Brachytherapy for Non-small Cell Lung Cancer and Selected Neoplasms of the Chest

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This article reviews the indications, techniques, and results of brachytherapy in the treatment of non-small cell lung cancer (NSCLC) and selected chest neoplasms. Various isotopes and techniques are used to place radioactive sources directly into a tumor, tumor bed, or the chest. Brachytherapy techniques can be tailored to the clinical situation and can be in the form of permanent interstitial volume or planar implants (radioactive sources permanently imbedded into the tumor or tumor bed) or in the form of temporary interstitial or endoluminal implants (where radioactive sources irradiate a tumor bed over a certain length of time and then are removed). These treatments can be delivered over a short interval (high-dose rate [HDR]) or over a more protracted time (low-dose rate). HDR treatments can be used intraoperatively to deliver a large dose of radiation to a determined target area with selective sparing of surrounding normal structures. Different methods of delivering HDR intraoperative radiation are under investigation. Most reports on brachytherapy for chest malignancies are retrospective and come from a few single institutions. Most of the published data relate to the treatment of NSCLC, but other intrathoracic malignancies, such as malignant pleural mesothelioma and malignant thymoma, have been treated with brachytherapy. To our knowledge, no major randomized trials accurately assess or confirm these retrospective studies yet, complicating the interpretation of these results. Nevertheless, brachytherapy is of value in selected situations and offers the clinician and the patient an innovative method of delivering conformal high-dose radiation to a defined target with preferential sparing of normal surrounding structures. With continued innovations in the development of radioactive isotopes, computerized treatment planning and targeting, and source delivery, brachytherapy should continue to offer an attractive alternative and complement to conventional treatment approaches, and may offer patients improved local control and survival. (CHEST 1997; 112:276S-286S)

Brachytherapy—the placement of interstitial or intracavitary radioactive sources into a desired target to facilitate the safe delivery of high radiation doses to tumors, with selective sparing of normal surrounding tissue—represents a novel approach to the limits of the therapeutic ratio for selected tumors.\(^1\)

Total dose of radiation required to eradicate tumor

Tolerance dose of surrounding normal tissue

\[ \text{Therapeutic ratio} \]

When the therapeutic ratio required to eliminate a tumor exceeds the tolerance of clinical normal structures, conventional external-beam radiation therapy (EBRT) rarely achieves local control without undue morbidity. Non-small cell lung cancer (NSCLC) and other selected chest neoplasms thus represent a difficult challenge. Dose-limiting vital structures, such as normal lung, heart, and spinal cord, limits the dose that can be delivered with conventional means. Brachytherapy has been explored as an alternative treatment modality to manage selected tumors arising in or metastasizing to the chest.

Brachytherapy for NSCLC has historical roots dating back approximately 60 years, when Graham and Singer\(^2\) first described seven cases of interstitial bronchial stump implantation with radon 222 (\(^{222}\)Rn) radioactive seeds after thoracotomy and pneumonectomy. Shortly thereafter, Henschke\(^3\) introduced modern afterloading techniques with gold 198 and iridium 192 (\(^{192}\)Ir), which led to a rapid increase in the use of these isotopes and techniques in the United States. Despite these technologic advances, this specialized area of radiation oncology failed to gain widespread use for several reasons. Many early isotopes available for implantation exposed physicians and hospital personnel to unacceptable levels of radiation. Isotopes were not always readily available. Additionally, both interstitial and endoluminal brachytherapy require a substantial level of surgical skill to be administered safely and efficiently.

The use of brachytherapy in the treatment of NSCLC has recently enjoyed renewed enthusiasm as a result of the introduction of newer isotopes (ie, iodine 125 [\(^{125}\)I] and palladium 103 [\(^{103}\)Pd]), improved treatment planning, increasing numbers of radiation oncologists who have been trained to perform these procedures, and the introduction of computerized technology and software to optimize treatment planning.\(^4\)

A fundamental goal of radiotherapy is to maximally deliver dose to tumor while minimizing dose to surrounding normal tissue. Brachytherapy represents one of the best means to accomplish this goal. Its several methods depend on the stage and location of the tumor, as well as the performance status and pulmonary function of the patient and previous radiotherapeutic intervention. Radioactive isotopes can be placed interstitially in a permanent setting or as a temporary afterloading implant. They can also be used to deliver localized radiation for intraluminal tumors involving the trachea and bronchial tree. This article describes the indications, techniques, and results achieved with brachytherapy for the treatment of NSCLC and other selected neoplasms arising in the chest.

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Techniques of Brachytherapy

Interstitial Permanent Volume or Planar Implantation

The optimal technique of intraoperative implantation and the selection of radioactive sources depend on the location of the tumor, the amount of residual gross disease, and the biological behavior of the tumor. When residual tumor volume exceeds 1 cm, a permanent volume implant is usually required. The area to be implanted is determined preoperatively by the surgeon and the radiation oncologist, then reevaluated intraoperatively. The dimensions are recorded. A volume nomogram is applied to integrate information obtained from the average dimension of the area to be implanted and the available isotopic seed strength, to determine the number of seeds and spacing of both seeds and needles (volume implant) required to deliver a minimum peripheral dose (MPD) to the tumor.

$^{125}$I and $^{103}$Pd are the two most common sources employed for permanent volume implant. The MPDs for $^{125}$I and $^{103}$Pd are typically in the ranges of 14,000 to 16,000 cGy and 10,000 to 13,000 cGy, respectively. Although the energies of $^{125}$I and $^{103}$Pd are similar (0.028 MeV and 0.021 MeV), their half-lives differ significantly (60 days and 17 days, respectively), resulting in different dose rates (7 to 8 cGy/h and 20 cGy/h). This theoretically implies a potential biological advantage to selecting $^{103}$Pd (short half-life, rapid dose rate) in the setting of rapidly growing tumors. Once the dosimetry is planned, hollow metallic trochars are inserted into the tumor. Radioactive sources are implanted with an applicator (Mick Applicator; Mick Industries; New York). Postoperatively, localization radiographs determine the delivered MPD, based on the geometry of the implanted seeds.

