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Empiric Radiotherapy for Lung Cancer Collaborative Group multi-institutional evidence-based guidelines for the use of empiric stereotactic body radiation therapy for non-small cell lung cancer without pathologic confirmation

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Abstract: The standard of care for managing early stage non-small cell lung cancer (NSCLC) is definitive surgical resection. Stereotactic body radiation therapy (SBRT) has become the standard treatment for patient who are medically inoperable, and it is increasingly being considered as an option in operable patients. With the growing use of screening thoracic CT scans for patients with a history of heavy smoking, as well as improved imaging capabilities, the discovery of small lung nodes has become a common dilemma. As a result, clinicians are increasingly faced with managing lung nodules in patients in whom diagnostic biopsy is not safe or feasible. Herein, we describe the scope of the problem, tools available for predicting the probability that a lung nodule is a malignancy, staging procedures, benefits of pathology-proven and empiric SBRT, considerations of safety based on location of the lesion of concern, and overall efficacy of SBRT.

Keywords: Stereotactic body radiation therapy (SBRT); empiric; pathologic confirmation; tissue diagnosis; radiographic

Introduction

The standard treatment of early-stage non-small cell lung cancer (NSCLC) has been surgical resection when feasible. However, in patients who are surgically or medically inoperable or by patient preference, stereotactic body radiation therapy (SBRT) has become established as an effective definitive modality to treat stage I NSCLC (1), and it is emerging as a viable modality for medically operable patients (2). Many patients treated with SBRT have poor pulmonary reserve and significant co-morbidities and are, therefore, also at significant risk of developing complications from biopsy. While a historical resolute mantra of cancer care is that no therapy is administered without pathologic proof of malignancy, clinicians are increasingly faced with the challenge of considering SBRT to be performed empirically for patients with radiographic findings consistent with early-stage lung cancer. We performed a thorough literature search and formed the Empiric Radiotherapy for Lung Cancer Collaborative Group to report the evidence regarding

empiric SBRT and guidelines for physicians to consider. Herein, we provide an expert commentary on how to apply "rationalism to empiricism," or when it is appropriate to treat a patient with SBRT without pathologic confirmation.

Scope of the problem

Lung cancer is the leading cause of cancer-related death in the United States in both men and women, with an estimated 154,050 deaths annually (3). The National Lung Screening Trial (NLST) randomized asymptomatic patients at high risk for lung cancer to either low-dose CT (LDCT) or chest radiography and found that LDCT identified more cases of lung cancer (1.1% *vs.* 0.7%) with a sensitivity and specificity of 93.8% and 73.4%, respectively (4). This study led to numerous professional organizations rapidly endorsing screening, including the United States Preventative Services Task Force (USPSTF) (5). Despite this recommendation, lung cancer screening is only slowly being adopted due to concerns over resources, radiation dose, and cost-effectiveness (5). The question of when to perform empiric SBRT will become increasingly critical in the era of screening (6-9). Also important is to recognize that false positive results were noted in 96.4% of the positive screening results in the LDCT group of the NLST. As such, there is great need to establish guidelines to improve the predictive yield of an abnormal screening result, with special reference to patients at high risk of invasive diagnostic complications and hence referred for empiric SBRT.

Indications for SBRT and accompanying risks and benefits

SBRT has emerged as a standard of care for inoperable stage I NSCLC with highly effective control of the primary tumor, but, like surgery, it similarly carries a challenging 5-year disease free survival of 45–63% (10-13). A pooled analysis of two randomized trials (STARS, ROSEL) of SBRT versus surgery in operable patients found equal relapse-free survival, although overall survival (OS) was improved in the SBRT arm potentially due to excessive toxicities associated with surgery (14). Therefore, while the most accepted use of SBRT is in the inoperable population, SBRT is increasingly being considered in the operable population as additional trials in medically operable patients are reported (15).

SBRT, while generally very well tolerated, carries a low risk of adverse events (16), including pneumonitis (17), chest wall pain syndrome and rib fracture for peripheral lesions (18), and concern for great vessel or airway injury for central tumors, defined as within 2 cm of the tracheobronchial tree (19). The concern for potentially lethal toxicity is greatest for central lesions and especially ultra-central lesions (20), although recent evidence supports safe fractionation for central lesions (21). Therefore, location can be one consideration for whether or not to perform empiric SBRT. It is also important to note that many patients with central or ultra-central lesions who are at a higher risk of toxicities from radiation are also not candidates for sub-lobar resections. SBRT, therefore, is an important aspect of curative intent treatment for these patients, with or without pathological diagnosis. In these guidelines, we only discuss the management of non-central lesions, as the risk-benefit ratio will be defined with evolving results from the prospective NRG Oncology RTOG 0813 trial.

