Tolerance of the aorta using intraoperative iodine-125 interstitial brachytherapy in cancer of the lung
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ABSTRACT
PURPOSE: A retrospective review to assess the efficacy and morbidity of surgical resection and 125I interstitial lung brachytherapy placed in approximation to the aorta.

METHODS AND MATERIALS: The records and postoperative films of 278 patients who had undergone intrathoracic 125I brachytherapy at our institution were reviewed. All patients had undergone a gross total resection of a non–small-cell lung cancer using segmental resection, wedge resection, or sublobar resection. Frozen section margins of resection were required to be negative before the intraoperative delivery of the implant. Of those reviewed, 29 patients were implanted with 125I impregnated Vicryl mesh that contacted greater than 50% with the aorta. Implants consisted of 125I seeds sewn into a nomographically guided geometric array. Only implants where 50% or greater of the implant volume directly approximated the aorta were selected for inclusion into this study. The mean aortic volume receiving the entire prescribed dose was 17.2 cc (mean surface area 5 34.4 cm2) and the mean prescribed dose was 114 Gy (range, 85–120) over the permanent life of the implant calculated by isodose curve distribution at a depth of 0.5 cm from the plane of the implant. Five patients have received postoperative mediastinal dose supplementation with external beam irradiation to further address occult mediastinal nodal disease not revealed during the intraoperative frozen section analysis.

RESULTS: All patients tolerated the surgery and brachytherapy well with no perioperative mortality. With a median followup of 45.3 months (range, 1–117), 1 of the 29 patients suffered a fatal hemorrhage from suspected great vessel rupture. A review of this case demonstrated that the interstitial therapy had been supplemented with 4500 cGy of external irradiation, which overlapped a small portion of the implant volume overlying the aorta. No other patients suffered even minor events referable to the implant and have continued to do well without symptomatic evidence of chronic sequelae as of the publication of this article or the time of their death. Local control has been achieved in all patients still living and had been achieved in all patients who died from subsequent progression of metastatic disease or other cause.

CONCLUSIONS: Interstitial 125I intrathoracic brachytherapy is a safe and effective method when used with sublobar resection in high-risk stage I non–small-cell lung cancer patients and may be used even in situations that require placement of the sources in close approximation to the aorta. The tolerance of the aorta seems to be greater than previously thought, and may well exceed 12,000 cGy over the permanent life of the interstitial implant. Interstitial 125I brachytherapy can safely be used to deliver significant radiation dose in direct contact with the aorta but supplemental, overlapping external beam irradiation should be avoided. © 2008 American Brachytherapy Society. All rights reserved.

Keywords: Aortic tolerance; Sublobar resection; Lung cancer; Brachytherapy; Vascular radiation tolerance

Introduction

Intrathoracic brachytherapy has enjoyed a long history of usage and has been proven a safe and effective method of delivery of high-dose permanent irradiation, yet little is known about the tolerance limits of the major intrathoracic
vascular structures (1–4). Recent reports have demonstrated efficacy and safety with virtually no increased morbidity in the treatment of Stage I non–small-cell lung cancer (NSCLC) (5). In animal models, vascular tolerance limits for single-fraction intraoperative electron beam irradiation have been described (6, 7), whereas only a few reports have speculated on human tolerance limits (8–10). Werber et al. have described an interstitial tolerance limit of rodent carotid arteries that may exceed 13,000 cGy (11). With the current use of neo-adjuvant therapy and more aggressive surgical management as well as the recent initiation of The American College of Surgeons Oncology Group Phase III trial comparing sublobar resection with or without brachytherapy in high-risk, early-stage patients (12), the likelihood of intervening with intrathoracic brachytherapy has significantly increased in those institutions so focused. Considering these developing issues, the tolerance of the great vessels to brachytherapy becomes a more central issue in the management of operable lung cancers.

The local recurrence rates of sublobar pulmonary resection are well documented in the literature (2, 5, 13, 14). As such concerns developed, previous independent single-institutional studies have reported the efficacy of sublobar resection and intrathoracic brachytherapy as an acceptable alternative to standard lobectomy or pneumonectomy (5). Our institution has adopted sublobar resection and intrathoracic brachytherapy as a modality well suited for an institutional environment that stresses the minimally invasive philosophy of intervention. We reviewed our experience at the Allegheny General Hospital (AGH) to assess the tolerance of the aorta to interstitial $^{125}\text{I}$ brachytherapy and also report its efficacy in terms of local control.

