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Primary treatment options for high risk/medically inoperable early stage NSCLC patients

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Abstract

Lung cancer is among the most common cancers worldwide, and the leading cause of cancer death in both men and women. For patients with early stage (AJCC T1-2, N0) non-small cell lung cancer the current standard of care is lobectomy with systematic lymph node evaluation. Unfortunately, medical comorbities often present in patients with lung cancer, may preclude the option of surgical resection . In such cases, a number of minimal to non-invasive treatment options have gained popularity in the treatment of these high-risk patients. These modalities provide significant advantages including patient convenience, treatment in an outpatient setting, and acceptable toxicities including reduced impact on lung function and a modest risk of post-procedure chest wall pain. This manuscript seeks to provide a comprehensive review of the literature including reported outcomes, complications and limitations of sublobar resection with or without intraoperative brachytherapy, radiofrequency ablation, microwave ablation, percutaneous cryoablation, photodynamic therapy and stereotactic body radiation therapy.

Introduction

Lung cancer is among the most common cancers worldwide, and the leading cause of cancer death in both men and women[1] (. In the United States alone, It is estimated that 226,150 cases of lung and bronchus cancer were diagnosed in 2012 and the disease accounted for 160,340 deaths [2]. Non-Small Cell Lung Cancer (NSCLC) accounts for greater than 85% of all lung cancer cases with approximately 15-20% of patients presenting with early stage (T1-2, N0) disease. Lobectomy with systematic lymph node evaluation is considered the optimal treatment in patients with early stage NSCLC. However, no randomized clinical data directly compare surgery alone to radiation alone or ablative techniques in the management of operable patients [3]. The acceptance of lobectomy as the optimal therapy is based on historical data, registry studies and retrospective series which consistently demonstrate 5-year overall survival (OS) rates ranging from 60 to 80% and 40-60% for stage I and II NSCLC, respectively [4-6].

For patients unable to tolerate lobectomy, alternative treatment options include best supportive care, limited resection (wedge resection or segmentectomy), external beam radiotherapy, and other modalities. Studies demonstrate that limited resections generally result in 5-year survival and recurrence rates of 59 and 50%, respectively [7]. Definitive external beam radiation therapy delivered in standard fractionation (45 to 66 Gy in 1.8 – 2 Gy/fraction) results in local relapse in 55 to 70% of patients with reported median survival of >30 months and 5-year survival rates of up to 30% [8]. These consistently inferior results as compared to lobectomy, have led to new therapeutic approaches in the management of such inoperable/high-risk patients as well as those who decline operative intervention.

This article seeks to provide a thorough review of the primary treatment options available for early stage NSCLC patients who are deemed high-risk/medically inoperable to include: limited resection with and without intraoperative brachytherapy, radiofrequency ablation (RFA), microwave ablation (MWA), percutaneous cryoablation (PCT), photodynamic therapy (PDT) and stereotactic body radiation therapy (SBRT).

Review Methods

A review of the NSCLC treatment literature was conducted. A comprehensive systematic literature search included the Cochrane Collaboration Library electronic database, PubMed, RTOG.org and ClinicalTrials.gov, using the following terms and keywords: NSCLC, early stage, surgery, lobectomy, limited resection, wedge resection, segmentectomy, EBRT, SBRT, RFA, MWA, cryoablation, PCT, brachytherapy and a combination of these terms. Studies were limited to those reported in the English language and involving human subjects. Review papers as well as original data from the last 30 years were reviewed independently.

Surgery

The standard treatment for operable, early-stage NSCLC is lobectomy with systematic lymph node dissection [9] . However, there are currently no universally-accepted definitions for medical operability [10, 11]. Factors including patient age, cardiopulmonary reserve, presence and extent of medical comorbidities, and overall performance status are included in the pre-operative assessment [12]. In addition to the determination of operability, accurate nodal assessment is considered critical due to the influence of nodal staging on both the primary and adjuvant treatment options for early-stage patients. One study of 100 NSCLC patients with ≤ 1 cm tumors demonstrated a 5% incidence of node involvement, implying that even in small tumors, nodal assessment cannot be ignored [13]. Methods for analysis of nodal involvement include computed tomography (CT) and/or positron emission tomography (PET), endobronchial ultrasound, transbronchial needle biopsy, and mediastinoscopy.

Although lobectomy is considered the gold standard, patients with severe COPD and poor lung function are at a substantially greater risk of post-operative complications. The risk of complications for a healthy individual with normal lung function undergoing resection is approximately 2 to 5% while those with pre-existing lung disease have up to a 50% risk. Thus, pre-operative studies including complete pulmonary function testing (spirometry) to

quantify baseline pulmonary function and reserve is generally recommended [11]. If the forced expiratory volume in 1 second (FEV1) is >2L or >80% of its predicted value, resection can be attempted with an acceptable risk of complications [10]. Patients with an FEV1 <40% or carbon monoxide diffusing capacity (DLCO) <40% are at increased risk of perioperative morbidity and mortality. Some investigators recommend non-operative management if the product of the percentage of predicted postoperative FEV1 and DLCO combined is <1,650, if the percentage of predicted postoperative FEV1 is <30%, or if the maximum oxygen uptake is less than 10 mL/kg/min[9].

In those with medical comorbidities, a more limited resection may be offered to reduce the impact of lobectomy on lung function and maintain the patient's quality of life. One report suggested that over 20% of patients with stage I or II NSCLC cannot undergo lobectomy due to comorbid health factors[14]. Limited resections are generally offered to patients with poor baseline cardiopulmonary function with tumors <2cm in diameter. In patients with small, node-negative tumors excised to negative margins, limited resection may result in local control (LC), overall survival (OS), and cause specific survival (CSS) comparable to lobectomy [6, 15-18].

In 1995, the Lung Cancer Study Group (LCSG) [5, 19] published the first randomized, prospective study comparing limited resection to lobectomy in the definitive management of T1N0 lung cancer. The study enrolled 247 patients with 125 randomized to lobectomy and 122 to a limited resection (82 segmentectomies and 40 wedge resections). With a median follow-up of 60 months, LC rates were 93.6% for the lobectomy group compared to 83% in those treated with limited resection (p=0.008). Although the OS was statistically comparable at 69.6 and 60.7% for lobectomy versus limited resection (p=0.088), the local recurrence rate (0.020 to 0.060 per patient/year, p=0.008) for the patients undergoing limited resection was tripled as compared to lobectomy. The high rate of local recurrence in the limited resection cohort resulted in critical evaluation regarding the definitive role of sublobar resection.

A Surveillance, Epidemiology, and End Results (SEER) registry study evaluated patients older than 65 years of age with stage IA lung cancer (tumors ≤ 2 cm without clinically or radiographically apparent lymph nodes) treated with either lobectomy or limited resection. This analysis found no significant difference in OS between the treatment groups, but there was evidence of an increased risk for lung cancer death after limited resection in patients with tumors measuring 2-3 cm [20]. Subsequently, Warren and colleagues[17] evaluated the outcomes of Stage I NSCLC patients with poor cardiopulmonary reserve. The authors reported a higher risk of locoregional recurrence in patients undergoing segmentectomy versus those who had a lobectomy (22.7 and 4.9%, respectively), although 5-year OS was equivalent.

Several other retrospective studies have demonstrated that lobectomy and limited resection yield equivalent survival for tumors ≤ 2 cm. For example, Okada and colleagues[21] reported 5-year survival rates of 87.1 and 87.8%, respectively for T1N0 tumors that are less than 2 cm and treated with extended segmentectomy (and lymph node dissection) versus lobectomy. Koike and colleagues [22] reported 5-year survival rates of 89.1 and 90.1%,

respectively for limited resection versus lobectomy for peripheral T1N0 tumors . Kodama and colleagues [23] conducted a retrospective analysis of patients with T1N0 lung cancer which again found no significant difference in 5-year survival in the lobectomy group (88%) compared with the limited resection group (93%). Kates and colleagues [24] queried the SEER database for Stage IA tumors less than 1 cm and found no significant difference in survival in 1402 patients who underwent lobectomy compared to 688 patients treated with limited resection.

Age at diagnosis is often an important determinant of outcomes in NSCLC in which patients present with an average age of 67 years and approximately 45% of patients 70 years or older at the time of diagnosis[25]. In fact, the postoperative mortality rate is 9.4% for octogenarians and 1.7% for patients under the age of 60 [15]. A SEER database study looking specifically at elderly patients with stage I and II NSCLC was published by Mery and colleagues [26]. The study identified 9875 patients treated with lobectomy and 1403 treated with limited resection with evidence to suggest a decrease in the utilization of lobectomy with an associated increase in the number of limited resections as patient age increased ($p<0.0001$). Survival decreased with increasing age with median survival times of 71, 47, and 28 months for patients <65, 65 to 74 and ≥75 years of age, respectively ($p<0.0001$). In this analysis, lobectomy conferred an OS benefit over limited resection in both the <65 ($p=0.03$) and 65 to 74 cohort ($p=0.0009$). However, for the group ≥75 years of age, there was no difference in OS ($p=0.47$) with a loss of the statistical difference in long-term survival (>25 months) in patients > 71 years of age in *post hoc* analysis.

Keenan and colleagues [27] investigated whether segmental resection offered an advantage in preservation of lung function compared to lobectomy. In a cohort of 201 patients with tumors less than 3 cm, in whom 147 underwent lobectomy and 54 underwent segmentectomy, post-operative pulmonary function to include FEV1 and forced vital capacity (FVC) were better preserved in the segmentectomy group at 1-year of follow-up. LC rates at 30 months (92.5 versus 88.9%; $p=0.22$), 4-year actuarial survival (67 versus 62%; p=−.406) and 4-year CSS (82 versus 74%; $p=0.71$) were comparable for lobectomy versus segmentectomy, respectively. In the absence of a significant difference in LC or OS, the authors concluded that segmentectomy could be offered to patients with small (<3 cm), node-negative NSCLC with improved preservation of pulmonary function. These results were supported by Okada [28] et al, who reported on a non-randomized study that segmentectomy in early stage IA NSCLC produced outcomes comparable to lobectomy in a group of 567 patients with 305 patients treated with lobectomy and 262 undergoing limited resection (230 segmentectomy, 32 wedge resection). LC at 71 months (93.1 vs. 95.1%; $p=0.3524$), 5-year OS (89.1 vs. 89.6%; p=−.106), and disease free survival (DFS) between the two groups were not significantly different in patients resected to a negative margin (≥2 cm) with a negative nodal assessment.