With increasing diagnoses of early stage lung cancer, clinicians are often faced with the question of surgery without a biopsy or empiric SBRT. Surgery provides a pathologic diagnosis (PD) and simultaneous lymph node analysis, and this information can guide therapeutic decision making such as conducting molecular analysis and need for adjuvant therapy. Most importantly, the vast majority of lung nodules identified are not lung cancer, with the positive predictive value in a high-risk population of the NLST of only 2.4% (4). Therefore, overtreatment of benign nodules with SBRT remains a potential concern. Another common clinical scenario is for patients who have undergone a prior surgical (lobar or sub-lobar) resection or SBRT with preceding tissue confirmation and are noted to have serial enlargement or development of a new lung nodule radiographically consistent with a new primary lung cancer. In this setting, proceeding with SBRT without an attempted biopsy in select patients can be a reasonable option since the risks of biopsy may be higher in patients having undergone prior surgery and the likelihood of cancer may be higher given the prior personal history of lung cancer in these patients.

In patients not undergoing definitive resection, histologic confirmation can be obtained via a transthoracic computed tomography-guided needle biopsy or via a transbronchial biopsy, which allows for simultaneous nodal evaluation via endobronchial ultrasound (EBUS) (*Table 1*). In addition to providing definitive diagnostic confirmation and staging, tissue diagnosis also may also allow for prognostication

Table 1 Benefits of pathology-proven and empiric SBRT

Benefits of pathology-proven SBRT	Benefits of empiric SBRT
Confirmation of malignancy	Avoid CT-guided transthoracic needle biopsy which for peripheral tumor which can be non-diagnostic in 5–35% of cases
Pathology for guidance of systemic therapy (i.e., small cell carcinoma or future therapies)	No risk of pneumothorax
If transbronchial biopsy is an option (i.e., central disease), EBUS nodal evaluation can be performed simultaneously	Safer than biopsy in patients on blood thinners, with tumors in difficult to biopsy locations, with numerous comorbidities
Avoid unnecessary SBRT if pathology is negative for malignancy	Biopsy can be obtained at relapse if needed
Increased cost-effectiveness (avoiding overtreatment of benign nodules)	–

SBRT, stereotactic body radiation therapy; EBUS, endobronchial ultrasound.

between NSCLC histologies (22) and between NSCLC and early stage small cell lung cancer (23) which can guide subsequent decisions for systemic therapy (24). However, arguments can be made against obtaining a pre-treatment histologic diagnosis. First, transthoracic computed tomography-guided needle biopsy carries approximately a 20% risk of pneumothorax and a 5% risk of serious complications such as chest tube placement. These risks can be as high as 35% and 10.7%, respectively, in a typical medically inoperable patient or those with limited pulmonary reserves (25). The diagnostic yield of a biopsy varies widely in the literature between 64–95%, so the risk of the procedure may be incurred without obtaining a definitive tissue diagnosis. If a patient subsequent to SBRT develops a recurrence, a biopsy can be performed on the recurrence, which may present in a more amenable location to biopsy and may be more molecularly insightful in guiding subsequent therapies than would a biopsy at the time of initial diagnosis.

Existing literature supporting empiric SBRT

There have been several publications examining the clinical outcomes of empiric SBRT (14,26-32) (*Table 2*). Although there are no specific prospective trials examining empiric versus biopsy-confirmed SBRT, many large prospective studies permitted patients to be enrolled without a biopsy, including the ROSEL trial (14), although most trials required biopsy-proven malignancy, such as in RTOG 0236 (11). As shown in *Table 2*, inoperable patients comprise 62–88% of the population in these retrospective studies. Toxicity rates, a critical consideration in empiric SBRT, are low, including radiation pneumonitis and rib fractures (<5%)

(26,27). In the two studies of 398 and 591 patients who had a PD versus no PD [clinical diagnosis (CD)], no differences in local control (LC), progression-free survival (PFS), or OS were identified, supporting the hypothesis that most of these CD patients who were empirically treated truly did have lung cancers (28,29).