For either close or positive margins or minimal residual disease (<1 cm), a permanent planar implant is performed. Less often, a permanent planar implant is used for early lesions. It is also indicated when tumor is partially resected, either because of proximity to critical vasculature or crossing fissure lines into adjacent lobes. The length and height of the visible target are defined and a planar nomogram is used to determine the number of seeds and spacing required to deliver a MPD of 14,000 to 16,000 cGy (for $^{125}$I) or 11,000 to 13,000 cGy (for $^{103}$Pd). The $^{125}$I or $^{103}$Pd seeds imbedded in polyglyactin (Vicryl) sutures are then either sewn onto a premeasured Dexion or polyglyactin mesh and then implanted onto the target, or directly sutured onto the target area. A similar technique employing $^{125}$I embedded into an absorbable gelatin sponge (Gelfoam) plaque has also been described. These differing approaches are used based on the proximity of the target area to critical structures that can or cannot be directly sutured. After implantation, localization radiographs determine the actual dose delivered to the target area as outlined by the radiation oncologist. Once the implant is performed and the incision is sutured, the dose cannot be adjusted, presenting a potential disadvantage.

Interstitial Temporary Implantation

Temporary interstitial implants are used to treat tumors arising or metastasizing to the anterior mediastinum, chest wall, or paraspinal region. Typically, after gross total or incomplete resection, the tumor bed is implanted with either low-dose rate (LDR) or remote afterloading high-dose rate (HDR) $^{192}$Ir or $^{125}$I. Relatively easy access via a percutaneous approach often dictates the use of this technique, either as a single treatment modality or in combination with EBRT.

The tumor bed is defined and then implanted intraoperatively through the skin of the chest wall. The skin is initially marked with a sterile pen to indicate the entry point for hollow metallic trochars that pierce the skin and chest wall. Afterloading closed-end catheters are introduced into the chest through the trochars and the trochars are removed. The catheter is then secured in the tumor bed with absorbable chromic or other (Dexon) sutures. Catheters are filled with stainless steel cables inside or radiopaque “dummy” seeds on a wire to prevent kinking and to allow for postoperative treatment planning. The process is repeated until the tumor bed is adequately covered. Plastic and stainless steel buttons threaded onto the catheters secure their placement at the skin entry point. The buttons are sutured to the skin with silk ties. Radioactive sources are afterloaded 4 to 5 days later to allow for wound healing and patient recovery. Localization radiographs of the implant are obtained, and dosimetric calculations are performed to determine the optimal treatment plan, generally in an LDR application. Doses of 2,500 to 4,500 cGy are delivered with $^{192}$Ir or $^{125}$I given over 2 to 5 days at a dose rate of 40 to 100 cGy/h. The total dose prescribed is predicated on previous or future EBRT.

Alternatively, HDR with high activity $^{192}$Ir can be delivered with an MDP of 1,000 to 1,500 cGy—typically in a single setting and less commonly, with multiple fractions delivered over 2 to 3 days.

With temporary implants, dosimetric adjustments can be made for inhomogeneities due to placement or anatomic limitations by varying source strength or source dwell times. Drawbacks include the need for higher activity radiation protection, the need for radiation-shielded single occupancy rooms, and the risk of infection posed by outdwelling catheters.

Endoluminal Brachytherapy

For T1 to T4 tumors of the trachea and/or bronchial tree without extraluminal extension or regional nodal involvement (stage I to III), and for recurrent or metastatic NSCLC, endoluminal brachytherapy (ILBRT) has evolved into a useful and convenient modality. Treatment can be performed either in the inpatient setting, with LDR-ILBRT, or the outpatient setting, with HDR-ILBRT delivered in several fractions. Prior to the development of high-activity sources (eg, $^{192}$Ir), a low-activity iridium or iodine wire was placed endoluminally to cover the visualized target area and appropriate margin. The source was left in place for approximately 1 to 4 days, depending on the prescribed dose, stage, and need to deliver additional EBRT. Advantages of LDR-ILBRT include the need for
only one procedure and the ability to monitor a potentially unstable airway or in the setting of excessive hemorrhage. Disadvantages include prolonged hospitalization, patient discomfort leading in some cases to dislodgment of the source due to excessive coughing, and personnel and physician radiation exposure.

HDR-ILBRT has now largely replaced LDR-ILBRT treatment at most participating institutions. Conventional HDR treatment has been delivered in a multifraction regimen given once weekly for two to five fractions. More recently, hyperfractionated HDR has been explored in a pilot study in which patients receive treatment twice daily over 2 consecutive days with efficacy and morbidity similar to LDR or conventional HDR treatment.9

If airway compromise from bleeding is a concern, or if the patient is undergoing laser resection or cauteryization, the procedure is performed under general anesthesia with the use of rigid bronchoscopy. A cricothyroid membrane puncture is performed with a cannula, and a guide wire precedes a Seldinger-type dilator into the tracheal lumen. The afterloading catheter is then passed through the dilator under bronchoscopic guidance. Once the dilator is withdrawn, the catheter is secured. The patient is then transferred to the brachytherapy afterloading suite after postoperative anesthesia recovery. A dummy seed catheter is placed into the lumen of the catheter, and both the position of the catheter and the radiation target area are confirmed via fluoroscopy. The dummy source is removed and the afterloading catheter is attached to the HDR machine for treatment. After treatment, the catheter is easily removed and the puncture site closed with petroleum jelly gauze and a bandage. Patients usually remain hospitalized overnight for observation.

In most cases, patients can be treated as outpatients with the use of local anesthesia and monitored sedation. After same-day admission in the surgical day hospital, the patient is brought directly to the brachytherapy suite and receives sedation. A flexible bronchoscope is passed transnasally into the tracheobronchial tree to localize the lesion. A separate port on the bronchoscope allows passage of a flexible afterloading HDR catheter. A slightly rigid plastic stylette within the catheter lumen allows passage and bending through tortuous bronchial lumens without kinking the catheter. Once the catheter is in place, the stylette is removed and replaced with a dummy seed guide wire to confirm the position of the catheter under fluoroscopy, and the target area is outlined. The catheter is secured at the entrance to the nasal cavity and attached to the HDR afterloading machine. The optimal dose and dose per fraction to treat endoluminal disease, while not yet fully defined, depend on prior or future additional EBRT, prior laser surgery, and the medical condition of the patient. However, fraction sizes of 500 to 1,000 cGy, given once weekly and prescribed 1 cm from the center of the source for three to five treatments, are typical.