In contrast, several studies have described significant differences in OS between lobectomy and limited resection. El-Sherif and colleagues [29] compared the outcomes of sublobar resection to lobectomy in 784 patients with peripheral tumors less than 2 cm confined within anatomic segmental boundaries. Lobectomy was performed in 577 patients and limited resection (consisting of either segmentectomy or wedge resection), in the remaining 207

patients. The median tumor size for the lobectomy and limited resection groups were 2.8 versus 1.8 cm. With a median follow-up of 31 months, LC for the lobectomy group was 95.8% compared to 92.8% for the limited resection group. The 5-year OS for the lobectomy group was 54% compared to 40% for the limited resection group (p=.0038), however no significant difference was identified between the two groups in regard to DFS. The authors suggested the improvement in OS was due to other variables given the similar DFS and evidence to support increased use of sublobar resection in patients with competing comorbidities and increased risk of death. Sienel and colleagues [30] evaluated outcomes in high risk T1N0 NSCLC patients treated with lobectomy compared to segmentectomy. The local recurrence rate was 16% in patients with segmentectomy compared to 5% for lobectomy. The CSS was 68% for segmentectomy and 83% for those patients treated with lobectomy (p=0.01). Similarly, raev and colleagues[31] compared 215 patients who underwent lobectomy to 74 patients treated with wedge resection for stage I NSCLC. In the entire cohort, there was a trend toward improved survival with lobectomy (5.8 vs. 4.1 years), while in patient with ≤3 cm tumors, there was a statistically significant improvement in survival (p=0.029).

Further retrospective reports have described mixed non-significant differences in survival between lobectomy and limited resection for patients with poor cardiopulmonary function. Errett and colleagues [16] reported a 6-year survival of 69 versus 75%, in favor of lobectomy while Pastorino and colleagues [32] found the 5-year survival for limited resection in high-risk patients was actually slightly better at 55% compared with 49% in the lobectomy group. Similarly, Read and colleagues[33] reported a higher 5-year survival, 84 and 74%, in 244 patients with T1N0 tumors treated with limited resection (n = 113) versus lobectomy (n = 131), respectively.

Martin-Ucar et al [34] reported on a case-matched analysis of segmentectomy versus lobectomy in high-risk (FEV1<40%) stage I NSCLC patients. Seventeen patients underwent segmentectomy and 17 underwent lobectomy. The study found that there was no significant difference in survival, local recurrence, or DFS between the two groups. There was an improvement in FEV1 (p=0.02) and quality of life following segmentectomy. A similar study of T1N0 NSCLC patients treated with either lobectomy or limited resection found that those treated with limited resection were older and had more comorbidities than the lobectomy cohort, however the 5-year survival of the two groups (64% for lobectomy and 66.7% for limited resection), was not statistically different [35].

Landreneau and colleagues[6] retrospectively evaluated two forms of limited resection – wedge resection via video assisted thoracic surgery (VATS) or open wedge resection and compared these techniques to lobectomy. Of 219 patients, 117 underwent lobectomy and 102 underwent wedge resection (42 via open wedge resection and 60 via VATS). The median tumor size by procedure was 2, 1.7 and 1.7 cm for lobectomy, VATS wedge and open wedge resection, respectively. With a median follow-up of 26 months, the local control by procedure was 91, 84 and 76% with post-operative complication rates of 31, 16 and 28%, respectively. One-year survival for the lobectomy group was 91% compared to 94% for the combined wedge resection group. Five-year survival was significantly better in the lobectomy group compared with the combined wedge resection group (70 vs 61.5%,

p=0.02). A more recent study[36] compared open wedge versus VATS resection in regard to outcomes and costs and demonstrated that VATS had several advantages including a reduction in expense, a decrease in adverse events, and decreased time spent in the hospital.

Shuchert and colleagues [37] reviewed 428 patients undergoing lobectomy or segmentectomy to interrogate the effect of margin status on outcome. Two hundred and forty six patients underwent lobectomy and 182 underwent segmentectomy. The average tumor size was 3.1 and 2.3 cm for the lobectomy versus the segmentectomy group, respectively. When analyzed collectively, the mean margin among patients with recurrence was 12.8 mm versus 18.6 mm in patients without recurrence. Margin/tumor diameter ratios exceeding 1 were associated with a significant reduction in recurrence rates compared to ratios of less than 1 (6.2 vs. 25 %, p = 0.001). Although follow-up varied between the 2 groups, outcomes were comparable. The LC rate was 95.2 versus 92.3 %and the 4-year OS estimates were 80 versus 83% for lobectomy versus segmentectomy, respectively, and there was no significant difference in DFS between the groups.

Table 1 provides a summary of the studies that have reported on sublobar resection for lung cancer. These demonstrate that limited resection may allow for improved preservation of pulmonary function and similar OS as compared to lobectomy at the expense of diminished LC. Importantly, limited resections also carry risks inherent to thoracic surgery including peri-operative complications such as rial fibrillation, prolonged air leaks, infection, and death [36]. Thus, lobectomy remains the standard treatment of early stage lung cancer with limited resection reserved as an option for high-risk patients.

Intraoperative Brachytherapy following Limited Resection

Intraoperative brachytherapy has the potential to improve LC following limited resection of early-stage NSCLC [38-40]. Such low dose-rate (LDR) brachytherapy techniques permit delivery of radiation doses to the high-risk surgical bed over a period of weeks to months with the additional advantages of predictable, focal, and highly conformal dose-distribution with decreased side-effects due to reduction of the irradiated normal tissue volume [41].

An early report [42] described 14 patients who received brachytherapy following wedge resection of peripheral lung cancers. The patients had an average FEV1 of 23% and tolerated the intervention well with no reported cases of radiation pneumonitis. Chen and colleagues [43] evaluated administration of Iodine-125 (I-125) mesh brachytherapy in high-risk stage I NSCLC patients. Twenty three patients underwent VATS and intraoperative brachytherapy to a total dose of 100-120 Gray (Gy) to the staple line and tumor bed plus a 1 cm margin. Post-operative pulmonary function testing performed at 3 months revealed no significant changes in FEV1 from baseline.

Voynov and colleagues [44] assessed the delivery of 100-120 Gy via I-125 vicryl mesh to the staple line plus a 2 cm margin in 110 patients with stage IA and IB NSCLC. The 5-year LC was 90%, locoregional control (LRC) was 61%, and OS was 18% with most deaths reported as non cancer-related. Lee and colleagues [45] evaluated 33 patients with early stage NSCLC (35 primary tumors) who were not candidates for lobectomy or pneumonectomy treated with limited resection and brachytherapy seed implantation along the resection margin. The 5-

year survival was 47% for all patients while those with T1N0 lesions had a 5-year survival of 67%; and those with T2N0 lesions demonstrated a 5-year survival of 39% with 2 local relapses and 6patients experiencing regional recurrence.

Santos and colleagues [46] analyzed data for high-risk NSCLC patients with poor cardiopulmonary reserve treated with surgical resection with or without permanent intraoperative I-125 brachytherapy prescribed to a dose of 100 to 120 Gy. Regional and distant failure rates as well as OS were not significantly improved with the addition of brachytherapy, however the rate local recurrence was decreased (2% vs 18.6%, *P*=0.001). A similar finding was reported by Fernando et al [47], who evaluated 291 high-risk patients with stage IA NSCLC, 60 of whom received brachytherapy in conjunction with a sublobar resection. In these patients, the addition of brachytherapy associated with a decreased local recurrence rate (17.2 vs. 3.3%, p=0.012).

Birdas and colleagues[48] looked at 167 patients with high risk stage IB NSCLC of whom 126 underwent lobectomy and 41 underwent sublobar resection with brachytherapy. The average tumor size was not equivalent between the two groups, reported as 4.3 cm for the lobectomy group and 3.3 cm for those in the brachytherapy group (p=0.007). The local recurrence rates (4.8%) were identical in both groups and there was no significant difference in 4-year DFS(43% and 42.8%). Pulmonary complications were increased in those treated with sublobar resection when brachytherapy was added(24.4% vs. 16.6%).

Parashar and colleagues [38] retrospectively reviewed 47 patients who underwent wedge resection and intraoperative brachytherapy versus stereotactic body radiotherapy (SBRT) alone for treatment of a single malignant lung nodule. Twenty-two patients were treated with brachytherapy following resection and 25 patients with SBRT alone. Local control, distant metastasis rates, survival, and toxicity were all comparable between the two cohorts with the caveat that there was a significant difference in age between the patients in each group ((66.6 years in the brachytherapy group and 75.9 years in the SBRT group, p=0.04).

Martinez-Monge and colleagues [49] provided preliminary data with brachytherapy alone in 7 patients who were deemed to have medically inoperable early stage NSCLC. Brachytherapy was performed via CT-guided placement of Palladium-103 or Iodine-125 sources in tumors with an average volume of 11.5 cm^3 resulted in no local or regional failure with a median follow-up of 13-months. Two patients died from stroke and liver failure while one developed a new primary lung tumor at eight months in the contralateral lung.