Tools available for predicting the probability of malignancy

To quantify a given patient's pretest probability of malignancy, multiple tools have been studied. In the screened population, a calculator was developed from the Pan-Canadian Early Detection of Lung Cancer Study and validated through the British Columbia Cancer Agency. Predictors of malignancy included older age, female sex, family history of lung cancer, emphysema, larger nodule size, location of the nodule in the upper lobe, part-solid nodule type, lower nodule count, and lesion spiculations. Their model had an impressive area under the receiver operating characteristic curve (AUC) of 0.94, even for small nodules (33).

There have also been prediction models developed in the non-screened population, where the prevalence of lung cancer diagnosed after imaging is higher (34). Investigators from the Mayo Clinic examined patients with non-calcified nodules between 4 and 30 mm in diameter, with risk calculated for age (OR 1.04), smoking history (2.2), extra-thoracic cancer <5 years before nodule detection (3.8), nodule diameter (1.14/mm), spiculations (2.8), and upper lobe location (2.2) (35,36). While positron emission tomography (PET) imaging can have clear benefits in diagnosis, staging, prognostication, and target volume

Table 2 Studies employing empiric SBRT

Study	Number of patients	Dose	Inoperable (%)	Biopsy attempted (%)	Median tumor diameter (mm)	Toxicity	3-year LC, PFS, OS (%)
Sakanaka et al. (27)	37	48 Gy/4 fx	70	67	20 [7–42]	Gr 2 radiation pneumonitis (RP): 5.4%; rib fracture (RF): 2.7%	94, 68.6, 74.2
Yoshitake et al. (30)	88	48 Gy/4 fx	77	NR	19 [8–40]	Gr 2 RP: 2.3%; Gr 2 RF: 6.8%	90, 67, 80
Inoue et al. (26)	115	30–70 Gy/2–10 fx	62	51	20 [5–45]	Gr 2: 8.8%; Gr 3: 5.3%; Gr 5: 1.8%*	≤20 mm/>20 mm: 97/95, NR/NR, 90/61
Harkenrider et al. (31)	34	30–55 Gy/3–10 fx	100	18	16 [5–33]	Gr 3–4 dyspnea: 8.8%	90, NR, 85 (2-year)
Wang et al. (32)	25	Individualized, median BED 136 Gy	92	0	NR (68% T1b, 32% T1a)	Gr 3: pneumonitis 8%, Gr 1–2: fatigue 20%, pneumonitis 8%	78.8, 66.3, 70.2
Studies incorporating tumors pathologically-confirmed (PC) and clinically diagnosed (CD)							
Takeda et al. (29)	398 (115 PD and 58 CD)	40–50 Gy/5 fx	73 (PD); 88 (CD)	52% of CD	28 [5–62] (PD); 26.5 [10–53]	Gr 2 RP: 16% (PC), 12% (CD); Gr 3 RP: 3% (PC), 9% (CD)	PD: 80/74/54; CD: 87/71/57
Chang et al. (14)	22 (ROSEL only 8 PD and 14 CD)	50–54 Gy/3–4 fx	0%	NR	18	Gr 3 10%	96/86/93
Verstegen et al. (28)	591 (209 PD and 382 CD)	60 Gy/3,5,8 fx	72 (PD); 69 (CD)	NR	34 [11–80] (PD); 28 [10–53]	Gr 3 RP: 3%; RF: 2%; Gr 3 chest wall pain: 1%	PD: 90/80/55; CD: 91/73/53

*, worsening of interstitial pneumonitis in a pt with tumor > 2 cm. NR, not reported. SBRT, stereotactic body radiation therapy; LC, local control; PFS, progression-free survival; OS, overall survival; PD, pathologic diagnosis.

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Table 3 Proposed acceptable pretest probability thresholds for empiric therapy for clinical stage I non-small cell lung cancer

Study	Proposed acceptable pretest probability thresholds (%)	PET/CT included in threshold calculation?
Gould *et al.* (34)	65	No
Louie *et al.* (42)	85	Yes
IASLC (8)	85	No
Senan *et al.* (43)	85	Yes

PET, positron emission tomography.

delineation in lung cancer (37-39), Herder *et al.* performed an external validation model of this Swensen analysis on the added value of 18-FDG PET and did not find the AUC was significantly different from the model without PET (40). In summation, studies have shown that these models are similar in accuracy to clinical judgment (41), but overall physicians tend to somewhat overestimate the risk of malignancy.