Intraoperative HDR Radiation

Conventional brachytherapy is not always applicable when the tumor is advanced and comprises a large area to be irradiated. In addition, the complexity of some anatomic regions within the chest can make either temporary or permanent interstitial implantation technically difficult and can result in suboptimal implant geometry. Intraoperative EBRT has been explored as an alternative to conventional brachytherapy in an attempt to overcome these limitations.

Intraoperative radiotherapy (IORT) can be delivered via two methods for tumors arising in the chest cavity. The more common and available approach is with the use of electrons delivered from a modified linear accelerator. A specially designed cone is attached to the linear accelerator to deliver a focused beam to the target area. Normal uninvolved structures may be retracted out of the intended field or covered with custom lead blocking. Electron energies are chosen to cover the appropriate depth, based on tumor thickness. Doses in the range of 1,200 to 2,000 cGy are delivered in the operating room. Several potential shortcomings mar the theoretic advantages of this technique: the expense of installing a linear accelerator in an operating room; the safety concerns and inconvenience of transferring a patient from the operating room to the radiation oncology unit when a linear accelerator is not installed; difficulty in targeting complex surfaces in the chest with available cone sizes; and the hazard of abutting two electron fields in a large target area leading to either underdosage or overdosage at the field junctions.10 Results with this technique have been mixed.11-14

Another technique of delivering HDR-IORT was recently developed at Memorial Sloan-Kettering Cancer Center (MSKCC). The procedure is accomplished employing an applicator (Harrison-Anderson-Mick applicator; HAM Industries, New York) consisting of a flexible pad of material (called “super flab”). The pad is 1-cm thick and contains an array of source guide catheters through the midplane of the pad (5 mm from either surface of the applicator). Each catheter is separated from adjacent catheters by 1 cm. The applicator is connected to an HDR afterloading machine in a specially designated surgical suite, and a high-activity 192Ir source is used to deliver the prescribed dose. The applicator, which comes in various sizes, allows flexibility in customizing treatment to conform to various surfaces within the chest. The applicator can be fixed in place with packing or sutures. Normal structures can be retracted or shielded with customized lead disks. A brachytherapy atlas has been developed to provide optimized treatment plans that comprise all of the potential dwell times and possible position arrays ranging from 3×3 cm to 20×24 cm.1 This new applicator is currently being employed for the treatment of malignant pleural mesotheliomas in a phase II trial at MSKCC.

Overview: Results of Brachytherapy

Stage I and II NSCLC

Surgical resection is widely recognized as the treatment of choice for early-stage NSCLC. Although EBRT has historically been used as an acceptable primary treatment for medically inoperable disease, the overall results have generally been inferior to surgical resection, with local
control rates ranging from 20 to 90% and 5-year survival rates ranging from 10 to 50% for radiation therapy.\textsuperscript{15,16,18a} Dose-response data for EBRT alone for unresectable early lesions show poor local control for tumors \(>4\) cm,\textsuperscript{19} due possibly to the inability to deliver high doses without unacceptable toxic reactions. This limitation can be overcome with intraoperative brachytherapy. Brachytherapy can be delivered alone in selected patients with N0 disease, in combination with EBRT as a boost to the primary lesion, or as regional mediastinal therapy for N1 disease.

Two clinical situations arise in which brachytherapy is indicated for early-stage disease: the first situation is when the surgeon determines intraoperatively that adequate removal of lung malignancy is not feasible. Such intraparenchymal lesions can be permanently seeded with either \(^{125}\text{I}\) or \(^{103}\text{Pd}\) in a volume distribution and can be boosted postoperatively with EBRT. Indications for the addition of EBRT would be in the case of poor dose distribution and implant geometry, and in the event of regional nodal metastases.

The second indication for early-stage brachytherapy is early endotracheal or endobronchial tumors (T1 to T4) without evidence of extraluminal or mediastinal spread. Mass screening programs have identified increasing numbers of occult carcinoma \textit{in situ} and invasive endobronchial lesions,\textsuperscript{16} and others are discovered incidentally on routine examination or with early irritative symptoms, such as a persistent cough or blood-tinged sputum. For patients presenting with disease not technically or medically amenable to surgery, EBRT has been employed, and—similar to observations of interstitial lesions—high rates of recurrence have been observed.\textsuperscript{17} Both LDR and HDR remote afterloading endobronchial radiation, either alone or combined with EBRT, have been used to treat these lesions with excellent results, low morbidity, and little inconvenience or cost to the patient.

When surgical resection for early-stage NSCLC cannot be done, the surgeon and the brachytherapist may decide to perform a permanent interstitial implant, either as primary “conformal” therapy or as a boost to additional EBRT. Although the data on this approach are limited, the results reported to date are impressive.

Hilaris and associates\textsuperscript{16} published a retrospective analysis of 55 patients with medically inoperable stage I or II NSCLC who underwent interstitial permanent radioactive seed implantation. Histologic condition of implanted tumors included squamous cell carcinoma in 33 patients and adenocarcinoma or large cell carcinoma in 22. A majority of patients underwent biopsy only (44 of 55), and the balance had a subtotal gross resection. \(^{125}\text{I}\) seeds were implanted in 45 tumors, \(^{225}\text{Rn}\) in one, and \(^{192}\text{Ir}\) in nine. Following surgery, additional EBRT was given to 24 patients (median dose, 40 Gy). Local control by T stage was 100\% for T1N0, 70\% for T2N0, and 70\% for T2N1 tumors. Actuarial 5-year local control and overall survival rates were 65\% and 32\%, respectively. Cause-specific survival results were not calculated. For the subset of patients with N1 disease, the addition of EBRT appeared to improve local control over those patients with N1 disease who received no further therapy (86\% vs 57\%).\textsuperscript{18}