American College of Surgeons Oncology Group (ACOSOG) Z4032 was a prospective study comparing sublobar resection with or without brachytherapy for high-risk operable patients (FEV1 < 50%) with NSCLC (< 3 cm). The study enrolled 224 patients with 115 patients randomized to surgery and 109 patients to surgery combined with brachytherapy. An initial presentation of the data at ASCO 2013 suggested that local recurrence and overall survival (OS) rates at 3-years were similar between arms. Fernando and colleagues [50] published the updated results with a median follow-up time of 4.38 years. Only 17 of 222 patients experienced local progression and there was no significant difference in the time to local recurrence or in the type of local recurrence with the addition of brachytherapy.

Interestingly, there was no significant improvement in local recurrence rate or OS with the addition of brachytherapy even among patients with potentially compromised surgical margins Intraoperative brachytherapy did not significantly worsen pulmonary function or dyspnea at 3 months and did not result in an increased rate of adverse events [51] as compared to surgery alone. To our knowledge, there have been no recent reports as to an overall trend in the use of intraoperative brachytherapy, however our general sense is that it has been offered less throughout the country in recent years. As the ACOSOG Z4099 sublobar resection with or without brachytherapy to SBRT in high risk operable patients was closed due to poor accrual in 2013, it is unclear at this time what role this treatment modality will play in the future.

Radiofrequency Ablation

Radiofrequency ablation is a relatively new treatment option for medically inoperable patients with primary NSCLC or metastatic lesions involving the pulmonary parenchyma. Following initial success in the treatment of hepatic malignancies[52], RFA was introduced in the treatment of lung tumors in medically inoperable patients and in those who refused surgery (Table 2).

The goal of RFA is to induce thermal injury to the tumor through electromagnetic energy deposition[53]. Alternating current produced by a radiofrequency generator moves from an active electrode inserted within the tumor to dispersive electrodes placed on the patient. During RFA, a high-frequency electrical current heats and coagulates tissue. The temperature within the tumor rises to >60 °C resulting in instantaneous cell death via protein denaturation and coagulation necrosis.

Advantages of RFA compared with resection include treatment in an outpatient setting and the ability to complete non-operative probe placement via CT-guidance with the use of local anesthesia. Damage to the surrounding normal tissues and lung parenchyma is limited due to the presence of air which provides an insulating effect allowing for dissipation of the energy and protection of nearby normal tissues, however the procedure can result in complications such as pneumothorax, hemoptysis, bronchopleural fistula, rib fracture and tissue injury. [54].

Limitations of RFA include the inability to treat tumors in close proximity to vascular structures and the size/location of the tumor. Vessels larger than 3 mm in diameter reduce the amount of energy delivered to the target due to the loss of heat through convection within the circulatory system, the so called “heat sink effect” [55]. Size is a limiting factor with evidence to suggest a loss of LC in over 50% of lesions greater than 3 cm in diameter. As the target volume increases, the periphery may not reach an ablative temperature resulting in diminished response and impaired local control [56]. Location is critical due to the risk of damage to adjacent non-pulmonary structures to including the esophagus and trachea. Finally, post-RFA recovery from thermally-induced inflammation may require several months and result in difficulty in interpreting tumor response with CT imaging.

Recent studies have examined the results of RFA as definitive therapy for early-stage NSCLC. Lee and colleagues[57] assessed the technical feasibility, efficacy and complications of percutaneous CT-guided transthoracic RFA in the treatment of inoperable NSCLC and

lung metastasis. Thirty patients with 32 lung tumors were evaluated. The average tumor size was 5.2 cm (2.8-7.6 cm) and patients had a median follow-up time of 12.5 months. Each patient received a single ablation. The complete necrosis rate (assessed by enhancement on CT imaging and read by an experienced radiologist) in the study was reported at 38%. Tumors smaller than 3.0 cm in diameter demonstrated higher complete necrosis rates compared to tumors larger than 5.0 cm (100 versus 8%) with a median survival of 18.6 months (+/− 2.2 months) as compared to 11.3 months (+/− 1.8 months), respectively (p=0.09). The authors reported a 10% rate of major complications including two pneumothoraces requiring tube thoracotomy and one patient with acute respiratory distress syndrome.

Huang and colleagues [58] performed a retrospective review of 329 patients with 436 lung tumors (237 primary and 92 metastatic lung tumors) treated with RFA due to refusal of surgery or inability to undergo surgical resection. RFA resulted in a median progression-free interval of 21.6 months. Local progression occurred in 23.7% of patients with a significant difference in the risk of progression in tumors >4 cm (p=0.01). Overall survival at 1, 2 and 5-years was 68.2, 35.3 and 20.1%, respectively, with a low 30-day mortality of 0.6%. A second study [59] evaluated 79 patients with 79 primary lung tumors treated with RFA to include 35 patients with Stage IA and 7 patients with Stage IB NSCLC. The study included 19 patients (24%) and 9 patients (11%) treated with adjuvant external beam radiation and concomitant brachytherapy, respectively. The median OS was 23 months and the overall recurrence rate was 43% (34/79) with local failure as the dominant pattern occurring in 38% (13/34). Increasing size of the tumor and stage were significant for increased likelihood of disease recurrence.

Fernando and colleagues[60] studied 21 tumors in 18 patients with a median tumor size of 2.8 cm. Each patient received one ablation, with CT and PET utilized to evaluate for response and recurrence. With a median follow-up of 14 months, the LC rate was 61.9%. One and two year survival rates were 83 and 83%, with median progression free survival of 16.8 months. Hiraki and colleagues[61] reported on 342 tumors in 128 patients with an average tumor size of 1.7 cm. For the 342 tumors, the authors performed 225 ablative sessions to include 49 repeat sessions for the treatment of local progression. Chemotherapy was administered for 193 tumors. With a median follow-up time of 12 months, the non-actuarial LC rate was 73%. The 2-year LC rate was 66% for tumors that were ablated once and 78% for those ablated more than once. They found that tumor size > 2cm and the use of an internally cooled electrode were independent risk factors for local progression.

Yan and colleagues[62] reported on 55 tumors (26 patients with Stage I/II NSCLC) in 55 patients with an average tumor size of less than 5 cm. With a median follow-up of 24 months, the overall local control rate was 62%. The median OS time for the entire cohort was 33 months with a median PFS of 15 months. The subgroup with stage I/II NSCLC demonstrated a 1-year survival of 92% and a 3-year survival of 69%. Multivariate analysis demonstrated lung metastasis >3 cm was independently associated with a reduced OS (p=0.003). Ambrogi and colleagues[63] studied 50 tumors in 50 patients with a mean tumor size of less than or equal to 5.0 cm. The average follow-up time was 31 months, and the LC was nearly identical at 61%. Another similar experience was reported by Pennathur et al [64]

with a documented local progression rate of 42% and 2-year OS of 49% following treatment of 19 patients with Stage I NSCLC.

Simon and colleagues[65] evaluated 153 consecutive patients with 189 primary NSCLCs (n=116) or stage IV colorectal pulmonary metastasis (n=73) to determine the long term survival, local tumor progression and complication rates following CT-guided RFA. Mean tumor size was 2.7 cm for tumors treated with curative intent and 6.1 cm for tumors treated with palliative intent. At a median follow-up of 20.5 months, the 1, 2, 3, 4, and 5-year LC rates for tumors <3 cm in diameter were 83, 64, 57, 47 and 47%, respectively. For tumors >3 cm, the 1, 2, 3, 4, and 5-year local control rates were 45, 25, 25, 25, and 25%, respectively. Stage I patients had 1- 2-and 5-year survival rates of 78, 57 and 27 % whereas the rates for colorectal pulmonary metastasis were 70, 54, and 44%, respectively. These results underscore the highly selective nature of patients chosen for this therapy in that outcomes varied widely based on tumor size and disease stage.

Lencioni and colleagues[66] described 183 tumors in 106 patients with a mean tumor size of 1.7 cm. Patients were divided into three groups: NSCLC (n=33), colorectal metastasis (n=53), and other metastasis (n=20). Each patient received one RFA treatment. The reported 1-year LC rate was 88% with a 1 and 2-year OS rates for patients with NSCLC were 70 and 48%, respectively and 89% and 66% for patients with metastases from a colorectal primary. Patients with stage I NSCLC had a 2-year OS and CSS of 75 and 92%, respectively. Lanuti et al. [67] reviewed 34 tumors in 31 patients with an average tumor size of 2 cm At a mean follow up time of 17 months, the LC rate was reported as 68.5%. The 4-year survival rate was 47% with a DFS at 2 and 3-years of 57 and 39%, respectively. As previously noted, the size of the target lesion is an important consideration in patient selection for RFA [68]. Simon and colleagues[65] demonstrated a 3-yr LC of 57% in tumors < 3 cm as compared to 25% in tumors > 3 cm in diameter. Bilal et al [69] performed a literature search to compare the results of RFA and SBRT in the treatment of early stage medically inoperable NSCLC patients. Based on a review of 16 representative publications, the authors concluded SBRT resulted in improved 5-year OS and decreased local progression as compared to RFA, 48 versus 20.1-27% and 3.5-14.5 vs. 23.7-43%, respectively.

In summary, RFA has generally been associated with inferior LC as compared to surgery and SBRT, where 3-year local control rates approximate 80-95%. Further studies with larger sample sizes and adequate follow-up are necessary to better delineate the role of this emerging modality. Trials such as ACOSOG Z4033, designed to evaluate RFA in the treatment of high risk patients with early stage NSCLC, will help determine in which patients this procedure will be most beneficial. This trial has completed accrual, but survival and recurrence data have not yet matured.

Microwave Ablation

Microwave ablation is a second heat-based ablation technique, similar to RFA in application and technique. MWA can be delivered either percutaneously under CT-guidance or via open surgical or laparoscopic techniques. In contrast to RFA, thermocoagulation of the target lesion is a result of an electromagnetic wave which produces excitation and oscillation of water molecules within the tissue surrounding the probe (antenna). Given the properties of

the electromagnetic wave, MWA does not require a grounding pad as intratumoral temperatures can be measured through placement of a separate thermocouple located adjacent to the microwave antenna[70, 71].

