tumor motion during treatment planning and accounting for this motion in radiation delivery. Figure 7 demonstrates an example of how this technique can be advantageous compared with treatment plans that do not take into account tumor motion. In patients with a great deal of tumor motion, the risk of marginal failures can be substantially increased. It is notable that structures in the lower portions of the thoracic cavity (closer to the diaphragm) tend to have more respiratory variation than superior structures,17,18 such that the magnitude of internal motion for thymic tumors would be expected to increase for treatment fields that have significant inferior thoracic extension.

As noted above, the International Commission of Radiation Units has expanded its definitions to include the ITV that is defined as the CTV plus internal motion. There have been several prior studies examining the feasibility and reproducibility of the addition of the ITV with 4D CT imaging in intrathoracic tumors, primarily in the setting of NSCLC. Redmond et al. examined 4D CT scans at simulation and from two rescans to determine whether the excursion of tumors at simulation was consistent at the time of rescanning. The authors concluded that the addition of the ITV was useful as a target volume, and that there was interfraction consistency in tumor excursion such that motion assessment at the time of simulation could direct therapy.19 Liu et al. quantitated the degree of internal motion caused by respiration in the setting of stage III or IV NSCLC. The authors found that tumor motion was associated with diaphragm motion, the superior-inferior location of the lung, the size of the GTV (with smaller tumors moving more), and the disease T-stage. Almost 40% of tumors moved $\geq 0.5$ cm in the superior-inferior direction, whereas approximately 5% or less of tumors moved $>0.5$ cm in the anterior-posterior or lateral directions. Therefore, the authors concluded that only a small percentage of patients would have internal motion $>1.0$ cm, and that the largest excursion was in the superior-inferior direction.

At our institution, because expanding the tumor volume by 1.0 cm or more could lead to significantly more normal
lung tissue receiving radiation (as the target volume would move in and out of normal uninvolved lung parenchyma), patients who exceed a threshold of 1.0 cm target volume motion are treated with radiation coordinated breathing control. That is, the target volume is contoured at a given phase of the respiratory cycle and treatment is delivered at that cycle. Patients are coached during both radiation simulation and the first treatment as to breathing patterns that will be the most reproducible, and the respiratory cycle is monitored in real-time with each fraction to ensure appropriate radiation delivery. Multiple studies have demonstrated that planning with radiation coordinated breathing control can decrease doses to normal tissues while maintaining target doses. In one such study, Vlachaki et al.20 found that with radiation coordinated breathing control in 10 patients, the volume of lung receiving doses of at least 20 Gy/10 Gy and above was 26%/31% for gated plans and 35%/40% for nongated plans. In another study, George et al.21 found that the learning curve for breath coaching was steep, and that the margins placed for residual motion during treatment were consistent. Therefore, although more time-consuming and requires more resources than the alternative of delineating an ITV, in well-selected patients, radiation coordinated breathing control is feasible and can spare lung tissue in patients with significant tumor motion.

ADAPTIVE RADIATION THERAPY

In addition to accounting for internal motion during treatment, current advances in technology have focused on adapting for changes in anatomy and target volume as a result of such factors as tumor response, inflammatory changes related to treatment, breathing patterns, and alterations in patient weight. Several investigators have examined the impact of these changes during the course of radiation therapy. Britton et al. obtained weekly 4D CT scans from 10 patients with NSCLC to examine the effects of interfractional changes on the doses to both the target volume and normal tissue. While the mean change in dose to the PTV was only 12%, the SD was 12%, implying that a meaningful percentage of patients experienced significant variations in the target dose distribution. In addition, while the mean lung dose and percentage of lung receiving greater than 20 Gy (V20) changed by an average of <5% during treatment, the maximum spinal cord dose change by an average of 34%. The authors concluded that because in a small percentage of patients interfractional changes had “dramatic dosimetric consequences,” repeat imaging should be considered during treatment, particularly in locally advanced NSCLC patients.22 Spoelstra et al. examined the role of adaptive radiotherapy from a prospective standpoint during concurrent chemoradiotherapy in 24 patients and assessed the benefit of routine gating of all patients at a given time point. All patients underwent gated radiation therapy delivery after 15 fractions, and plan modification was initiated by either a >5% reduction in PTV coverage or an unacceptable increase in normal tissue dose. The authors found that 15 patients had an average reduction in PTV of 8% after 30 Gy, and that the PTV increased in the remaining 6 patients. However, in only one patient the increase was >20%, and the patient was replanned.
for progression of disease. As only one patient required replanning, the conclusion of the study was that although repeat imaging may provide utility in the setting of conformal treatment methods for certain patients, daily gated radiotherapy may reduce the need for adaptive planning. At our institution, we routinely perform repeat 4D simulations at approximately midway through treatment for patients with intact thymoma due to the proximity of these tumors to several critical structures, with more frequent adaptive simulations being done in patients with large-volume disease. A decision regarding replanning is then made on discussion among the treating physician, the planning dosimetrist, and the physicist.

**FIGURE 8.** Patient with stage III invasive thymoma treated with proton therapy postoperatively. A and B, The preoperative site of disease (blue arrow) with an adjacent pleural effusion. C, An axial view of the treatment plan. D, A sagittal view. It is apparent that the dose volume is steep and that the stopping power of proton therapy allows for significant sparing of the surrounding normal structures.

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**PROTON RADIATION**

In the past decade, there has been a surge of proton centers in the United States for treatment of a wide array of malignancies, and many more treatment centers are planned. Although no studies have been dedicated to thymomas, several dosimetric investigations have established that for intrathoracic tumors, the favorable dose distribution of protons in comparison with photons (in the form of the “Bragg Peak”) can maintain a high conformal dose to the target tissue while minimizing the dose to normal structures. Chang et al. published a study that compared normal tissue dose with conformal techniques (3D conformal treatment or IMRT) versus that with proton therapy in stage I or stage III NSCLC.
With a detailed dosimetric analysis, the authors found that doses to several organs, including the spinal cord, heart, esophagus, and the integral radiation dose, were all lower with proton therapy as compared with the photon techniques. In another study, Chera et al. compared three different involved nodal irradiation techniques for stage II Hodgkin lymphoma patients: conventional radiation, IMRT, and 3D proton radiotherapy. The authors found that proton therapy significantly reduced the dose to the breast, lung, and total body. Several prospective studies are currently underway assessing whether these dosimetric advantages translate to long-term clinical advantages in terms of local control, particularly toxicity.

At our institution, we strongly consider proton radiation therapy in any patient being treated with invasive thymoma due to the location of the disease in the anterior mediastinum, a location in which the Bragg Peak could be effectively applied to the location of the disease in the anterior mediastinum, a steep. Many institutions, including ours, are currently in the process of applying the conformal advantages of IMRT with the techniques of 4D CT imaging and adaptive planning in invasive thymoma, the goal is to provide a culmination of the technologic advantages over the past decade to maximize the therapeutic ratio and thus to provide long-term local control while maintaining a high quality of life in this curable disease.

REFERENCES