More recently, Fleshman and associates\textsuperscript{19} published similar results in a smaller cohort of patients with stage I medically inoperable NSCLC. After mediastinal lymph node staging, 14 patients underwent \(^{125}\text{I}\) volume implantation via either median sternotomy or lateral thoracotomy approach. With a minimum follow-up of 1 year, the local control rate was 71\% and median survival was 15 months. Local control was influenced by tumor size; for tumors \(\leq 3\) cm in average dimension, six of seven patients achieved local control. For those with tumors intermediate in size (3 to 5 cm), four of five patients achieved local control. Tumors \(>5\) cm were not controlled.\textsuperscript{19}

The published experience with intraluminal brachytherapy as either a single-modality therapy or in combination with EBRT for early-stage NSCLC is also limited, in part because of the development of other treatment modalities such as laser and photodynamic therapy. An advantage of intraluminal brachytherapy over laser therapy is the avoidance of potential bleeding from laser ablation and the risk of laser perforation. Also, laser treatment is ineffective for tumors invading the outer layer of the bronchial cartilage and may be technically difficult, depending on the site of disease.\textsuperscript{16}

Tredaniel and associates\textsuperscript{20} reported the results for 29 patients with stage I and II disease managed with endoluminal therapy alone. Tumors were treated with \(^{192}\text{Ir}\) afterloading sources prescribed to a depth of 1 cm from the source center. Therapy consisted of sessions of two exposures, each delivering 7 Gy and repeated every 15 days, for a maximum of six exposures. Patients were evaluated with follow-up bronchoscopies and biopsies. Complete macroscopic regression was seen in 21 of 25 evaluable patients, with histologic complete responses (CR) in 18 of 25 (72\%). After 23 months’ follow-up, median survival has not been reached.\textsuperscript{20} No significant complications were reported.

Fuwa and colleagues\textsuperscript{21} published a report on eight cases of intraluminal brachytherapy for occult NSCLC with an LDR source with similar results. Sutedja and associates\textsuperscript{22} treated two patients in a similar fashion with a good response. Both of these studies treated too few patients to yield definitive conclusions, and neither was prospective.

Saito and colleagues\textsuperscript{16} reported the results of a prospective phase II trial using a combination of EBRT (40 Gy in 20 fractions) followed by LDR intraluminal brachytherapy (25 Gy in five fractions) in 41 patients with stage I NSCLC. A unique technique was described in which four \(^{192}\text{Ir}\) thin wires were used (5-cm long, 0.3 cm in diameter) as radiation sources, placed in parallel, and fixed to avoid becoming dislodged. The flexibility of both the applicator and the radiation source, coupled with the thin diameter of the wire, allowed placement of the radiation source into the superior bronchus, segmental bronchus, and subsegmental bronchus. Another advantage of this approach was the ability to maintain a constant distance between the source and the bronchial wall. With a median follow-up of 24.5 months, disease recurred in only 2 of 40 evaluable patients at 7 and 9 months.\textsuperscript{16} Both patients underwent salvage surgery. Thirty-nine of 40 patients were alive at the time of analysis. Complications were limited to two pa-
patients who developed radiation pneumonitis requiring steroid treatment to return pulmonary function to baseline.

Not surprisingly, the incidence of second primary cancers in this population was high (19 of 40 in total), including 10 patients who developed separate cancers arising in the lung, six in the stomach, and one each in the larynx, pancreas, esophagus, and prostate. One of the technical challenges in treating endobronchial lesions is the obvious difference in luminal diameters at different segments of the tracheobronchial tree, and the need to prescribe the dose to customized distances from the source center. This problem was addressed in this trial by setting distinct diameters at different segments of the tracheobronchial tree and customizing the dose evaluation point (anywhere from 9 mm to 3 mm from the source center) depending on the airway diameter at the site of disease.\textsuperscript{16}

Intraoperative HDR radiation has also been examined for early-stage disease. Juettner et al\textsuperscript{13} reported on 21 patients who received 1,000 to 2,000 cGy for medically unresectable NSCLC with negative nodes on mediastinal dissection. Patients received additional EBRT postoperatively at doses ranging from 4,500 to 4,600 cGy. A 33% CR rate was demonstrated by serial CT scans, and disease-free survival was 90% (19/21) at a median follow-up of 1 year. One patient died as a result of treatment. The preliminary success may have been due in part to the N0 stage of the patients treated and the fact that many had early-stage, technically resectable tumors.

Pass et al\textsuperscript{12}, however, reported the results of a National Cancer Institute feasibility study with IORT for NSCLC and demonstrated significant morbidity: two of four patients died as a result of treatment, and two developed life-threatening fistulas.

**Stage III NSCLC**

**T3-4N0 NSCLC:** The role of intraoperative brachytherapy for resected T3 to 4N0 NSCLC invading the chest wall, carina, or mediastinum is unclear, and the literature addressing this subgroup of patients is sparse and conflicting. The suggestion has been made to offer additional treatment because of the high rate of local failure, yet to our knowledge, no randomized prospective data exist, in part because of the relative infrequency of this clinical presentation. Patients undergoing en bloc complete resection for tumors invading the chest wall, diaphragm, or mediastinal or pericardial pleura in the absence of nodal metastases can expect a 5-year survival in the range of 50% with no apparent impact from the addition of RT.\textsuperscript{23} Patients with tumors directly invading the mediastinum do poorly with primary surgery alone.

Martini et al\textsuperscript{17} published the results of surgical resection for 102 patients with NSCLC invading the mediastinum with no evidence of regional nodal spread. This included 58 patients with T3 lesions (invasion into pulmonary vessels, pericardium, pleura, or phrenic or vagus nerves) and 44 with T4 lesions (aorta, vena cava, esophagus, trachea, spine, or ariatum). Complete resection was possible in only 46 patients (45%) (T3, 66%; T4, 18%). The implantation of radioactive seeds into either gross residual disease or suspected positive margins was performed in 43 patients; 40 had incomplete (n=10) or no (n=30) resection. The three additional patients had a complete resection and brachytherapy because of suspected microscopic residual disease.