Theoretical advantages of MWA over RFA include enhanced thermocoagulation of tumor cells due to improved energy deposition in aerated lung and increased heating near blood vessels. MWA allows for increased intratumoral temperatures with generation of a larger ablation zone (up to 2cm from the probe tip) in a shorter period of time as compared with RFA[72]. Additionally, MWA may allow for improved treatment of both peripheral and central lesions due to a reduction in pain with the use of microwaves and minimal heat sink effect associated with the vasculature. Similar to RFA, microwave ablation is associated with risk of pneumothorax, post-procedural pain, hemoptysis and rare pulmonary toxicity. Relative contraindications for both RFA and MWA include possible interference with the electromagnetic current of implantable cardiac devices and unpredictable pattern of ablation due to the presence of surgical clips[70, 73, 74].

Much like RFA, MWA was first implemented as a treatment strategy for hepatic tumors [75] with gradual expansion into the treatment of pulmonary lesions. Feng et al. [76] reviewed the results of MWA in the treatment of 28 lesions in 20 peripheral lung cancer patients (8 primary and 12 metastatic). With an overall response rate of 57.1%, a greater than 50% ablation was noted in 13 (46.4%) with a complete response in 3 (10.7%). No significant side-effects or complications were observed. Wolf and colleagues [77] retrospectively reviewed the results of percutaneous CT-guided MWA in 82 lung lesions in 50 patients. With a mean follow-up of 10 months, the 1-year LC was 67%, with 26% of the patients demonstrating residual disease at the ablation site. Kaplan-Meier analysis demonstrated an actuarial survival at 1-, 2- and 3-years of 83, 73 and 61%, respectively. Interestingly, cancer-specific mortality was not significantly affected by index size of larger than 3 cm or the presence of residual disease.

Limited outcomes data is available to support the use of MWA in the treatment of early stage NSCLC. As with RFA, MWA can be considered in the treatment of recurrent disease or in combination with other techniques to provide palliation of progressive pulmonary lesions. Future studies will hopefully clarify the role of MWA in the treatment of high-risk NSCLC.

Percutaneous Cryoablation

Percutaneous cryoablation, another thermal-based ablative technique, utilizes cold temperatures as opposed to heat. The therapeutic role of cryoablation is based on the Joules-Thompson effect with utilization of a gas, typically argon, which rapidly decreases to subzero temperatures (as low as −150 °C) upon transition from a liquid to gaseous state. Experiments have demonstrated that a 2 to 3 mm diameter probed can result in a freeze area of 2 to 3 cm in diameter and 4 cm in length. The probe temperature is measured potentiometrically with a needle placed approximately 2 mm from the tip. The freeze cycle is alternated with a thaw cycle during which helium gas is administered to raise the temperature to approximately 40 °C. The diameter/number of probes and the number of freeze/thaw cycles is dependent on the size, location and clinical scenario.

The alternating freeze/thaw cycles of PCT result in cell death through both direct and indirect mechanisms. Rapid freezing results in formation of both intracellular and extracellular ice crystal which disrupt the cell membrane and internal cellular processes. Indirect actions include vasoconstriction and occlusion of blood vessels secondary to osmotic changes and local tissue edema resulting in hypoxic tissue injury and coagulative necrosis[56, 78-81]. Additionally, cryoablation generates immunologic interactions and promotion of inflammatory cytokines[82] which may also exert a tumoricidal effect.

Similar to RFA, PCT is recommended for lesions less than 3 cm due to difficulty with probe geometry in the treatment of large or irregular lesions resulting in increased risk of recurrence. Successful ablation requires generation of a cryozone approximately 1 cm beyond the radiographically imaged tumor and a minimum isotherm of −20 °C to result in cell death. PCT also suffers from the heat/cold sink effect as with RFA.

In contrast to RFA, PCT is recommended for treatment of central tumors due to the relative resistance of collagenous architecture allowing for minimization of damage to adjacent organs[83]. Due to the delayed effects of cryotherapy, with development of non-hemorrhagic necrosis 8-14 days following treatment, the technique is not recommended for immediate debulking or management of an obstructing lesion[84]. Cryotherapy may result in less pain in the treatment of tumors along the pleura and chest wall[56]. The main complications of PCT include pneumothorax, hemorrhage, fistula formation and bronchospasm, similar to RFA and MWA[78, 85].

Cryoablation initially gained acceptance in the intraoperative management of prostate and hepatic malignancies. Bronchoscopically-directed cryotherapy has been utilized since the 1980's to treat superficial endobronchial lesions, both in the definitive and palliative settings[56]. Maiwand and colleagues [86] treated 521 patients with advanced obstructive tracheobronchial malignant tumors with cryotherapy and demonstrated that the treatment provided a palliative benefit with reduction in hemoptysis, cough, dyspnea and chest pain in 76.4, 69, 59.25 and 42.6% of patients, respectively. Improvement in one or more symptoms was noted in 86% of patients with a median survival of 8.2 months. Other investigators have demonstrated the safety and efficacy of cryotherapy delivered via direct thoracoscopic guidance in the treatment of symptomatic inoperable lung cancer.

Wang and colleagues [78] reported their experience on the use of PCT in the treatment of 234 pulmonary masses in 187 patients. The review included a heterogeneous patient population with 89% diagnosed with advanced pulmonary malignancies in which prior treatment including surgery, chemotherapy and radiation had failed. Stage I and II primary lung tumors represented only 17 and 20 lesions, respectively. The authors concluded CT-guided PCT may allow for improved therapeutic benefit as compared to other ablative modalities with a low procedural morbidity and accurate treatment localization. Kawamura and colleagues [85] performed PCT in the treatment of 35 metastatic lung tumors in 20 patients over 22 sessions. With a median follow-up of 21 months, 20% of tumors recurred with complications to include pneumothorax in 11 sessions, hemoptysis in 8 and 1 case of phrenic nerve palsy. One-year survival was estimated at 89.4%.

Choe and colleagues [87] investigated the efficacy of PTC and RFA in the management of 76 lesions in 65 patients with inoperable lung malignancies. Sixty-seven total lesions were treated with RFA while 9 tumors were managed with PCT. Twenty patients in the RFA group and 3 patients in the PCT cohort were diagnosed with stage I NSCLC. With a median follow-up of 20.8 months, complete ablation was achieved in 76.2% of patients treated with RFA and 85.7% in the PCT group when the lesion was less than 3 cm in diameter. Larger lesions resulted in an inferior CR rate of 43.3 and 66.7% in the RFA and PCT patients, respectively.

Zemlyak et al [88] compared the results of RFA, sublobar resection and PCT in 64 patients with biopsy positive stage I NSCLC deemed unfit for lobectomy. With a median follow-up of 33 months, 3-year CSS for SLR, RFA and PCT was 90.6, 87.5, and 87.5%, respectively. Overall survival was 60.8, 87.1, and 77%, respectively. The authors noted a trend toward increased local (33%) and regional/distant recurrence (25%) in the RFA cohort. Yamauchi and colleagues [89] retrospectively reviewed the results of 34 tumors in 22 patients with histologically proven stage I lung cancer patients. With a median follow-up of 23 months (range 12-68 months), local tumor progression occurred in only 1 tumor (3%). The mean maximal tumor diameter was 1.4 cm. The median overall survival was 68 months with 2- and 3-year DFS of 78 and 67%, respectively.

The limited number of early-stage NSCLC patients and predominant retrospective nature of the PCT literature does not allow for an appropriate comparison to RFA or SBRT. The report from Zemlyak et al [88] included only 9 patients treated with PCT of which only 3 lesions were Stage I NSCLC. Although the toxicity profile appears favorable and PCT may allow for improvement in the therapeutic ratio as compared to RFA and MWA, generalization of this treatment modality in the definitive management of early-stage NSCLC requires prospective evaluation with increased patient numbers and longer follow-up.

Photodynamic Therapy

The utilization of PDT in the treatment of thoracic malignancies has increased over the last several years[90]. PDT involves the systemic delivery of a photosensitizing agent, typically porphyrin-based, followed by direct excitation of the compound by a wavelength of light that correlates to the absorption band of the infused drug. The resulting photodynamic reaction results in the production of singlet oxygen and local reactive cytotoxic agents. The mechanism of cell death is multi-faceted and believed to be due to direct cell killing via both apoptosis and cell necrosis. Indirect damage also occurs as a result of injury to the tumor vasculature and a local inflammatory response with associated anti-tumor immunogenic factors[90-93]. Reported complications include hemorrhage, respiratory compromise and skin burns related to systemic administration of the agent and exposure to UV light[84].

Simone and colleagues [90] at the University of Pennsylvania published an exhaustive review of the role of PDT in the treatment of NSCLC. As described, the role of PDT in early stage NSCLC is generally limited to small (≤1 cm) endobronchial lesions without extracartilaginous invasion or lymph node involvement. The ability for light to penetrate the

target tissue and activate the photosensitizing agent is a limiting factor in the role of PDT with therapy most effective in the treatment of minimally invasive lesions[94, 95].

Furuse et al [96] published the results of a phase 2 study with photofrin II in the treatment of 59 early-stage, centrally-located, squamous cell carcinomas in 49 patients. Overall, 85% of the lesions demonstrated a complete response with a median duration of response of 14 months. The CR rate was 100% in smaller tumors <5 mm as compared to 38% in tumors >20 mm. Kato et al [97] treated 264 central early-stage NSCLC in 204 patients of which 70% were stage 0 and 30% were stage I. The maximum tumor dimension was <20 mm in 87% of patients with a reported complete response rate of 95% in tumors with a length <5 mm, 94% in those 5 to 9 mm, and a decrease to only 44% in lesions >20 mm. Several series report complete response rates with PDT ranging from 62 to 100% with the longitudinal length of the tumor being an important determinant in response[94].

