Lung cancer is the leading cause of cancer mortality in the United States. Local recurrence after surgery for operable disease has long been recognized as a hindrance to long-term survival. Postoperative radiation therapy was logically explored as a means to improve local control and survival. Multiple randomized trials were conducted, many showing improved local control, but none demonstrated a statistically significant survival benefit.
An extraordinarily influential and controversial 1998 report by the Postoperative Radiation Therapy (PORT) Meta-analysis Trialists Group showed that postoperative radiation therapy (RT) was associated with a 21% relative increased risk of death in patients with lung cancer.[1] Interestingly, this was not the first meta-analysis suggesting that an adjuvant treatment was potentially detrimental. Three years earlier, the Non-Small Cell Lung Cancer Collaborative Group published a meta-analysis of adjuvant chemotherapy trials,[2] demonstrating a 15% relative increased risk of death at 2 years with long-term alkylating agents. Knowing that distant metastases develop in a significant proportion of patients, further studies successfully sought to optimize chemotherapy delivery (appropriate agents, number of cycles, etc). Local failure, as will be shown, is also a considerable obstacle to cure in resected lung cancer. How postoperative RT can be optimized to safely decrease this risk and improve survival will be the focus of this review.
Local/Regional Failure: Defining the Risk
An accurate assessment of the risk of local (ie, local/regional) recurrence after surgery is necessary to guide postoperative therapy. In malignancies in which the risk of local recurrence is relatively high, postoperative RT generally improves outcomes (eg, cancers of the breast, rectum, and central nervous system). On the other hand, in malignancies with low rates of local recurrence after surgery, postoperative RT has not generally produced a benefit (eg, cancers of the colon, bladder, and kidney).

![Table 1: Rates of Local/Regional Failure After Surgery for Stage I NSCLC](image)

In lung cancer, unfortunately, determining the risk of local recurrence after surgery is not a straightforward task. Most prospective studies have not reported patterns of failure. When rates of local failure are reported, these are typically given as crude percentages in lieu of actuarial rates. Crude rates are influenced by the length of follow-up (Figure 1) and risk of death from other causes, and will always underestimate the true risk.

Furthermore, many studies only report first sites of failure. Distant metastases commonly develop
after surgery for lung cancer and are typically easier to assess radiologically than local/regional failures. Unless there is a thorough evaluation at the time of relapse (to assess for a concurrent local failure), this may also underestimate the true risk.

Finally, the definition of local failure varies in both prospective and retrospective studies. For example, in the recently published Adjuvant Navelbine International Trialist Association (ANITA) trial,[3] local failure was defined as an "ipsilateral mediastinal relapse." Other sites of failure, such as the contralateral mediastinum, were scored as distant failures. This is clearly a narrow definition of "local" failure and is potentially misleading. Most investigators would define a local (ie, local/regional) relapse as a failure at the surgical margin or in ipsilateral hilar and/or mediastinal lymph nodes.

With an understanding of these limitations, an attempt to define the risk of local recurrence follows.

<table>
<thead>
<tr>
<th>Lead Author (Location)</th>
<th>Type</th>
<th>N</th>
<th>Median follow-up</th>
<th>Local/Regional Failure</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sawyer[9] (Mayo)</td>
<td>Retrospective</td>
<td>107</td>
<td>28 mo</td>
<td>38% (23% crude rate)</td>
<td>Actuarial (5 yr)</td>
</tr>
<tr>
<td>Luzzi[45] (Italy)</td>
<td>Retrospective</td>
<td>116</td>
<td>49 mo</td>
<td>25% overall 7% with pneumonectomy 34% lobectomy</td>
<td>Crude</td>
</tr>
<tr>
<td>Kim[46] (Korea)</td>
<td>Retrospective</td>
<td>98</td>
<td>51 mo</td>
<td>20% overall 9% with pneumonectomy 30% with sleeve resection</td>
<td>Crude; only R0 resections</td>
</tr>
<tr>
<td>Lardinois[43] (Switzerland)</td>
<td>Retrospective</td>
<td>23</td>
<td>89 mo</td>
<td>35% overall 17% with mediastinal dissection 57% with mediastinal sampling</td>
<td></td>
</tr>
<tr>
<td>Feng[47] (China)</td>
<td>Prospective</td>
<td>82</td>
<td>NS</td>
<td>29%</td>
<td>Crude</td>
</tr>
<tr>
<td>Immerman[44] (Northwestern)</td>
<td>Retrospective</td>
<td>22</td>
<td>&gt; 60 mo</td>
<td>41%</td>
<td>Crude</td>
</tr>
</tbody>
</table>