Methods and materials

Since 1998, intrathoracic brachytherapy has been incorporated into the treatment algorithm at the Allegheny General Hospital for high-risk patients with Stage I NSCLC amenable to segmental or wedge resection. To date, we have used this technique in over 300 patients. In an attempt to define the radiotherapeutic tolerance limit of the intrathoracic aorta, we reviewed our total experience selecting 29 patients with nonmetastatic NSCLC who underwent sublobar resection with microscopically negative margins and intraoperative placement of an $^{125}\text{I}$ Vicryl (Ethicon Corp., Somerville, NJ) mesh graft along the staple line in an attempt at maximizing local control (Fig. 1). These 29 patients were selected from the large group using strict criteria as follows:

1. The procedure was limited to those patients without evidence of documented or suspected distant metastatic disease.
2. Patients were not deemed lobectomy candidates by one of the three thoracic oncolgic surgeons.
3. The area and volume of the implant approximating the aorta constituted at least 50% of the total implant. This value was arbitrarily set to demonstrate that a significant volume of the implant was directly in contact with the aorta.
4. The implant was performed in patients who were able to undergo complete gross resection of all known disease.

Patient selection

After the establishment of radiographic abnormalities sufficient to warrant operative intervention, a standard metastatic workup was obtained that included computerized axial tomographic images of the chest, abdomen, and pelvis. $^{99m}$-Technetium osteography was performed as well as routine hematologic serology that included a liver function profile, complete blood count, serum metabolic assay, and a coagulation panel. As it became available, positron emission tomography was incorporated into the staging process. Those patients selected for surgery had solitary radiographic abnormalities demonstrating a localized and ongoing malignant process. Five of 29 had a previous history of NSCLC and demonstrated a first recurrence. Nineteen total patients had a diagnosis of NSCLC including these five. A total of 4 patients demonstrated adenocarcinoma, whereas 6 patients demonstrated squamous cell carcinoma. All patients either had a biopsy-proven diagnosis of NSCLC before resection or had frozen section confirmation of NSCLC before the placement of the brachytherapeutic mesh. The median age of the patients was 65.6 years (range, 50–71). Patients were then selected for operative suitability based on history and physical examination data, and the results of the metastatic workup. All patients were assessed, as well, for surgical operability by one of the three staff thoracic oncologic surgeons. These patients were excluded from lobectomy secondary to underlying comorbid conditions (most commonly poor pulmonary reserve as demonstrated by pulmonary function studies). All patients selected were known to demonstrate a Karnofsky score of 70 or greater.

Fig. 1. $^{125}\text{I}$ Vicryl mesh implant.
Treatment technique

The surgical technique used varied according to operative need, and ranged from traditional thoracotomy to video-assisted thoracoscopic surgery. At the time of surgery, no patient demonstrated evidence of nodal metastatic disease; however, 5 patients were identified with microscopically positive nodal disease at the time of permanent sectioning of the pathologic specimens.

A description of the brachytherapy technique has been extensively described elsewhere (1, 6) and therefore will be only briefly detailed here. After sublobar resection is performed, the radiation oncologist evaluates the staple line and constructs an $^{125}\text{I}$ implant (Fig. 1). On the basis of an in-house nomogram, these implants were designed to deliver a minimum dose of 100–120 Gy at a distance of 0.5 cm from the plane of the implant. All implants were designed to deliver full dose to the staple line with a minimum margin of 1.0 cm in the respective plane of the implant. Because the implants are uniplanar, and the depth of prescription was 0.5 cm from the plane of the implant, we calculated the dose at 0 cm depth (abutting the aorta) in a planar fashion. This Contact dosimetric analysis revealed dosages in excess of 18,000 cGy. Fidelity of the implant positioning was confirmed by careful comparative analysis of the orthogonal films (used for dosimetric analysis in the initial 25 patients) or CT planning (used for dosimetric analysis in the final 4 patients), and the followup diagnostic CT scans done every 3 months for the first-year postimplant. Once the $^{125}\text{I}$ mesh implant is made by the radiation oncologist, the thoracic surgeon then sutures it into place along the sublobar resection staple line so as not to restrict the pulmonary function at re-expansion (Fig. 2). After surgical closure, radiation exposure was measured and determined to be, on average, 0.1 mREM/h. All patients underwent permanent dosimetric calculation at 3–4 weeks postprocedure, initially using orthogonal radiography; however, this was substituted for by CT-based simulation when commissioned in our department. All dosimetric calculations were performed with three-dimensional planning, and evaluated with multiplanar reconstruction. Because many patients were imaged with two-dimensional orthogonal radiographs, dose–volume histogram was not reported.

Followup consisted of a complete interim history and physical evaluation on an at least every third month basis. Contrast-enhanced computerized axial tomography of the chest was performed immediately before all followup visits and, when available, positron emission tomography was added to the postoperative schema.