Okunaka et al. [98] evaluated the role of PDT as a novel therapy for patients with peripheral lung tumors <1 cm in size deemed unfit for surgery or radiation. Patients received a photosensitizer followed by CT-guided percutaneous insertion of needles with internal catheters to allow for light administration. Nine patients were treated with seven achieving a partial remission and two experiencing pneumothorax.

PDT is considered a safe and effective method of treatment for non-invasive (dysplasia and carcinoma in-situ) and early-stage central NSCLC and in patients requiring focal palliative therapy[94]. Extensive endobronchial and aerodigestive lesions may require a debulking procedure prior to the application of PDT due to limited light penetration. Insufficient data exists to support a role in the management of peripheral NSCLC without an endobronchial or central component.

Stereotactic Body Radiation Therapy

In patients with early-stage NSCLC unable to tolerate surgical resection, radiation therapy was historically considered the standard alternative treatment. Definitive external beam radiation therapy, delivered in standard once daily fractions (1.8 – 2 Gy per fraction) resulted in long-term survival rates of 15-30% with local failure rates exceeding 50%[8, 99, 100]. Sibley et al [99] evaluated the results of 10 studies assessing the treatment of medically inoperable NSCLC patients with radiation therapy. With a median dose of 60 to 66 Gy, 25% of patients died of intercurrent disease, 30% with distant metastatic disease and 30% with local failure alone illustrating the lack of primary tumor control with conventional fractionation.

The published results of primary radiation therapy are inferior to surgical resection for several key reasons. First, the majority of patients treated with primary radiation are inoperable due to significant life-limiting medical comorbidities. Thus, the surgical and radiation groups essentially consist of two very different patient populations with a significant bias in regard to long-term outcomes and overall survival. Second, surgical patients typically undergo formal pathologic staging and assessment of regional lymph nodes allowing for consideration of adjuvant therapy to include post-operative radiation and/or chemotherapy as indicated. In contrast, patients treated with definitive radiation may

never undergo surgical lymph node sampling with treatment options based exclusively on clinical and radiographic staging. Finally, the historical doses delivered with conventional radiotherapy may have been biologically inadequate for long-term LC.

Mehta et al. [101] described the radiobiological rationale for dose-per-fraction escalation based on evidence that doses in excess of 85 Gy are required to achieve 50% long-term LC when utilizing standard fractionation (2 Gy per fraction). Thus, the total dose to the tumor must be increased from the standard range of 60-66 Gy in order to deliver an adequate biologic effect to improve the LC of these tumors. With conventional fractionation, a protracted radiation schedule requiring periods of up to 10 weeks may be required to deliver such a dose. However, the total duration of radiation therapy is of pivotal importance in the treatment of NSCLC with modeling to suggest a 1.6% per day loss in survival with prolongation of the treatment beyond 6 weeks due to accelerated tumor repopulation[101-103].

Stereotactic radiosurgery (SRS) was first developed in the 1950's for the treatment of small intracranial lesions or the ablation of functional intracranial regions[104] with the intent of delivering a high dose of radiation in a single session with submillimetric precision through the utilization of stereotactic guidance. Stereotactic Body Radiation Therapy (SBRT) represents an extension of these principles to sites outside of the central nervous system. In 1994, Lax et al.[105] provided the first description of a stereotactic frame developed at Karolinska University Hospital and discussed the methodology for delivery of stereotactic radiation therapy to extracranial tumors. Subsequently, Blomgren et al. [106] were the first to report on the use of the stereotactic frame and fixation device in the treatment of 42 tumors (liver and lung) in 32 patients with a reported LC of 80% during a follow-up period ranging from 1.5 to 38 months.

SBRT, also known as stereotactic ablative body radiotherapy (SABR) is characterized by the use of a rigid and reproducible immobilization device intended to minimize and regularize respiratory and patient motion with collection of precise measurements to account for tumor motion during both treatment planning and delivery of each fraction. The use of highly conformal dose distributions with rapid dose fall off and daily image guidance allow for a reduction in the high-dose treatment volume allowing for decreased irradiation of surrounding normal tissues with an associated reduction in toxicity[107]. Treatment is typically delivered in three to five fractions over a one to two week period, ranging on average from 10 to 20 Gy per fraction (although single fraction and more protracted regimens are also in use). With SBRT, the radiobiologic principle of tumor repopulation is of diminished importance due to shorter overall treatment times, often less than 2 weeks [108], and the ability to deliver an increased biologic effective dose (BED) as compared to traditional fractionation[109]. The resulting biologic equivalent dose (BED) of SBRT is typically in excess of 100 Gy in contrast to a BED of 79.2 Gy with standard fractionation (66 Gy in 2 Gy per fraction) assuming an alpha/beta ratio of 10 for acutely responding tissue (tumor). Fowler and colleagues [110, 111] at the University of Wisconsin provided the first analysis of the radiobiologic implications of SBRT and the role of linear quadratic modeling to describe the effect of doses up to 23 Gy per fraction on both the tumor and surrounding normal tissues.

Timmerman et al.[112, 113] demonstrated the safety of SBRT in the treatment of early-stage NSCLC in a phase I, dose-escalation trial conducted at the University of Indiana. The investigators utilized an extracranial frame with incorporation of a fiducial stereotactic coordinate system and an abdominal compression device designed to minimize tumor motion through a reduction in respiratory excursion. Thirty-nine medically inoperable patients with clinical stage IA or IB (T1 or T2, ≤7 cm) NSCLC received SBRT with peripheral tumor doses initiated at a dose of 24 Gy (8 Gy per fraction × 3 fractions) with escalation up to 60 Gy (20 Gy per fraction × 3 fractions) in the T1 cohort without exceeding the maximum-tolerated dose. Patients in the T2 cohort, with tumors larger than 5 cm, experienced excessive toxicity at the 72 Gy dose (24 Gy per fraction × 3 fractions) with the maximum tolerated dose defined at 66 Gy (22 Gy per fraction × 3 fractions).

A phase II trial[114] followed this experience to further assess toxicity and LC in inoperable patients with early-stage NSCLC. Seventy patients were treated with doses ranging from 60 to 66 Gy in 3 fractions as per the results of the phase 1 study. With a median follow-up of 17.5 months, the reported LC at 2 years was 95% with a 2-year OS of 54.7% and median overall survival of 32.6 months. Grade 3 to 5 toxicity was documented in 14 patients with a 2 year freedom from severe toxicity in 83% with peripheral lesions as compared to 54% in patients with perihilar/central tumors. Bradley et al.[115] reviewed the results of 91 patients enrolled into a prospective database with 83 patients referred for SBRT due to underlying comorbidities and the remaining 8 patients refusing surgery. Eighty-three tumors were peripheral while eight were central (defined as ≤2 cm from the bronchus or esophagus or located adjacent to the brachial plexus). Peripheral tumors received 54 Gy (18 Gy per fraction × 3 fractions) while central tumors received a reduced dose of 45 Gy (9 Gy per fraction × 5 fractions) based on the toxicity data from Timmerman et al. The median tumor diameter was 2 cm with no tumor >5 cm . Fifty-eight patients with T1N0 tumors, 22 patients with T2N0, 2 patients with T3N0 (chest wall) and 6 patients with T1N0M1 disease were included. With a median follow-up of 18 months, the 2-year LC was 86% with distant metastasis or second lung cancer as the predominant pattern of failure.

In 2010, Timmerman and colleagues[116] reported the results of the Radiation Therapy Oncology Group (RTOG) 0236, a phase II trial with inclusion of 55 medically inoperable patients with peripheral tumors < 5 cm (T1-2, N0) treated with SBRT. With a median follow-up time of 34.4 months, the 3-year LC , DFS, and OS were 97.6, 48.3 and 55.8%, respectively. The rate of disseminated recurrence at 3 years was 22.1% (11/55) with only 2 patients experiencing regional failure. Treatment-related morbidity was relatively low with grade 3 events occurring in 12.7% and grade 4 in 3.6% of patients. There were no reported SBRT-related patient deaths, possibly due to ineligibility of patients with central tumors.

At ASTRO's 56th annual meeting, Timmerman et al presented updated 5 year data from the RTOG 0236 trial. The updated results showed only 4 primary tumor failures among 55 patients, resulting in a 5-year primary failure rate of 7%. The rate of local recurrence was 20%, owing primarily to intra lobar recurrence. Additionally, 5-year loco regional and distant recurrence rates were 38% and 31% respectively. Updates on toxicity revealed two additional episodes of grade 3+, but no grade 5 toxicities.[117] This update is significant as it shows local recurrence rates with SBRT appear to be similar to lobectomy series at 5 years,

with minimal increased severe toxicity after 3 years. The RTOG 0236 trial served as the basis for RTOG 0813, a phase I/II protocol designed to determine a safe and effective dose for central tumors. The study was closed to accrual in 2013 and results have not yet been published.

Since Timmerman's first experience, a number of platforms capable of SBRT have come into popular use including standard linear accelerator-based options, Cyberknife, Tomotherapy, Viewray, proton-based options, and others. Additionally, various immobilization devices, respiratory-tracking, and tumor motion-gating options have been developed. Each have advantages and disadvantages and vary considerably in their costs of installation and maintenance, required treatment time, beam angle capabilities, and beam modifiers. As the technology has developed, an expanding number of institutional reports of SBRT for early stage NSCLC are now available and are summarized in Table 3.

Le et al.[118] completed a phase I dose-escalation study designed to investigate the optimal single-fraction SBRT dose in the treatment of inoperable lung tumors. Thirty-two patients (21 T1-T2N0 NSCLC and 11 metastatic tumors) received SBRT with tumor doses initiated at 15 Gy with escalation to a dose of 30 Gy. The 1-year OS was 85% with a 1-year freedom from local progression of 91% with doses >20 Gy as compared to 54% in patients who received less than 20 Gy (p=0.03). The overall rate of complications increased with doses greater than 25 Gy with increased risk of pulmonary toxicity in patients with treatment volumes greater than 50 cc and in those with a history of pulmonary radiation.