*Included in Figure 1.
NS = not stated; NSCLC = non-small-cell lung cancer.

**Stage I/II**
It is generally believed that the risk of local recurrence after lobectomy for stage I non–small-cell lung cancer (NSCLC) is low. However, there is substantial variation in the literature, with rates ranging from 6% to 45% (Table 1 and Figure 1). It is noteworthy that studies with local control as a primary endpoint[4-6] have generally reported higher rates of local failure than those with other primary endpoints, such as disease-free survival.[7,8] It is likely that the diligence with which local control is assessed and recorded is affected by this detail.
The incidence of local recurrence after surgery for stage II NSCLC is generally higher than with stage I. Crude rates range from 7% to 55% (Table 2 and Figure 1). The only study reporting an actuarial rate was from the Mayo Clinic, which demonstrated a 38% risk of local failure at 5 years (crude rate was 23%).[9]

**Stage III**

Similar to early-stage disease, reported rates of local recurrence after surgery for stage III NSCLC vary dramatically (Table 3 and Figure 1). However, most studies, especially those reporting actuarial rates, indicate that the risk is substantial (> 50%). Such high rates of local failure are not surprising. Microscopic deposits of tumor likely infiltrate throughout the mediastinal lymphatic network, making a curative en bloc "cancer resection" impractical.

**Chest Wall Invasion**

Patients presenting with invasion of the chest wall represent a small but heterogeneous population, ranging from limited invasion of the parietal pleura without regional nodal involvement (T3, N0) to extensive chest wall invasion with involved mediastinal lymph nodes (T3, N2). The most consistent negative prognostic factors are involved regional lymph nodes[10-15] and positive surgical margins.[13-15] The surgical literature is replete with single-institution, retrospective series. The surgical approach and use of postoperative RT is variable. The risk of "local recurrence," usually referring to chest wall recurrences, is reported to range from 1% to 13%.[11,13-16] Regional recurrence rates are a bit higher—up to 26%. As noted above, these reported rates should be taken as lower estimates of the true risk of relapse.
Predictors of Local Recurrence

Several clinical and pathologic features are associated with a higher risk of local recurrence (Table 4). Not surprisingly, the extent and completeness of surgery are the most consistent factors. The Lung Cancer Study Group randomized 247 patients with T1, N0 NSCLC to lobectomy vs a more limited resection (wedge or segmentectomy).[17] A "local failure" was defined as a recurrence confined to the ipsilateral lung or mediastinum (failures involving both local and distant sites were not scored as local failures). The crude local recurrence rate was 6% in the lobectomy arm and 17% in the limited-resection arm. Several retrospective studies have also demonstrated higher rates of local recurrence with more limited surgery.[18-21]

Positive surgical margins, as would be expected, substantially increase the risk of local recurrence, even with postoperative RT.[20,22-24] Several retrospective studies have demonstrated an increased risk of local recurrence with systematic mediastinal sampling compared with mediastinal dissection.[21] However, stage migration resulting from more thorough pathologic examination is likely a contributing factor. Indeed, two small randomized trials have shown equivalent rates of local recurrence with either approach.[25,26] Results from the American College of Surgeons Oncology Group (ACOSOG) Z0030 trial, which randomized 1,111 patients with stage I/II NSCLC between mediastinal sampling and dissection, are maturing.