Determining the appropriate pretest probability threshold for empiric SBRT

The pretest probability threshold above which it is acceptable to perform a therapeutic procedure in this setting, either surgery or SBRT, is not well-defined. The American College of Chest Physicians (ACCP) Evidence-based Clinical Practice Guidelines states that it is reasonable to consider SBRT above a pretest probability of 65% (34); however, other organizations have suggested a higher threshold, including the International Association for the Study of Lung Cancer (IASLC) suggesting that no more than 15% of surgical specimens resulting from a positive screened population should result in benign findings (8) (*Table 3*). Despite this recommendation, 25% of procedures performed in the NLST had benign findings (4), and the positive predictive value was only 3.8% for 4 mm or larger nodules. These threshold differences in pre-test probability previously recommended between surgical and SBRT populations may, in part, be based on differences in toxicity profiles between surgery and SBRT.

The question of an appropriate threshold has also been examined specifically within the context of SBRT. Louie *et al.* constructed a decision tree and Markov model to evaluate the relative merits of surveillance, a PET-directed SBRT strategy (without pathology), or a PET-biopsy-SBRT strategy. They found that the threshold between the two

strategies was 85%, which they confirmed on probabilistic sensitivity analysis. The threshold was most sensitive to the diagnostic sensitivity of transthoracic biopsy and the detection rate of false negatives on CT surveillance (42). This is in keeping with the threshold of IASLC and that has been proposed by other investigators (43).

Understanding the combination of clinical and radiographic findings recommended before performing empiric SBRT

As is detailed below, appropriate patient selection for SBRT should be based on a combination of clinical and radiographic findings, including interval lesion growth, size of the suspected malignancy, radiographic appearance of the nodule, patient smoking and prior lung cancer history, and FDG avidity on PET/CT.

Staging procedures recommended for patients undergoing empiric SBRT

In addition to CT chest and PET imaging, NCCN guidelines recommend MRI brain for all patients with a ≥3 cm lesion. A recent institutional report identified a 2.4% risk of asymptomatic brain metastases in tumors <3 cm and 5.6% in tumors up to 5 cm who were radiologically node negative (44). None of the stage II patients were found to have brain metastases, whereas 6.1% of stage IIIA had asymptomatic brain disease. As such, while we recommend that all empiric SBRT patients with lesions >3 cm undergo MRI brain, the requirement could potentially be relaxed for PET-CT and pathologically confirmed node negative patients with tumors >3 cm but ≤5 cm. Whenever feasible, we recommend nodal staging with EBUS for all lesions, acknowledging that it may be acceptable to forego this procedure in patients with no evidence of radiographically

Table 4 Lung-RAD® suspicious categories

Category	Finding
4A	Solid nodule(s): ≥8 to <15 mm at baseline or growing <8 mm or new 6 to <8 mm
	Part solid nodule(s): ≥6 mm with solid component ≥6 mm to <8 mm or with a new or growing <4 mm solid component
	Endobronchial nodule
4B	Solid nodule(s): ≥15 mm or new or growing, and ≥8 mm
	Part solid nodule(s) with: a solid component ≥8 mm or a new or growing ≥4 mm solid component
4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy

enlarged or metabolically active lymph nodes on diagnostic CT chest and PET/CT, respectively, and especially in those with <2 cm lesions and peripherally located lesions (34,45,46). Patients should also undergo pulmonary function testing to better assess their risk of pulmonary complications from treatment and basic laboratory studies to evaluate for an active infection that could be presenting falsely on imaging as a clinical lung cancer.

Considerations for empiric SBRT for suspected tumors >3 cm

If a suspected tumor is >3 cm and identified on either a screening or non-screening scan, it is considered a mass and is malignant until proven otherwise, although still it is important to recognize that that many lesions >3 cm are benign. PET/CT should be obtained. If the tumor is FDG-avid, a biopsy cannot be safely obtained, and there is no clinical suspicion for a benign process, we suggest proceeding with empiric SBRT. If the mass is not FDG-avid, it is much less likely to be malignant. In such cases, we recommend further workup for a benign process and, if no diagnosis is obtained, short-interval serial imaging. As SBRT is increasingly being considered in tumors >5 cm, these same considerations can be applied (47,48). However, as the risk of nodal failures is particularly high in patients with large primary tumors with radiographically negative nodal disease (49), nodal sampling with primary tumor biopsy should be considered whenever clinically feasible.