Hof and colleagues [109] reported on 42 patients with stage IA (17), IB (21), or IIB (4) NSCLC. Patients were treated with 15-30 Gy prescribed to the isocenter with the 80% isodose covering the PTV. With a median follow-up of 15 months, LC and OS rates at 1, 2, and 3-years were 89.5, 67.9, 67.9% and 74.5, 65.4, and 37.4%, respectively. Koto and colleagues[119] reported on 31 patients with a median tumor size of 2.5 cm with a median follow-up of 32 months. Patients were treated with either 60 Gy in 8 fractions (if the tumor was close to an organ at risk) or 45 Gy in three fractions. The 3-year LC rate for stage IA patients (n=19) was 77.9%, compared to 40% for stage IB patients (n=12). The 3-year OS and CSS rates for the entire cohort were 71.7 and 83.5%, respectively.

Onishi and colleagues [120] reported on an amalgamation of multi-institutional data from Japan which included 257 patients (164 stage IA patients and 93 stage IB) with a median tumor size of 2.8 cm (range: 0.7-5.8 cm). Of the 257 patients, 99 were medically operable but refused surgery. The median follow-up period for the entire cohort was 38 months. Given the heterogeneity of radiation therapy dose prescriptions, the cohort was dichotomized into 2 groups with 215 patients receiving ≥100 Gy BED and the other 42 patients receiving <100Gy BED. The overall LC rate for the entire cohort was 86% (87.8% for stage IA and 82.8% for IB, which was deemed to significantly different, p=0.21). The group that received ≥100 Gy BED had a LC rate of 91.6% while those who received a BED <100Gy had a LC rate of only 57.1% (p<0.001). The 3 and 5-year OS for the entire cohort was 56.8 and 47.2%, respectively. The 5-year OS for the BED ≥100 Gy cohort was 53.9%, compared with only 19.7% for <100Gy (p<0.05). With a median follow-up of 58 months,

the operable group treated with SBRT alone to a BED >100 Gy demonstrated 5-year OS and local PFS rates comparable to historical lobectomy controls[85].

Lagerwaard and colleagues [121] published the results of 206 patients with tumor sizes of ≤6 cm treated with a variety of fractionation schemes based on tumor stage and risk of toxicity to surrounding normal tissue (20 Gy × 3, 12 Gy × 5 and 7.5 Gy × 8 fractions). With a median follow-up of 12 months, the LC was 97% with median OS at 1 and 2-years of 81 and 64%, respectively. The 1 and 2-year CSS were 83 and 68%. Severe late toxicity was observed in less than 3% of patients. Baumann and colleagues[122] reported on 57 patients with an average tumor size of 2.5 cm (range: 0.6-2.5 cm). The median follow-up was 35 months with a 3-year LC was 92%. In terms of OS, the 1, 2, and 3-year rates were 86, 65, and 60%, respectively. The CSSat these time intervals was 93, 88, and 88%, respectively.

Inoue et al.[123] studied 115 patients with a median tumor size of 2 cm at a median follow-up of 14 months. Tumors ≤2 cm had a LC of 96.6%, compared to 94.7% for larger tumors. Overall survival rates for the group with ≤2 cm tumors at 3 and 5-years were both 89.8%. The OS of the group with tumors >2cm at 3 and 5-years were 60.7 and 53.1%, respectively. Guckenberger and colleagues[124] reported on 124 patients in their study which included 41 patients with NSCLC and the remainder with pulmonary metastases. Average tumor size for those with NSCLC was 8 cm^3. The median follow-up time was 14 months with a 3-year LC was 83%. For the NSCLC patients in the study (n=41); the 3-year OS and CSS were 37 and 59%. This group also evaluated the impact of BED and found that 3 year LC was 89 vs. 62% in favor of BED >100 Gy. Fakiris and colleagues[125] reported on 70 patients with tumors ≤7 cm. The average follow-up time was 50.2 months, and the LC at 3 years was 88.1%. The OS and CSS at 3 years were 42.7 and 81.7%, respectively.

A retrospective report from the Cleveland Clinic explored the effect of two different fractionations on tumor control and toxicity. Eighty-six consecutive patients (with 94 lesions) with medically inoperable stage I NSCLC received either 50 Gy in 10 Gy fractions or 60 Gy in 20 Gy fractions. The change in fractionation reflected a change in institutional practice based on date of treatment delivery rather than a clinical treatment selection. Local control for the 50 and 60 Gy cohorts at 1 year were 97.3% and 100% and OS was 83.1% and 76.9%, respectively which were not significantly different. The only significant difference between the cohorts was the incidence of mild (grade 1 or 2) chest wall toxicity which was higher in the 60 Gy group (18% versus 4%, $p = 0.028$). Thus, authors concluded that tumor control was not affected by this change in fractionation, but chest wall toxicity was increased with 60 Gy in 20 Gy fractions.[126]Haasbeek et al.[127] retrospectively reviewed the role of SBRT in patients ≥75 years of age with early stage NSCLC (118 T1 tumors and 85 T2 tumors) deemed medically inoperable or in those who refused surgery. Two-hundred and three tumors were treated in 193 patients with utilization of 3 risk-adapted fractionation schemes based on the location of the tumor (20 Gy × 3; 12 Gy × 5, 7.5 Gy × 8 fractions). OS at 1- and 3-years were 86 and 45%, respectively, with a median survival of 32.5 months. The 3-year LC was 89%. The authors noted minimal acute toxicity with uncommon severe late toxicity with ≥grade 3 late toxicity in less than 10% of patients.

Bishawi and colleagues [39] reviewed 30 patients with Stage I and II NSCLC treated with SBRT alone (60 Gy in 3 fractions). The main focus of the review was to assess the effects of SBRT on FEV1 and DLCO . FEV1 before and after treatment did not change dramatically in patients with and without COPD (39 ± 5 vs. 40 ± 9, p=0.4; 77 ± 0.5 vs 73 ± 24, p=0.9). DLCO, on the other hand, significantly improved for those who did not have COPD but not for patients with COPD (60 ± 24 vs. 69 ± 22, p=0.022; 49 ± 13 vs. 50 ±, p=0.8).

Sher and colleagues[40] compared costs of SBRT, 3D-conformal radiation therapy, and RFA for treatment of medically inoperable stage I non-small-cell lung cancer. In their study, a model was created to describe the health status of a 65-year old man with early stage NSCLC treated with one of the three modalities listed above. It was assumed that patients received supportive care at recurrence. Data for cost and recurrence were adapted from the literature and utility values were computed. The incremental annual quality-adjusted life years' (QALYs) value of SBRT over RFA and 3D-CRT were 14,000 and 6,000 USD, respectively.

From the literature, it can be concluded that LC and OS for patients with NSCLC treated with SBRT are superior to conventional radiation therapy and appear similar to surgical outcomes. However, given their predominantly retrospective nature, inherent selection biases and limited follow-up, it is important to complete further prospective trials. Another important caveat is that SBRT is commonly performed in medically inoperable patients in which histological confirmation through biopsy is often avoided due to risks of the procedure. In the Haasbeek et al. experience for instance, the rate of histologic confirmation of malignancy was only 39%, which they report as being in-line with other similar studies[127]. In the absence of pathology, institutions and national organizations are developing consensus guidelines for establishing a diagnosis of malignancy using radiographic criteria such as FDG uptake and documented growth. A recent publication by Louie et al describes an inventive model for comparison between several approaches in this situation[128]

To address several of the critical issues surrounding SBRT, the RTOG conducted a number of a recent trials. The RTOG 0915 study compared two SBRT fractionation schedules including 48 Gy in 4 fractions and 34 Gy in a single fraction. The study met its accrual objective and was presented as an abstract at the 2013 ASTRO annual meeting with 20.6 months of followup. At 1 year, the single fraction regimen met pre-specified criteria with respect to adverse events and tumor control, thus this regimen has been selected as the experimental arm for a planned phase III trial.

The RTOG 0618 trial studying the use of SBRT in operable, early-stage patients closed to accrual in 2010 and the RTOG 0813 studying the treatment of centrally located tumors was closed in 2013. Both studies met their accrual objectives with data maturing at the present time. Unfortunately, the RTOG 1021/ACOSOG Z4099 comparing sublobar resection with or without brachytherapy to SBRT in high risk operable patients was closed in 2013 due to slow accrual as were the Dutch ROSEL and Accuray STARS trials, both comparing lobectomy and SBRT.

Conclusion

In summary, patients with early stage non-small cell lung cancer deemed high-risk or medically inoperable, or otherwise refuse lobectomy have new options for treatment with evidence to support promising results and manageable toxicities. Such techniques, including RFA and SBRT, provide options for patients unable to undergo lobectomy or even limited resection, and allow for the possibility of improved LC and OS as compared to historical controls. Further studies are required to better define the optimal treatment of patients with early-stage NSCLC to include a definitive comparison of SBRT to surgical resection in operable patients.