Postoperatively, 44 patients received EBRT, five received chemotherapy alone, and three received a combination of the two. Overall survival was 27% at 3 years and 19% at 5 years (median, 18 months).\textsuperscript{17} Complete resection and histologic type were the only two factors influencing survival. Only those patients with completely resectable T3 tumors achieved a 5-year survival rate of 36% and median 32-month survival.\textsuperscript{17} For those with completely resected T4 tumors, 5-year survival was only 12%. Patients with squamous cell carcinomas did significantly worse than those with adenocarcinomas. Although no clear survival advantage was observed for patients who underwent brachytherapy following incomplete resection or no resection, some patients were salvaged with brachytherapy, however, evidenced by 3- and 5-year survivals of 16% and 14%, respectively (median survival, 13 months).

In 51 patients in whom the first site of recurrence was recorded, 25 had locoregional, 21 had distant, and five had combined locoregional and distant failure.

No efforts were made to analyze the actual size of locoregional failure in relation to the implantation, to determine true in-field failure or whether EBRT affected the site and pattern of failure in patients with incomplete resections. No mention was made of the external-beam dose or whether elective nodal irradiation was carried out.\textsuperscript{17}

**T1-4, N1-2 NSCLC:** Prior to Martini et al,\textsuperscript{17} Burt and colleagues\textsuperscript{24} reported their experience regarding patients with T3 to T4 primary disease undergoing surgery and brachytherapy with inclusion of patients with N1 to N2 mediastinal nodal disease. From 1974 through 1984, 225 patients undergoing thoracotomy had pathologic T3 to T4, N0 to N2 NSCLC. Two-thirds of patients (68%) had N2 disease; 48% had multiple sites of mediastinal involvement, and major mediastinal structures were invaded in 48% (T4). Four modes of therapy were performed, including the following: complete resection without brachytherapy (group 1); incomplete resection with brachytherapy, using either 125I interstitial implantation or 192Ir afterloading (group 2); no resection with brachytherapy alone (group 3); and incomplete or no resection without brachytherapy (group 4). Thirty-three patients (15%) were in group 2 and 101 patients (45%) constituted group 3.

Overall actuarial survival for all patients was 22% at 2 years and 13% at 3 years. The respective overall actuarial survival at 2 and 3 years for group 2 patients was 30% and 22%, respectively, very similar to the 2- and 3-year actuarial survival in group 1 patients (20% and 21%, respectively), arguably the best prognostic group with the least tumor burden.\textsuperscript{24}

In contrast to the findings of Martini et al\textsuperscript{17} long-term survivors were observed in group 3, with 2- and 3-year actuarial survivals of 21% and 9%, respectively, although the group did fare worse than group 2. No impact of histologic type was identified. A local control rate of 70%
was quoted in this study, which appears quite impressive given that most patients had residual disease. The success may have been due in part to the addition of adjunctive EBRT preoperatively in nine patients and postoperatively in 70. However, local control rates with EBRT for locally advanced disease are historically poor. In a prospective multi-institutional trial from France using combination high-dose EBRT (65 Gy) and concurrent multidrug chemotherapy for locally advanced NSCLC, the local control based on repeat posttreatment bronchoscopy was a meager 17%, emphasizing the need for substantial improvement in the local management of disease. Most failures in the study by Burt et al were, in fact, distant. No analysis of the local failures was performed to determine whether failure was indeed within the actual implanted volume. Nevertheless, this study appears to suggest a positive correlation between the extent of locoregional therapy and survival, with some benefit directly associated with the addition of brachytherapy in patients with incomplete resections.

Hilaris et al conducted a separate analysis of 100 poor-prognosis stage III patients (T1 to T3, N0 to N2 NSCLC; 86% N2) who underwent combined surgery and interstitial implantation for gross residual disease (n = 47) or close (n = 36)/positive (n = 17) margins. All patients received postoperative mediastinal radiation to a median dose of 40 Gy 4 to 6 weeks after surgery. Doses ranged from 30 Gy in 10 fractions to 40 Gy in 20 fractions. Temporary 108I implants were performed in 55 patients in the setting of subclinical disease in the superior mediastinum or chest wall, and permanent 125I implants were placed in the balance of patients with gross residual disease.

Local control was dependent on the extent of surgical resection performed. Local control for patients with gross residual disease who received an implant was 72%, compared with 77% local control for patients with no residual disease remaining. Within the cohort of patients with no residual disease, margin status affected local outcome: 89% of patients with negative margins achieved local control vs 53% with histologically positive margins. Analysis of the dose of EBRT relative to the surgical margin status also yielded a difference in local outcome. In general, patients receiving 40 Gy had better local control than those who received less. This relation was particularly evident in the group with positive margins, in which local control was 75% with the addition of 40 Gy EBRT compared with 53% with a lower dose. Local control in patients with gross residual disease treated with intraoperative brachytherapy who received 40 Gy was 72% vs 29% in patients receiving lower doses. The extent of resection also affected survival, with 30% of patients with gross removal of disease surviving 5 years vs 13% of patients who had incomplete resections. Finally, the incidence of pneumonitis attributed to the implant was 7%.

Armstrong et al reported the long-term results of a recent prospective phase II trial of aggressive induction chemotherapy, surgical resection, selective intraoperative brachytherapy, and postoperative EBRT for patients with NSCLC and clinically evident N2 mediastinal nodal metastases. Of the 41 patients initially entered, 28 of 30 (68% of all patients) who responded to chemotherapy and an additional six who had minimal to no response went on to thoracotomy. Intraoperative brachytherapy for gross residual disease in the primary site or mediastinum was performed in nine patients, with one additional patient undergoing 125I implant for a hilar mass adherent to the pulmonary artery. (The frozen section specimen of the mass was benign.)