Results

All patients tolerated surgery and brachytherapy well with no perioperative mortality. The mean length of stay was 9.3 days (range, 5–26). The mean number of $^{125}\text{I}$ seeds used was 54 (range, 20–80) impregnated into a Vicryl mesh gauze. The mean activity per seed was 0.42 mCi (range, 0.22–0.57), whereas the mean total activity was 20.57 mCi (range, 11.1–32). The mean dose delivered to the prescription point was 114 Gy (range, 85–120). Serial postoperative computed tomographic studies revealed no seed migration and only localized parenchymal pulmonary fibrosis in the immediate vicinity of the implant.

With a median followup of 45.3 months (range, 1–117), there have been no local failures. At the time of reporting, 11 patients remain alive and free of disease, and 10 patients had succumbed to metastatic disease, whereas 7 patients were alive with evidence of metastatic disease that had not locally recurred. One of the 29 patients suffered an acute and fatal hemorrhage from suspected aortic rupture associated with the treatment, which occurred 22 months postprocedure. Careful examination of this case revealed that this patient received postoperative mediastinal irradiation that delivered an additional 4500 at 180 cGy per fraction, which was completed 3 months postoperatively. Analysis of the orthogonal radiographic films of this particular case revealed that the external beam portals marginally overlapped the significant implant volume.

Discussion

Patients affected by carcinoma of the lung many times have limited pulmonary capacities, either from long-term damage due to a significant past history of smoking or any one of a number of physiologic reasons. These patients may not tolerate traditional thoracotomy and lobectomy. Potential treatment options for these high-risk or medically inoperable patients include sublobar resection with or without $^{125}\text{I}$ lung brachytherapy (5), definitive external beam radiation (15–17), radiofrequency ablation (18, 19), and the emerging technique of body stereotactic radiotherapy (20, 21).

Sublobar resection via a minimally invasive approach such as video-assisted thoracoscopic surgery is a viable
treatment option for these patients but is associated with an increased local failure. The Lung Cancer Study Group conducted a Phase III randomized study comparing lobectomy to sublobar resection in good-risk NSCLC patients. In this study, sublobar resection was associated with a three-fold increase in local failure when compared to lobectomy (13). Overall survival, however, was not significantly different between the two treatments.

The placement of I25I brachytherapy along the staple line at the time of sublobar resection has been reported to be a highly tolerable procedure with impressive local control and acceptable toxicity (5). In theory, brachytherapy potentially sterilizes the staple line resection bed helping to maximize local control. Brachytherapy potentially also has an advantage over external beam radiation by providing limited local high-dose radiation in patients who have limited pulmonary reserve. The obvious advantage of brachytherapy in these patients is sparing the remaining compromised pulmonary parenchyma from fibrosis secondary to irradiation.

Definitive conclusions from our current review of I25I lung brachytherapy placed in proximity to the aorta are difficult to make because this is a retrospective study with limited patient sample size. A review of the literature has revealed only sparse data on the tolerance of the aorta with brachytherapy. Therefore, even with the limitations of this study, this analysis does provide useful clinical outcomes. Our study has demonstrated that the use of brachytherapy in direct contact with the aorta is feasible. The estimated contact dose suggests that the tolerance limit of the great vessels in general, and the aorta in specific, is in excess of 12,000 cGy as a total dose over the life of the implant. It is our policy at AGH to perform I25I lung brachytherapy only in cases where less than 50% of the implant is in contact with the aorta and in all cases attempt to limit the volume of aorta receiving significant dose. Caution is required when placing an I25I implant directly on the aorta and the decision ultimately lies at the discretion of the treating physicians. Informed consent describing the risk of fatal hemorrhage is recommended.

Extreme care should also be used in patients who require adjuvant external beam irradiation to the chest, and it is our recommendation that patients be selected carefully both preoperatively and intraoperatively to avoid serious and potentially fatal complications. When mediastinal nodal positivity is identified intraoperatively at frozen section, mesh brachytherapy should be deferred unless the projected implant site is sufficiently distant to the mediastinum so as to prevent overlap.

Conclusions

Interstitial I25I intrathoracic brachytherapy is a safe and effective method when used with sublobar resection in high-risk Stage I NSCLC patients, and may be used even in situations, which require placement of the sources in close approximation to the aorta. The tolerance of the aorta seems to be greater than previously thought, and may well exceed 12,000 cGy total dose over the life of the interstitial implant. Interstitial I25I brachytherapy can safely be used to deliver significant radiation dose in direct contact with the aorta, however, supplemental, overlapping external beam irradiation should be avoided.

References

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