PORT Meta-analysis
The PORT meta-analysis included individual patient data (N = 2,128) from nine randomized trials conducted between 1965 and 1995. Radiotherapy details from these studies can be found in Table 5. Collectively, postoperative RT was associated with a 21% relative decrease in survival, corresponding to a 7% absolute decrease at 2 years (Figure 2). Postoperative RT was more detrimental in patients with early-stage disease (N0/1). For patients with N2 disease, no evidence of benefit or detriment was seen (Figure 3).

The PORT meta-analysis clearly shows that postoperative RT, as administered in the individual studies, was detrimental. Treatment-related mortality, likely from cardiopulmonary toxicity, was probably responsible for the survival detriment. Whether the oft-cited criticisms of radiation delivery (nonconformal treatment planning, doses > 50–54 Gy, fraction sizes > 2 Gy/d, poor RT technique) were responsible cannot be ascertained. Several of the individual studies showed that RT decreased the risk of local failure (Table 6). Indeed, the meta-analysis demonstrated an overall 24% reduction in the risk of local recurrence. However, it is unclear whether this was secondary to improved disease control or simply accelerated mortality in the RT arm occurring before local failures could arise.
The stage-dependent detriment in survival is intriguing. The studies in the PORT meta-analysis generally treated all patients the same, regardless of disease stage. Thus, the absolute rate of treatment-related mortality would be expected to be similar regardless of disease stage. Collectively, postoperative RT was associated with a 7% absolute detriment in survival at 2 years. The hazard ratio (HR) for all patients was 1.21 but it was > 1.50 for patients with stage I disease. Thus, the absolute detriment in survival for stage I patients was larger than 7%, although this number is not provided in the PORT meta-analysis. Patients with stage III disease were likely exposed to that same absolute risk of treatment-related death. However, RT was actually associated with a very slight, but not statistically significant, improvement in survival (HR = 0.97) in these patients. This suggests that the increase in cancer-specific survival and treatment-related toxicity were both fairly large but completely offset each other. Therefore, if RT-induced toxicity can be reduced, PORT should improve both cancer-specific and overall survival.

The other primary consideration in interpreting the PORT meta-analysis is the lack of systemic therapy. Patients at highest risk of developing a local recurrence (higher stage, increasing number of involved lymph nodes) are also those at highest risk of developing distant metastases. Improved local control will only affect overall survival if distant micrometastases are treated. With more effective systemic therapy, local control will became a more pressing issue.
Cause of death is often difficult to ascertain, especially in older patients with lung cancer and other medical comorbidities related to smoking. This may be one reason that cause of death was not reported in many of the postoperative RT randomized trials. Two studies did report higher intercurrent death rates with postoperative RT.\[27,28\] These were primarily, but not exclusively, related to cardiopulmonary disease. The published survival curves in the PORT meta-analysis show an almost immediate separation, which becomes readily apparent by approximately 4 to 6 months, suggesting that most treatment-related deaths were occurring relatively quickly after completion of therapy. It is possible that acute toxicities generally considered to be transient, such as esophagitis, predisposed this population of patients to lethal respiratory and cardiac complications.

Attempts have been made to assess whether modern radiation treatment planning and delivery is associated with a lower intercurrent death rate. Using Surveillance, Epidemiology and End Results (SEER) data from 1983 to 1993, Lally et al demonstrated that postoperative RT was associated with an increase in heart disease mortality during the early years of the period (HR = 1.49, P = .01) but not during the latter years (HR = 1.08, P = .64).\[29\] Interestingly, the heart disease-specific survival curves in patients treated between 1983 and 1988 began to separate approximately 3 years after diagnosis. This is in contrast to the PORT meta-analysis data, which showed divergence much earlier, suggesting an additional cause for mortality beyond heart disease.