125I in either a planar (three patients) or volume (six patients) implant was used with an MPD of 14,700 cGy. Eight patients received postoperative chemotherapy and EBRT (median dose, 4,800 cGy in 180- to 200-cGy fractions). Despite the adverse prognostic factors in the brachytherapy group (gross residual disease and N2 metastases), actuarial thoracic progression-free survival at 2 and 5 years was 66% and 50%, respectively. All patients with gross residual disease died of their disease within 2 years, predominately due to distant failure. The median survival of the group with incomplete resection that received implants and postoperative EBRT was 19 months, reasonably similar to the 22-month median survival achieved by patients with complete resections who did not receive adjunctive radiation.

Intraoperative HDR radiation for locally advanced NSCLC has also been reported. Unlike the encouraging preliminary data published by Juettner et al for earlier stage disease, the data are less favorable with advanced disease. Calvo et al reported results on 34 patients with unresectable or incompletely resected primary or nodal tumors who received IORT ranging from 1,000 to 1,500 cGy followed by 4,600 to 5,000 cGy postoperative RT. Only 30% remained free of thoracic progression, with a median survival of 12 months. Acute pneumonitis occurred in 35% (12/34).

The use of HDR-ILBRT as a component of therapy for locally advanced NSCLC has been described but must be considered investigational, as no benefit has yet been proved. It has been used primarily as a boost for previously untreated patients in conjunction with high-dose EBRT. To our knowledge, no study has yet shown a survival benefit over EBRT alone. This is an area for future controlled, randomized study. High-dose ILBRT may also be used in the setting of locally advanced lung cancer in which a large amount of the patient’s collapsed lung precludes distinguishing tumor from normal lung tissue when attempting to define treatment portals. HDR-ILBRT will open the airway in most cases, allowing a smaller target volume to be treated with high-dose EBRT. Bastin et al calculated an average reduction of 32% of normal lung tissue spared in 21 patients treated with this approach when intraoperative brachytherapy opened the airway, providing additional blocking prior to EBRT.
**NSCLC of the Superior Sulcus**

Intraoperative brachytherapy has been used in the setting of incomplete resection and/or close or positive margins for superior sulcus tumors (Pancoast tumors) to improve local control. The first published experience (to our knowledge) using brachytherapy in this setting was a case report that described the use of $^{222}$Rn seeds.\(^{30}\)

Hilaris et al\(^ {31}\) reported results from 129 patients undergoing thoracotomy, attempted curative resection, and intraoperative brachytherapy for tumor from 1960 through 1982 at MSKCC. The patients’ mean age was 54 years (range, 33 to 72 years), and Karnofsky performance status was $\geq 80\%$ in all patients. Histologic type included squamous cell carcinoma in 66 and adenocarcinoma/large cell in 63 patients. Prior to surgery, 82 patients (64\%) received preoperative EBRT; 81 patients (63\%) underwent an attempted complete or partial surgical resection. A total of 103 patients (80\%) received interstitial brachytherapy for either gross disease or to address concerns about margin status at the time of surgery.

For all study patients, median and 5-year survival was 20 months and 25\%, respectively. For patients who had incomplete resections and brachytherapy, 5-year survival was 20\%. Patients who underwent complete resection and intraoperative brachytherapy achieved 25\% 5-year survival. Univariate analysis of prognostic factors identified histologic type, mediastinal nodal status, preoperative radiation, and the completeness of resection as variables that affected eventual outcome. In multivariate analysis, however, only nodal status and the use of preoperative radiation were predictive. Given the historically poor results of patients in that era who could not undergo surgical resection, the addition of brachytherapy appeared to benefit this subgroup.\(^ {31}\)

More recently, Ginsberg and associates\(^ {32}\) have attempted to reassess the role of brachytherapy in the treatment of superior sulcus tumors, primarily in the setting of a complete resection. This retrospective study analyzed 124 patients presenting with untreated superior sulcus tumors between 1974 and 1991 who underwent thoracotomy with or without brachytherapy as a component of treatment. Ninety-one patients presented with T3 to 4N0M0 disease, and 27 had regional nodal metastases (N2 to N3). Four patients were excluded from analysis after intraoperative findings of metastatic pleural spread (M1) or lung parenchyma. The majority (n=79) had received preoperative radiotherapy (median dose, 40 Gy), and an additional 28 had postoperative radiotherapy. Ten patients received both preoperative and postoperative radiotherapy. A small subset of patients also received induction chemotherapy in the setting of clinical N2 disease.

The extent of surgical resection included 69 patients who underwent complete gross resection, 31 who had incomplete resection, and 24 who had biopsy alone. Of the 69 patients who had a complete resection, 49 underwent permanent implantation because of concern about margins that later turned out to be negative. Patients with either residual gross tumor or close/positive margins as determined by frozen section (n=55) also received permanent intraoperative interstitial implants with $^{125}$I, $^{192}$Ir, or $^{103}$Pd sources. Postoperative RT was provided to patients who received no preoperative treatment and to supplement the implant dose in patients with implants.

The overall actuarial 5-year survival for the entire group (n=124) was 26\%.\(^ {32}\) Complete resection was the most significant predictor of outcome, with a 41\% 5-year survival rate observed vs 9\% for patients with incomplete resections. Brachytherapy did not appear to benefit patients with complete resections when compared with the subgroup that did not receive an implant and had a complete resection (n=20). The 5-year survival rate was 54\% without brachytherapy and 35\% with the addition of brachytherapy. Despite the improved survival results in the patients with complete resections, local failure as a component of overall failure was still unacceptably high (69\%) and not significantly different from the group with incomplete resections (77\%). Brachytherapy may have provided some patients with local control, although it is not clear what the true pattern of local failure was in relation to the implant, and no differences in outcome were seen between patients who underwent incomplete resection or biopsy alone followed by brachytherapy.\(^ {32}\)

One of the difficulties with implanting radioactive sources in the setting of close/positive margins within the superior sulcus is that the local anatomy has inevitably been disturbed despite adequate visualization, potentially masking the true extent of the margins at risk. It is important to attempt to correlate preoperatively the extent of disease as seen on CT or MRI and consider implanting the preoperative volume rather than the residual area of concern, which in many cases represents a judgment call by both the surgeon and the brachytherapist. At our institution, patients are currently seen by the brachytherapist prior to surgery to decide with the referring surgeon if brachytherapy is a potential option and to gain an understanding of the extent of disease.