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Table 1

Studies including sublobar resection. Lob- Lobectomy, LR- Limited Resection, Seg- Segmentectomy, Loc. Rec- Local Recurrence, W- Wedge, Op Mortality- Operative Mortality, SL- Sublobectomy, SL/Br- Sublobectomy/Brachytherapy

Author (Year)	# Patients (Tumors)	Dz Stage	Tumor Location	Tumor Size (cm)	Months (Mo.) F/U	LC Rate	1-Yr Sur (%)	2-Yr Sur (%)	OS	Cause Specific Survival	Complications	Lung Function Criteria
LCSG (1994, 1995)	247 total 125-Lob 122-LR (85 Seg., 40 Wedge)	T1N0	Peripheral	< or =3cm	60mo.-Mean 36mo.-Minimum (53-min for Lob, 54 LR)	Lob- 93.6% LR- 83% (p=.008)	Lob- 95% (from review: Fernando, 2005)	Lob-80% (from review: Fernando, 2005)	Lob-69.6% LR-60.7% (p=.088)	NA	NA	Preop FEV1 >or=50%:
Landreneau (1997)	219 W=102 Lob=117	Stage I NSCLC	Peripheral	Median: W-1.8cm Lob-2cm	Mean: W=27mo. Lob- 26mo.	W-81% Lob-91%	W-94% Lob- 91%	W- ~72% Lob-~87%	5Yr:W-61.5% Lob- 70% (p=.02)	NA	Resp Failure, empyema, wound infection, air leak, myo infarction, arrythmias, sepsis	COPD- 66.5%, 14% FEV1- 65%, 88% DLCO- 62%, 81%
Keenan (2004)	201 Lob-147 Seg-54	Stage I NSCLC Lob- 126 IA, 21 IB Seg- 47 IA, 7 IB	NA	Lob-NA Seg- 55.5% <or=2cm, 44.4% btw 2 and 3 cm	Lob-32.9mo. +/− 1.6 Seg-27.4mo. +/− 2.2 (not sig)	Lob- 92.5% Seg- 88.9% (p=.22)	Lob- 78% Seg-81.5% Act. Surv- Lob- 95% Seg- 92%	NA	4 Yr Act. Surv-Lob- 67% Seg- 62% (p=.406)	4 Yr- Lob- 82% Seg- 74% (p=0.71)	Op Mortality-Lob- 4.8% Seg- 5.6%	FEV1-55.3%
Okada (2006)	567 SL- 305 (230 Seg, 32 W) Lob- 262	SL,Lob: IA(266,2 17),IB(7, 10),IIA(10,12),IIB(2,2),IIIA(14,15),IIIB(6,6)	Peripheral	< or = 2cm SL-1.57(mean) Range-.5-2cm Lob- 1.62cm (mean) Range-.8-2cm	SL- 72mo. (median) Range: 29-155mo. Lob-71mo. (median) Range: 22-158mo.	SL-95.1% Lob-93.1% (not significant)	SL- 98% (from review-Fernando, 2010)	SL-96% (from review-Fernando, 2010)	5 Yr SL-89.6% (not sig. between types; (p=.4335)) Lob-89.1% (not significant)	DFS- Figure 2 No Sig. Difference (p=.2778) SL-(not sig. between types; (p=..8667) DFS @5yr SL 85.9%; Lob 83.4%	SL-6.6% Lob-7.3% (p=.7429)	FEV1 (W (n=18), Seg (n=168), Lob (n=168)): PreOp 2.29 +/− 0.59, 2.32 +/− 0.64, 2.32 +/− 0.58 PostOp: 2.21 +/− 0.84, 2.10 +/− 0.62, 1.93 +/− 0.58
El-Sherif (2006); ***analysis based on SL not W/Seg***	784 SL (122 Wedge, 85 Seg)- 207 Lob- 577	Stage I NSCLC SL-161 IA, 46 IB Lob-288 IA,289 IB	NA	SL-1.8cm (median) Lob- 2.8cm (median)	31mo. (median)	Local/Regional SL-86% Lob-92%	NA	NA	5Yr SL-40% Lob-54% (p=.0038)	DFS no sig difference	Perioperative Mortality SL-1.4% Lob-2.6%	NA
Sienel (2007)	199 Seg-49 Lob- 150	Stage IA NSCLC	NA	2.03cm +/− .96 Seg- 1.8cm +/− .75 Lob- 2.8cm +/− 1.04	54mo. (median)	Seg- 84% Lob- 95% (p=.005)	NA	NA	5Yr- 79% CRS*: Seg- 67% Lob- 83%; p=0.01	CRS-Significantly Diff Seg- 67% Lob- 83% (p=.01)	NA	Median FEV1: Seg- 45% Lob-44%
Schuchert (2007)	428 Seg- 182 Lob- 246	Seg- IA (109) IB (73) Lob- IA(114) IB(132)	NA	Seg- 2.3cm (.2-7.0) Lob- 3.1cm (.5-11.2)	Seg- 18.1mo. (mean) Lob- 28.5mo.	Seg 92.3% Lob 95.1% (p>0.05)	Seg ~98% Lob ~96%	Seg ~88% Lob ~90%	Seg- ~83% Lob- ~80% (not sig.)	DFS- Figure 1A- No significant difference	Seg- 32.4% Overall, 13.2% Major Lob- 33.7% Overall, 13.8 Major A.F.: 9.2%	FEV1 (%)=Seg- 1.7 (70) Lob- 1.81 (74) DLCO(%)=Seg- 13.9 (66) Lob-15.1 (69)
Wisnivesky (2010)	1165 Lob-969 LR-196	Stage I NSCLC	NA	</= 2cm	59 mo	NA	NA	NA	Hazard Ratio:1.09	Hazard Ratio: 1.39	NA	NA

Author (Year)	# Patients (Tumors)	Dz Stage	Tumor Location	Tumor Size (cm)	Months (Mo.) F/U	LC Rate	1-Yr Sur (%)	2-Yr Sur (%)	OS	Cause Specific Survival	Complications	Lung Function Criteria
				Lob- 1.59cm +/ Lob- 2.59cm +/ LR- 1.49cm +/ − .41cm					Not significant difference	Not significant difference		
Zemylak (2010)	64 SLR (n=25) RFA (n=12) PCT (n=27)	Stage I NSCLC	NA	Not Defined	33 mo	SLR 88% RFA 67% PCT 89% (p>0.05)	NA	NA	3-yr OS SLR 87.1% RFA 87.5% PCT 77%	3-yr Cancer Specific Survival SLR 90.6% RFA 87.5% PCT 90.2%	Pneumothorax, and hemoptysis	Major Criteria FEV1<50% predicted DLCO<50% predicted Minor Criteria FEV1 51-50% DLCO 51-60% Pulmonary HTN

Table 2

Studies including radiofrequency ablation. ARDS – Acute Respiratory Distress Syndrome, PT – Pulmonary Thrombosis, PE – Pulmonary Embolism, Pneu - Pneumonia, Pl. Ef. – Pleural Effusion, PCP – Pneumocystis Carinii Pneumonia

Author (Year)	# Patients (Tumors)	Patients per disease stage	Tumor Location	Tumor Size (cm)	Months F/U	LC Rate	1-Yr Surv (%)	2-Yr Surv (%)	Overall Survival	Cause Specific Survival	Complications
Lee(2004)	30 (32)	10-Stage IA/B, 1-IIB, 15- III/IV, 4- Mets	Central- 18 (56%) Peripheral- 14 (44%)	5.2cm +/−2.4	12.5mo. Range: 1-24mo.	38% with complete necrosis at least for 9mo	NA	NA	Mean Survival: <3cm: 18.6 mo +/ − 2.2 months >3cm: 11.3 mo. +/− 1.8 (p=.09)	NA	10% major complication ARDS or severe PT all central tumor
Fernando (2005)	18 (21)	9- I, 2-II, 3-III, 4-IV	Peripheral	2.8cm (median) Range: 1.2-4.5 cm	14mo. (median)	61.9%	83%	83%	NA	PFS: Mean and Median Intervals: 16.8 and 18 mo. Stage I: Mean Interval: 17.6 mo.	PT: 38.9% Pneu: 11.1% Air Leak: 5.6% PE: 5.6%
Hiraki (2006)	128 (342)	25- Primary, 317- Mets	Central- 90 (26%) Peripheral- 252 (74%)	1.7cm +/− 1.2	12mo. (median)	73% (1-30 months after first ablation)	NA	NA	NA	NA	NA
Yan (2006)	55	26- I/II, 29 -III/IV, Colorectal Pulmonary Mets	Central- 10 (18%) Peripheral- 45 (82%)	<5cm	24mo. (Range 6-40mo.)	62% (at time of last F/U-40 months)	I/II 92% III/IV 79%	I/II 3yr 69% III/IV 3yr 38%	33 median OS Actuary Surv: 1Yr, 2Yr, 3Yr: 85%, 64%, 46%	PFS: 15 Mo.	PT: 29% Fever: 11% Pl. Ef: 7.2% PCP: 3.6%
Pennathur (2007)	19	11- Stage IA, 8- Stage IB	Peripheral	2.6cm (mean) Range: 1.6-3.8	29mo.	58% (@ 27 months)	95%	68%	NA	NA	PT: 63% Air Leak: 5%
Simon (2007)	153 (189)	116 -I NSCLC, 73 -IV colorectal	NA	2.7cm(mean) for LC 6.1cm (mean) for palliation	20.5mo (median)	1, 2, 3, 4, 5Yr- 83%, 64%, 57%, 47%,47% (<3cm); 1,2,3,4,5 Yr-45%, 25%, 25%, 25%, 25% (>3cm)	I 78% IV 70%	I 57% IV 54%	I 5yr 27% IV 5yr 44	NA	PT: 28.4% Chest tube insertion: 9.8%
Ambrogi (2007)	50	30 -I NSCLC, 14 -IV	1cm frrom mj bld vessles or airways	2.4cm (mean)	31mo.	61%	NA	NA	I NSCLC 28.9 mo; all 25mo	NA	NA
Lencioni (2008)	106(183)	33- I NSCLC, 53- Colorectal Mets, 20- Other Mets	1cm from trachea, main bronchi, R/: pulm a	1.7cm (mean)	Up to 2 years	1Yr- 88%	NA	NA	NSCLC 70% 1yr, 48% 2yr; IV colorc 89% 1yr, 66% 2yr Other 92% 1yr, 64% 2yr	-NSCLC 92% 1yr, 73% 2yr; -IV colorc 91% 1yr, 68% 2yr -other 93% 1yr, 67% 2yr	PT: 20%
Lanuti (2009)	31 (34)	29- T1N0, 5- T2N0	Peripheral	2.0cm +/− 1.0	17mo.	68.5% @ 17mo	85%	78%	3Yr- 47% Med OS 30mo	DFS: 2 Yr-	PT: 13% Pneu: 16%