The Eastern Cooperative Oncology Group (ECOG) E3590 trial randomized patients with resected stage II–IIIA NSCLC to observation or cisplatin-based chemotherapy. All patients received postoperative RT (50.4 Gy in 1.8 Gy fractions). The observed intercurrent death rate was not significantly different from the expected rate, based on mortality rates for age- and gender-matched controls.\[30\] Retrospective data from the University of Pennsylvania demonstrated that the risk of death from intercurrent disease was not increased when doses < 54 Gy were utilized.\[31\]

Evidence-Based Treatment Recommendations

Stage I/II

In the absence of positive surgical margins, postoperative RT is not currently recommended for stage I NSCLC. This stance, it must be emphasized, is not necessarily based on a low risk of local recurrence, but on convincing data demonstrating a rather large detriment in survival with postoperative RT from treatment-related toxicity. For example, RT was associated with approximately a 50% relative decrease in survival in patients with stage I disease in the PORT meta-analysis. Whether improved RT techniques could overcome this striking statistic is unknown.

A recent randomized study from Italy,\[5\] not included in the 1998 meta-analysis, assessed the utility of postoperative RT directed at only the surgical stump and ipsilateral hilum. Three-dimensional treatment planning was utilized, and the total dose was 50.4 Gy in conventional fractionation. In this small study of 104 patients with pathologic stage I disease, the investigators found statistically significant improvements in local control (98% vs 77%, P < .01) and 5-year survival (67% vs 58%, P = .048). However, a recent update of the PORT meta-analysis\[32\] reports that with further follow-up and corrections to the original database, the survival advantage is no longer statistically significant (P = .22). A trial update has not been published to date.

Similar to stage I NSCLC, postoperative RT cannot be routinely recommended for patients with stage II (T1/2, N1) disease. The PORT meta-analysis demonstrated decreased survival with postoperative RT in both stage I and II disease (Figure 3). Similarly, a recent analysis of SEER data also suggested a detriment in patients with stage II disease, with a hazard ratio for survival of 1.097.\[33\] However, since SEER data are retrospective, it is possible that patients with more adverse pathologic factors (close or positive margins, inadequate mediastinal sampling, multiple positive lymph nodes, etc) were those in whom postoperative RT was administered.

The ANITA study allowed postoperative RT at the discretion of the individual centers, and like SEER data, was not controlled. Five-year survival for patients with N1 disease was 56% with chemotherapy alone and 40% with chemotherapy and postoperative RT. In those who did not receive chemotherapy, 5-year survival was 43% with postoperative RT and 31% without RT. Because the use of RT was not controlled in either arm (chemotherapy or observation), it is not possible to make any conclusions. Despite a relatively high risk of local recurrence, the routine use of postoperative RT for patients with N1 disease is questionable.
Stage III

Only one randomized trial limited eligibility to patients with stage III (N2) disease. Conducted in Slovenia, this study randomized 74 patients to observation or RT (30 Gy in 10 fractions). Five-year survival was 28% with observation and 33% with RT, a difference that was not statistically significant. Several other randomized studies included patients with stage III disease (Table 6). An overall survival advantage for postoperative RT was not demonstrated in any individual study (on subgroup analysis) nor collectively in the PORT meta-analysis. Indeed, the meta-analysis showed that stage III patients statistically fared neither worse nor better with RT.

However, the risk of local/regional failure after surgery, with or without chemotherapy, is high for patients with involvement of mediastinal lymph nodes (Table 3). Recent studies have shown that adjuvant chemotherapy improves survival in stage II–IIIA NSCLC.[3,34,35] Two recent trials have allowed postoperative RT and provide some insight into the potential role of RT in stage III disease using relatively contemporary doses and techniques.

The most recent randomized trial is the ANITA study. This trial randomized 840 patients (stage IB–IIIA) between 1994 and 2000 to adjuvant chemotherapy (cisplatin and vinorelbine) or observation. As mentioned previously, the use of postoperative RT was not randomized but given at the discretion of the participating center. RT doses ranged from 45 to 60 Gy in 2-Gy fractions and were given after completion of chemotherapy. A higher percentage of patients in the control arm received RT than in the chemotherapy arm (33% vs 22%). Specific statistical analyses of the effects and outcomes for patients receiving postoperative RT were not published.