Despite aggressive surgical and radiotherapeutic combinations to treat Pancoast tumors, the local outcome generally remains dismal, with the exception of patients undergoing a complete en bloc resection with a negative mediastinum. This has led to recent efforts to incorporate induction chemotherapy into a combined trimodality approach. In addition, different methods of delivering intraoperative brachytherapy for Pancoast tumors are under investigation.

Martinez-Monge and associates\(^ {33}\) have reported the results of a novel pilot trial in 18 patients with Pancoast tumors employing induction chemotherapy with mitomycin, vinblastine or cyclophosphamide, and cisplatin (MVP/ MCP); concurrent radiation (46 to 50 Gy); and chemotherapy (MVP, MCP, or cisplatin and fluorouracil), followed by surgical resection and 10 to 15 Gy intraoperative electron-beam radiation.

Complete resection was achieved in 76\% of patients, with positive margins in 3 patients (17\%). Analysis of surgical specimens revealed a striking 70\% CR rate.\(^ {33}\) Tumors measuring <5 cm achieved a 100\% CR to induction treatment compared with 45\% CR for patients with larger tumors. With a median follow-up of 24 months, the 4-year actuarial local control rate is 91\%.\(^ {33}\) The overall
actuarial survival at 4 years, 56%, was substantially higher in patients with no viable tumor in the specimen (87%). Although active, this regimen was not without toxic reaction. Three patients died of treatment-related complications, including one who died of hemoptysis prior to surgery and two patients who died postoperatively after developing empyemas. Although promising, this study cannot adequately assess the impact of IORT owing to the lack of a control arm. 31

Stage IV NSCLC

Brachytherapy for stage IV NSCLC or intrathoracic endobronchial metastases from sites other than lung is an alternative palliative option. The most common method used today is through HDR-ILBRT, which has largely replaced direct permanent implantation into endobronchial tumors. The largest reported experience with this approach is from MSKCC. From 1946 through 1984, 133 patients underwent permanent insertion of radioactive 222Rn or 125I via rigid bronchoscopy. The majority of successful treatments occurred with tumors arising in the trachea or at the bronchial stump. 34 Local control was observed in 56% of patients with primary tumors when brachytherapy was used as a component of treatment and 60% in the group with recurrent disease. 35 Despite the fact that a significant number of patients achieved palliation, resultant morbidity included airway perforation, hemorrhage, or ventilatory arrest, leading to subsequent investigation of remote afterloading therapy. 36

The technique of administering endoluminal therapy has been described previously. The introduction of flexible bronchoscopes with a separate port for afterloading catheter placement has simplified the procedure immensely. Overall, hemoptysis is relieved in approximately 50 to 90% of cases, dyspnea improves in 50 to 65%, and intractable coughing is abated in about 60% of patients. 8 The median duration of symptomatic palliation ranges from 4 to 6 months—the median survival time of most patients. Treatment can be delivered in single or multiple fractions, with the dose per fraction and final dose dependent on tumor location, previous laser or external-beam treatment, and the patient’s medical condition.

Several single institutions and private groups have reported their experiences regarding the efficacy of HDR-ILBRT (Table 1). 36, 37 Mehta et al. 9 in a novel pilot study, compared sequential LDR with hyperfractionated HDR endoluminal treatment. Thirty-one patients with malignant occlusions received 4 Gy×4 fractions over 2 days 2 cm from the source center. This regimen was compared with LDR treatment delivered in one setting to 61 patients with a median implant duration of 45 h. Symptomatic improvement (79% vs 78%) and overall radiographic response (85% vs 78%) for HDR and LDR, respectively, were similar. The overall fistula rate was 7 of 101, with no differences between regimens. This offers a convenient, cost-effective, and safe way of delivering HDR treatment. 9

The incidence of overall complications ranges from 3% to as high as 35%; complications have included fistula formation, radiation bronchitis, pulmonary hemorrhage, tracheobronchial perforation, ulceration, stenosis, or necrosis. 38 In one series, the high incidence of hemorrhage was observed more frequently in upper lobe tumors, where catheters were placed in proximity to the pulmonary artery. 39

Malignant Pleural Mesothelioma

Hilarsi et al. 35 published the initial experience at MSKCC regarding the use of brachytherapy for malignant pleural mesothelioma in 1984. Forty-one patients with malignant pleural mesothelioma confined to one hemithorax underwent thoracotomy from 1976 to 1982. Surgery consisted of complete or as near as complete gross resec-

Table 1—Results With HDR-ILBRT for Palliation of Incurable or Recurrent NSCLC*

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>No. of Patients</th>
<th>Mean Fx/ Mean Total Dose, Gy</th>
<th>Overall Response, %</th>
<th>Patients Maintaining Palliation Through Life, %</th>
<th>Overall Improvement in Symptoms, %</th>
<th>Improv in Hemoptysis, %</th>
<th>Improv in Cough, %</th>
<th>Improv in Shortness of Breath, %</th>
<th>Median Survival, mo</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustafson et al., 1995</td>
<td>46</td>
<td>3/21</td>
<td>69</td>
<td>38</td>
<td>74</td>
<td>8</td>
<td>62</td>
<td>60</td>
<td>7% Fatal hemoptysis</td>
<td></td>
</tr>
<tr>
<td>Gollins et al., 1994</td>
<td>406</td>
<td>1/15</td>
<td>67</td>
<td>66</td>
<td>88</td>
<td>62</td>
<td>60</td>
<td>4</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Nori et al., 1993</td>
<td>32</td>
<td>3/15</td>
<td>80</td>
<td>97</td>
<td>100</td>
<td>86</td>
<td>100</td>
<td>4</td>
<td>0%</td>
<td></td>
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<tr>
<td>Mehta et al., 1992</td>
<td>31</td>
<td>4/16</td>
<td>57</td>
<td>79</td>
<td>87</td>
<td>50</td>
<td>52</td>
<td>7% Fistulas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speiser, 1993</td>
<td>342</td>
<td>3/22.5</td>
<td>99</td>
<td>85</td>
<td>86</td>
<td>5.6 Palliative vs 6.5 recurrent</td>
<td>7% Hemoptysis, 11% radiation stenosis and bronchitis</td>
<td></td>
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</tr>
</tbody>
</table>