Author (Year)	# Patients (Tumors)	Patients per disease stage	Tumor Location	Tumor Size (cm)	Months F/U	LC Rate	1-Yr Surv (%)	2-Yr Surv (%)	Overall Survival	Cause Specific Survival	Complications
										57%; 3 Yr-39% Median 57%; 3 Yr-39% Median DFS:25.5 mo.	Pl.Ef: 21%
Huang (2010)	329 (436)	NSCLC (n=237) I-33, II- 50, III- 109, IV- 45, Metastases (n=92)	NA	<3 cm: 253 3-4 cm: 102 >4 cm: 81	Median progression free period: 21.6 mo.	76.3% Overall >4 cm: 58%	68.2	35.3	1-year: 80.1% 2-years: 45.8% 5-years: 24.3%	NA	34.3% of pts overall Pneumothorax in 19% Hemoptysis in 4.2% 30-day mortality of 0.6%
Beland (2010)	79 (79)	NSCLC (n=79) IA -56 IB - 13 IIB - 3 IIIB - 4 IV - 3	Central- 15 (19%) Peripheral- 64 (81%)	2.5 cm (range 1-5.5 cm)	Mean follow-up: 16 months	57% (recurrent or residual tumor in 43%)	NA	NA	Median disease-free survival: 23 months	NA	Adjuvant RT in 19 pts(24%) Concomitant brachytherapy in 9 pts (11%)

Table 3

Studies including stereotactic body radiation therapy (SBRT). COPD – Chronic Obstructive Pulmonary Disease, FEV1 – Forced Expiratory Volume in 1 Second, DLCO - Carbon Monoxide Diffusing Capacity.

Author (Year)	# Patients	Patients per disease stage	Tumor Location	Tumor Size	Dose	BEDiso	Months (mo.) followup	Local control rate	1-Yr Survival	2-Yr Survival	OS	Cause Specific Survival	Complications/ Toxicities	Lung Function Criteria
McGarry (2005)	47	19-IA 28-IB	No Location Criteria, all patients accepted	≤ 7 cm	T1 stratum: 24 to 60 Gy T2 stratum: 24 to72 Gy to 80% isodose	T1: 43.2 to 180 Gy T2: 43.2 to 244.8 Gy	T1: 27.4 mo. T2: 19.1mo.	78% (9/10 occurred at doses ≤16 Gy per fraction)	NA	NA	NA	NA	≥ Grade 3 in 72 Gy cohort	Inoperable: 14 pts oxygen dependent
Le (2006)	32	21 - NSCLC 11 - Metastatic	No Location Criteria, all patients accepted	2.0 -6.2 cm (tumor diameter)	15 -30 Gy < 20 Gy (n=10) 25 Gy (n=20) 30 Gy (n=2)	37.5 - 120 Gy	Not Defined	91% (>20 Gy cohort) 54% (<20 Gy cohort)	89%	NA	NA	NS	Increased pulmonary toxicity >25 Gy with prior RT and volumes >50cc	NA
Hof (2007)	42	17-IA 21-IB 4-2B	Peripheral	IA<3cm IB>3cm	15-24Gy to 80% isodose in a single fraction	24Gy-81.6Gy	15mo.	1Yr-89.5% 2Yr-67.9% 3Yr-67.9%	74.5%	65.4%	3Yr- 37.4%	1Yr-70.2% 2Yr-49.1% 3Yr-49.1%	Only mild reactions; no grade 3 or 4 toxicities	FEV1 at least 0.8L
Koto (2007)	31	19-T1 12-T2	30-Peripheral 1- Central	2.5cm (median)	20 Pts.-45Gy/3/1 Week 11 Pts.-60Gy/8/2 Weeks	45Gy Group: 113Gy 60Gy Group: 105Gy	32mo.	3Yr-IA-77.9% IB-40%	NA	NA	3Yr- 71.7%	3 Yr-83.5%	24 Pts- Grade 1 Pneumonitis 3 Pts- Grade 2 Acute Pneumonitis 1 Pt- Grade 3 Acute Pneumonitis	NA: Not surgical candidates, refusal of surgery
Onishi (2007)	257	164-IA 93-IB	No Location Criteria, all patients accepted	2.8cm (median) Range: 0.7-5.8cm	18 to 75 Gy in 1-22 Fractions	111Gy (Median) 215 Pts: ≥100Gy (117Gy Median) 42 Pts: <100Gy (79.6 Gy Median)	38mo.	86% IA- 87.8% IB- 82.8% (p=.21) BED≥100 Gy: 91.6% BED<100 Gy: 57.1% (p<0.001)	NA	NA	3Yr, 5Yr-56.8%, 47.2% (5 Yr-BED>100Gy: 53.9% BED<100Gy: 19.7%) (p<0.05)	3 Yr-76.9% 5 Yr-73.2%	1Pt- chronic segmental bronchitis and wall thickening (atelectasis) 2Pts- Grade 3 Esophagitis 3Pts- Grade 3 or 4 Dermatitis 4Pts- Rib Fracture Adj. to Tumor	ECOG: 0- 109 1-103 2-39 3-6
Lagerwaard (2008)	206	129-T1 90-T2	63%-U.L. 31%-L.L. 6%- M.L. Periph-p.689	<6cm	93-20Gy/3 99-12Gy/5 27-7.5Gy/8	3-180Gy 5-132Gy 8-105Gy	12mo.	97%	81%	64%	3Yr ~50% Figure 1	1Yr-83% 2Yr-68% (Other Survival Rates Reported)	64 Pts.- Fatigue 25 Pts- Local chest wall pain 19 Pts- Nausea 12 Pts- Dyspnea 12 Pts- Cough 6 Pts- Grade 3 or higher Pneumonitis	FEV1=54 %
Baumann (2009)	57	40-T1 17-T2	Peripheral	2.5cm Range: .6-5cm	45Gy/5/3 15×3@67% isodose line	Periphery-113 Central-211	35mo.	3Yr-92%	86%	65%	3Yr- 60%	1Yr- 93% 2Yr- 88% 3Yr- 88%	16 Pts-Grade 3	FEV1-64% Mean
Inoue (2009)	115	93-T1 22-T2	Peripheral	2cm (median) Range: .5-4.5cm	30 to 70 Gy in 2-10 Fractions	106Gy Range: 56-141Gy	14mo.	≤2cm: 96.6% >2cm: 94.7%	NA	3Yr:<or=2cm:89.8% >2cm=60.7%	5 Yr-<2cm: 89.8% >2cm: 53.1%	NA- OS reported based on two size groups	≤2cm: 2Pts- Grade 2 >2cm: 5 Pts- Grade 2 3Pts- Grade 3 1 Pt- Grade 5	ECOG 0-2 (WHO)

Author (Year)	# Patients	Patients per disease stage	Tumor Location	Tumor Size	Dose	BEDiso	Months (mn.) followup	Local control rate	1-Yr Survival	2-Yr Survival	OS	Cause Specific Survival	Complications/ Toxicities	Lung Function Criteria
Guckenberger (2009)	124 (159 lesions)	118-mets 41-NSCLC (13-IA 19-IB 9-T3N0)	Central,TW,Periph: NSCLC-6,9,26 Mets-16,24,78	CTV=29cc PM=8cc	~12.5Gy/3 to 65% isodose ~26Gy/1 to 80% isodose ~10Gy/3 to 65% isodose	~84Gy ~94Gy ~60Gy	18mo. (mean) 14 mo. (median)	3Yr-83%	NA	Na	3Yr 37%:NSCLC 16%:mets	3 Yr NSCLC-59%	Acute (24 Pts) 19 Pts, 1 Pt.-Grade 2, 3 Pneumon. 2 Pts-II PT 2Pts- II PE Late (6 Pts.) 3Pts-II Dyspnea 2 Pts.-II PT 1 Pt- III Esoph. Ulcer	Karnofsky Index 77, 89
Fakiris (2009)	70	34- T1 36- T2	48-Peripheral 22- Central	<7cm	T1- 20 Gy/3 T2- 22Gy/3	T1 - 180Gy T2 - 211Gy	50.2 mo.	3 Yr-88.1%	NA	NA	3 Yr- 42.7%	3 Yr-81.7%	6 Pts- Grade 3 1 Pt- Grade 4 5 Pts- Grade 5	FEV1< 40% DLCO< 40%
Bradley (2010)	91	58-T1N0M0 22-T2N0M0 2-T3N0M0 6-T1N0M1	83-Peripheral 8-Central	2cm (median) Range: 1-5cm	Peripheral-18Gy/3 Central-9Gy/5	18Gy Group-151Gy 9Gy Group- 85.5Gy	18mo.	2Yr-86% 3Yr=~86% (Fig. 1)	NA	NA	3Yr- ~60% 4Yr- ~50%	3Yr- ~73% 4Yr- ~65% Figure 4	3Pts- Grade 2 Pneumon. 4Pts- Rib Fracture or Chest Wall Pain 1 Pt- Brachial Plexopathy	FEV1-46% DLCO-49%
Timmerman (2010)	55	44- T1 11- T2	Peripheral	<5cm	18Gy/3	151.2Gy	34.4mo.	87.2%	~87%		3Yr- 55.8%	3 Yr- 48.3%	7 Pts- Grade 3 2 Pts- Grade 4	FEV1: <40% DLCO: <40%
Haasbeek (2010)	193 (203 tumors)	118-T1 85-T2	83-Peripheral 8-Central	2cm (median) Range: 1-5cm	69-20Gy/3 101-12Gy/5 33-7.5Gy/8	3-180Gy 5-132Gy 8-105Gy	12.6 mo.	3 Yr-89%	85.7%	NA	3Yr- 45.1% Median OS 32.5 mo.		≥3 pneumonitis 2.1% Cough 5.7% Chest wall pain 2.6% Dypena 5.2%	Severe COPD in 25% 80% inoperable 20% declined surgery