It was noted that in patients with stage III disease randomized to receive chemotherapy, 5-year survival for those who received postoperative RT was 47% vs 34% for those who did not receive RT. In patients randomized to observation, the 5-year survival was 21% with postoperative RT and 17% without. The authors concluded that although there were no data to substantiate the use of postoperative RT, its use "could be considered" for those with N2 disease. It should be emphasized that postoperative RT was not a randomized variable and, therefore, no conclusions concerning the
strategy's effectiveness (or lack thereof) can be drawn from these data.

The International Adjuvant Lung Cancer Trial (IALT) evaluated the effect of adjuvant cisplatin-based chemotherapy compared to observation for patients with pathologic stage I–III disease. Postoperative RT was given at the discretion of the participating center to a dose of 60 Gy or less with "conventional fractionation." Approximately 25% of all patients in the study received RT to a median dose of 50 Gy. Patients randomized to chemotherapy received RT after completing chemotherapy. As in the ANITA study, slightly more patients in the control group received RT (28% vs 23%). While there was no significant interaction between RT and chemotherapy with respect to survival (P = .66), RT outcomes were not specifically reported.

SEER registry data have also been used to assess the value of postoperative RT in the modern era. Data from nearly 7,500 patients with stage II/III NSCLC (including ~2,000 with N2 disease) were analyzed by Lally et al.[33] All patients underwent either lobectomy or pneumonectomy, and most were not expected to have received chemotherapy, since this was not standard practice during the study period (1988–2002). The study found that the general use of postoperative RT did not have a significant impact on survival but appeared beneficial for those with N2 disease (HR = 0.855; 95% confidence interval [CI] = 0.762–0.959). As mentioned previously, the use of postoperative RT was associated with a significant decrease in survival for those with N0 or N1 disease. This retrospective analysis provides a compelling rationale for prospective trials evaluating the role of postoperative RT for patients with N2 disease in the modern era.

In summary, there is insufficient evidence from randomized trials to support the routine use of postoperative RT in stage III NSCLC. Two cooperative group trials were initiated comparing chemotherapy against chemotherapy and postoperative RT, but both were closed due to poor accrual. A French randomized trial (IFCT 0503) of chemotherapy vs chemotherapy and postoperative RT is currently in progress. For now, patients must be counseled concerning the risk of local recurrence and the uncertain benefit of postoperative RT administered with modern techniques.

Chest Wall Invasion
After complete resection of disease involving the chest wall, the reported risk of local (chest wall) recurrence is relatively low. The preponderance of data, albeit retrospective, does not support routine postoperative RT.[11,12,14,16] However, from first principles, aggressive cancers that invade into adjacent normal structures (eg, the chest wall) typically have a relatively high rate of local relapse. The local relapse rates noted above are "low" estimates of the true relapse rate. Indeed, local invasion of adjacent normal tissues is typically considered an indication for postoperative RT in almost every other disease site. Thus, in these patients, it is reasonable to consider postoperative RT, albeit without good supporting data. Patients with involved lymph nodes, particularly N2 disease, have a much worse prognosis. As is the case for stage IIIA disease in general, postoperative RT should be considered in this population.[12]

RT Techniques
Field
Traditional postoperative RT fields are rather large and encompass virtually all sites of potential subclinical disease in the chest including the surgical stump, ipsilateral hilum, and entire mediastinum. Inclusion of the ipsilateral supraclavicular field is sometimes advocated for upper-lobe tumors or when high paratracheal lymph nodes are involved. All of the randomized studies in the PORT meta-analysis utilized such fields. Assuming the detrimental effect of RT arose from normal tissue injury, one must question whether this tactic is advisable.