*aLC=local control; Fx=fractions.
tion as possible followed by implantation, when feasible, of residual gross disease with 125I permanent radioactive seeds. Residual diffuse disease was either implanted with temporary 192Ir sources or with postoperative instillation of phosphorus 32 (32P). Mixed-beam EBRT was delivered postoperatively to the involved hemithorax to a dose of 45 Gy. Median survival and 1- and 2-year survivals were 21 months, 65%, and 40%, respectively. Median disease-free survival was 11 months, with 1- and 2-year disease-free survivals of 44% and 13%, respectively.35 Seven patients experienced relapses in the treated mediastinum alone (17%), and an additional 22 patients had failures both distally and locally (54%). This analysis appeared, however, to show an improvement over historical survival rates (median, 6 months; 1- and 2-year survival rates, 25% and 7%).33

More recently, Mychalczak et al40 updated this experience by analyzing a larger cohort of patients. From 1976 through 1988, 105 patients were treated with the same approach. Fifty-four patients (51%) received implants—either permanent 125I (n=46) and/or temporary 192Ir (n=14). Forty-one patients had minimal residual disease and did not receive an implant. Overall median survival was 12.6 months, with 1- and 2-year survival rates of 52% and 23%. In multivariate analysis, patients with epithelial histologic types demonstrated superior survival outcome. For this subgroup, median survival was 18 months, and 1- and 2-year survival rates were 60% and 30%. For patients with either sarcomatous or mixed histologic types, median, 1-, and 2-year survival rates were 11 months, 30%, and 11%, respectively.40 Patients with minimal residual disease also demonstrated superior outcomes vs patients with gross residual disease, evidenced by median, 1-, and 2-year survival rates of 15 months, 68%, and 35%, respectively. Patients with gross residual disease undergoing brachytherapy achieved median, 1-, and 2-year survivals of 11 months, 41%, and 15%, respectively. Finally, patients with implants at only one site fared better than those with implants at three or more sites. The survival in this group was no different than in the group of patients who underwent no implant due to extensive gross diffuse disease (n=10).

Patients with epithelial histologic types and minimal residual disease had the best outcome, demonstrating median, 1- and 2-year survival rates of 23 months, 85%, and 41%, respectively.40 Local failure or disease progression occurred in 64 patients (61%). There were 20 reported complications including 12 with radiation pneumonitis and 8 with pericardial tamponade. The role of brachytherapy in contributing to the complications is not clear. Debulking surgery in this study appeared to be of benefit, with possible benefit also seen with the use of brachytherapy for minimal residual gross disease only. Patients with three or more implant sites did not benefit from brachytherapy.38

Currently, a phase II trial is underway at MSKCC to investigate a combined approach to the treatment of malignant pleural mesothelioma combining gross surgical resection, HDR intraoperative RT using the HAM applicator, and EBRT to the involved hemithorax.

### Invasive Thymoma

Sidebotham et al41 reported the results of 15 patients treated with brachytherapy as a component of their management for invasive primary and recurrent thymoma from 1979 through 1994. Patients underwent surgical resection, followed by either permanent 125I implant alone (n=12), combined 125I and temporary 192Ir implant (n=2), or 192Ir followed by intrapleural 32P (n=1). Eight patients had primary thymoma at evaluation and the balance had recurrent disease. Implants were placed in 10 patients for positive microscopic margins; 5 received implants for gross residual disease. Postoperatively, nine patients received adjuvant EBRT (median dose, 45 Gy). The median follow-up was 4 years.

The crude locoregional control rate was 85% (11 of 13 evaluable patients). The actuarial locoregional control rate at 5 years was 83%.40 One patient had failure with multiple pleural-based metastases 3 years after implantation and eventually developed distant spread; the other patient who died was found incidentally at autopsy to have local recurrence after dying of intercurrent disease 6 years after implantation. Actuarial 5-year survival rate was 91%. Interestingly, the survival rate was no different between primary and recurrent cases, with two thirds of recurrent cases controlled with the addition of brachytherapy, suggesting a potential for salvage for this poor-prognosis group. Both failures occurred in patients who underwent subtotal gross resection; notably, neither failure occurred within the implanted volume.41

### Conclusion

Despite current advances in multimodality therapy for malignancies arising in the chest, a large proportion of patients develop local and/or regional failures. To improve the therapeutic ratio, radiation oncologists have attempted to develop novel strategies for delivering high-dose radiation to the tumor or tumor bed with selective sparing of surrounding normal structures. Some of these strategies include interstitial permanent and temporary implantation, LDR- and HDR-ILBRT, and intraoperative RT through the use of either modified linear accelerators or, more recently, the HAM applicator. The continuing evolution of new isotopes and methods of delivery should help to improve existing results. The data to date appear to suggest that brachytherapy may improve local outcome and, possibly, survival in selected situations, and should be considered as a viable treatment option in planning a multimodality approach.

In general, the treatment is well tolerated with few reported complications. Longer follow-up is needed to truly assess long-term complications, especially in implants for Pancoast and paraspinal tumors. Patients with locally advanced disease in which the primary cause of death is distant failure may not have lived long enough to develop complications.

Future directions for the use of brachytherapy include the following: potential use of video-assisted thoracoscopy as a minimally invasive method for the placement of radioactive sources in an unresectable tumor in the lung or...
chest wall; percutaneous brachytherapy for superficial lesions of the chest wall; and radiolabeled monoclonal antibodies for direct targeting of tumor cell antigens. HDR intraoperative RT brachytherapy for a variety of pediatric malignancies arising in the chest is also currently under investigation at MSKCC to limit the amount of EBRT in this population, in which the sparing of normal tissues and future quality-of-life issues are of paramount importance.

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