Empiric SBRT for solitary pulmonary nodules ≤3 cm

There are multiple approaches to consider in the evaluation of patients with solitary pulmonary nodules ≤3 cm. First, we can consider the AACP division of nodules. They separate

their management recommendations into solid nodules >8 and ≤8 mm. For nodules >8 mm, if the risk of malignancy is 5–65%, they recommend PET/CT be performed. If the risk if >65%, they recommend against PET/CT and instead recommend a surgical diagnosis. Surgical diagnosis should also be pursued if the nodule is FDG-avid on PET or positive by another functional imaging test and when a fully informed patient prefers a definitive diagnostic procedure. As shown in *Table 3*, many advocate instead for a clinical probability threshold of >85%, and we agree this is a good threshold. If the pretest probability using the Mayo Clinic calculator is >85%, then it is likely acceptable to proceed with empiric SBRT (32). If the pretest probability is between 65% and 85%, PET/CT is a reasonable approach, and, if FDG-avid to proceed with SBRT. If the nodule is not FDG-avid, patients can undergo short-interval CT at 3 months, and clinicians should use the volume doubling time (VDT) guidelines as described below.

An alternative approach is to use the more recently developed Lung-RAD® system (*Table 4*), which was created by the American College of Radiology in 2014 as a lexicon to describe lung nodules on screening (50). They increased the size of a positive non-solid (ground-glass) nodule to 2 cm from 6 mm, and the nodule can be considered benign if stable over 3 months (versus 2 years in the NLST). Lung-RAD® has been shown to increase the positive predictive value in CT-screened patients by a factor of 2.5, to 17.3%, without increasing the number of false-negative results (51). Patients who fall into Lung-RAD® category 4A or 4B can undergo PET/CT.

If the nodule is FDG-avid (SUV ≥2), then empiric SBRT is a reasonable approach. If it is not FDG-avid, then serial observation is likely reasonable. Based on the NELSON CT-screening study, the lesion was considered positive if it had growth on serial scans (defined in this study as 25% growth by volume) and if the VDT was <400 days, or if a

new solid component had emerged in a previously non-solid nodule (52). Therefore, if the projected VDT is <400 days based on short-interval scan, the argument for empiric SBRT is further strengthened. In summary, if the pretest probability is >85% based on any calculator, then empiric SBRT is an acceptable option.

Empiric SBRT for ground glass nodules

For pure ground glass nodules without a solid component, the AACP recommends annual surveillance for nodules >5 mm. For larger, part-solid but >50% ground glass nodules, lesions should be managed as solid nodules >8 mm (34), and thus managed according to the discussion above.

Conclusions

We have attempted to apply rationalism to empiricism; we have discussed the strongest evidence currently available and clinical considerations regarding the often-encountered and challenging situation of empiric SBRT for patients with peripheral clinical stage I NSCLC, where biopsy confirmation is too high-risk from a pulmonary function perspective or unable to be obtained safely for other medical or accessibility reasons. We have discussed the scope of the problem and the risks and benefits of empiric SBRT, and we defined the appropriate pretest probability threshold and tools available for predicting this threshold. We provide considerations and recommendations for the clinical and radiographic findings to warrant empiric SBRT, and we divide our recommendation first by size, taking into account recent data from the screened and non-screened populations.

We endorse the American Society for Radiation Oncology guidelines on SBRT for early stage NSCLC recommending that a biopsy prior to SBRT be obtained whenever possible to confirm a histologic diagnosis of malignancy (53). We also recommend that patients without tissue confirmation of malignancy should be discussed in a multidisciplinary manner to reach a consensus on whether the lesion is radiographically and clinically consistent with a lung cancer. The decision to proceed or not proceed with empiric SBRT must be an individualized and multidisciplinary decision, taking into account patient- and tumor-specific factors as outlined in these guidelines. Future research will help further define the pretest probability and continue to improve outcomes after SBRT (54,55).

Acknowledgements

Footnote

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