In the absence of prospective data, no firm recommendations in this regard can be made. The bronchial stump has been shown in several retrospective analyses to be the most likely site of local tumor recurrence.[36,37] At a minimum, the bronchial stump, ipsilateral hilum, and involved mediastinal lymph node stations should be treated. Inclusion of other sites must be individualized and based on a rational understanding of lobe-specific lymphatic spread,[38,39] patterns of failure after surgery,[37] and patient-specific factors such as pulmonary function. It is possible that the therapeutic ratio may be improved if only those sites most at risk are treated (with less normal tissue exposure), as opposed to all possible intrathoracic sites.
Fraction Size
It is an established principle in radiobiology that the risk of late effects increases when higher radiation fraction sizes are utilized. Several of the randomized studies in the PORT meta-analysis used daily doses in excess of 2 Gy.[28,40,41] In a randomized study by the Groupe d'Etude et de Traitement des Cancers Bronchiques (GETCB),[28] patients were treated with daily doses ranging from < 2 Gy to 2.5 Gy. Non-cancer-related deaths occurred in 7% of patients in the control arm, 16% to 18% of patients who received ≤ 2 Gy/fraction, and 26% of patients who received > 2 Gy/fraction. Since this was not a random comparison, it is possible that confounding factors contributed to these findings. However, it is strongly recommended that daily doses of 1.8 to 2 Gy are utilized in the postoperative setting.

Total Dose
The dose necessary to provide a high rate of local control after surgery is not known with certainty. The studies in the PORT meta-analysis used a wide range of doses. Using the linear-quadratic model, the biologically equivalent dose (in 1.8- to 2-Gy fractions) ranged from 33 to 64 Gy. There are simply no prospective studies addressing this issue, and retrospective dose-response data are limited.[22] Several randomized studies showed an improvement in local control with RT using doses of 50 to 54 Gy, with control rates exceeding 90%.[5,27,42] Postoperative RT doses for other carcinomas range from 45 to 50 Gy (gastric, cervical, endometrial) to greater than 60 Gy (prostate, breast, head and neck). To some degree, the dose is constrained by what can be safely delivered. Retrospective data from Machtay et al suggest that intercurrent death rates rise with doses above 54 Gy.[31] After a margin-negative resection, doses from 45 to 54 Gy are certainly reasonable. In cases of positive margins, treatment should be boosted to a higher dose (60–66 Gy).

When treating patients in the postoperative setting, the number of malignant cells within the irradiated volume may vary widely (eg, from 1 to 109). Therefore, the dose needed to sterilize residual local/regional disease will also vary widely. It is reasonable to consider that those patients with a high residual tumor burden (theoretically requiring a higher RT dose) are most likely to harbor systemic micrometastases, and are thus less likely to derive a survival benefit from postoperative RT. Conversely, those with a lower tumor burden (theoretically requiring a lower RT dose) may be less likely to harbor systemic disease and more likely to benefit from this local effect. Thus, the therapeutic ratio of postoperative RT may be higher at lower doses.

Incorporation With Chemotherapy
Positive margins are a poor prognostic factor, even with postoperative RT. In this relatively rare circumstance, assuming re-resection is not feasible, concurrent chemotherapy and radiation therapy may be considered. Most contemporary studies (IALT, ANITA) delivered postoperative RT after completion of adjuvant chemotherapy. A sequential approach likely decreases the magnitude of acute side effects of thoracic RT and may decrease the risk of late effects. In the absence of definitive studies to the contrary, a sequential approach is recommended.

Conclusions
Non-small-cell lung cancer remains the leading cause of cancer mortality in the United States and abroad. Even patients with early disease are at relatively high risk of disease recurrence and death. Modern chemotherapy regimens have decreased the risk of developing distant metastases and have provided modest survival gains. However, local recurrence remains a significant obstacle to cure for all stages of disease. Postoperative RT has the potential to have a significant impact, especially when combined with effective systemic therapies.

The PORT meta-analysis has been instrumental in promoting necessary changes to RT delivery. The modern standards of conformal treatment planning, modest doses, and rational field design are vital in ensuring that patients benefit from treatment. However, there remains little definitive evidence for postoperative RT in any setting. Given the recognized risk of local recurrence and the established ability of RT to control microscopic disease, combined with modern radiation techniques and more effective systemic therapies, a reanalysis of postoperative RT seems prudent.

This article is reviewed at the following links:
Does PORT Have a Role in Lung Cancer?
PORTable Indications in Non-Small-Cell Lung Carcinoma

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