A Decade of Advances in Treatment for Early Stage Lung Cancer

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INTRODUCTION

Early stage non-small cell lung cancer (NSCLC) refers to stage I or stage II disease. While patients with lung cancer who meet this criterion have the highest five year survival and lowest recurrence rates, their prognosis is still poor relative to other early stage cancers. In patients with early-stage NSCLC, the ability to achieve complete surgical resection remains the most definitive treatment in current medical practice. Surgically resected stage I NSCLC has only a 70% 5-year survival and a 55–75% recurrence rate [1–4]. Five-year survival after surgical resection decreases to 40–50% for stage II disease [5]. The large database informing the most recent international lung cancer staging system demonstrated 5-year survival for stages IA, IB, IIA and IIB of 73%, 58%, 46% and 36% respectively [4]. Unfortunately, lung cancer is detected in an advanced stage in approximately 70% of patients, making it one of the leading causes of death in America, with only a 16% overall 5-year survival [6].

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The last decade has witnessed a litany of advances in the treatment of early stage lung cancer. In the past, patients who were inoperable due to poor lung function were relegated to few options with rather dismal survival results. Now, more options are available including technologic advances in chest radiotherapy, a growing interest in the utility of sublobar resections, and an increase in the use of video assisted thoracoscopic surgery (VATS).

Lung cancer screening has also undergone significant change during the past decade. The National Lung Screening Trial (NLST) compared chest radiograph versus low dose helical chest computed tomography (CT) in screening for lung cancer in 53,000 older patients with extensive (> 30 pack-year) smoking history. The trial was stopped early due to a 20 percent reduction in lung cancer death among patients screened with CT scan compared to those screened with chest radiograph [7]. In the NLST, the majority of patients were diagnosed at early stage. Ninety-three percent of patients with stage I lung cancer detected by CT scan and 88% of patients with Stage I lung cancer detected by chest radiograph underwent surgery with curative intent [7].

One of the most important advances over the last decade was the development and implementation of the 7th edition of the international lung cancer stage classification system. The effect of tumor size on survival was studied in detail and incorporated in defining the new T descriptors. Additional size criteria for the primary tumor (2, 5 and 7 cm) now further subdivide previous cutoff values. T1 is now divided into T1a (2 cm) and T1b (> 2 cm but 3 cm). T2 is divided into T2a (> 3 cm but 5 cm) and T2b (> 5 cm but 7 cm). Tumors > 7 cm are now considered T3 as this group of patients has survival comparable to other definitions of T3 [4].

There is a growing recognition that smaller tumors (2.0 cm) have a more favorable prognosis, prompting an increased consideration of sublobar as opposed to lobar resections for this group. Additionally, the last decade has witnessed the development and application of lung stereotactic radiation in nonsurgical candidates, as well as the demonstration of benefit of adjuvant chemotherapy in patients with large stage IB and stage II NSCLC [8].

LOBECTOMY VS. SUBLOBAR RESECTION

The first lung cancer surgeries involved complete pneumonectomies, and frequently resulted in death [9]. As technology improved, surgery has evolved and become vastly safer and more effective. Patients now have additional surgical options including lobectomy (the surgical removal of one complete lobe and its lymph nodes) and sublobar resection (anatomic segmentectomy or wedge resection). The surgical approach may be open thoracotomy or VATS. Despite the advances in surgery for early stage lung cancer over the past decade, questions still remain, such as whether lobectomy is uniformly superior to sublobar resection. The two procedures often differ with regard to the extent of parenchymal lymph node sampling and potentially the adequacy of surgical margins. The two procedures also have been associated with different mortality and/or recurrence rates.

Sublobar resections are typically used in patients who have an impaired pulmonary reserve and would not tolerate a full lobectomy. (This evaluation is discussed in further detail in separate articles in this issue by F. Von Groote-Bidlingmaier and colleagues and H. Mehta and colleagues). These procedures can be done via open thoracotomy or VATS [10]. Wedge resections are most often recommended for smaller tumors (< 2cm) that are peripheral in location [10]. The tumor is resected without regard for anatomical bronchial segments and fissures. The benefits are preservation of lung volume and less perioperative morbidity and mortality. The major disadvantages of wedge resection are that N1 (intrapulmonary) lymph node sampling is not possible, and that assessment of the surgical margin between staple line and tumor is difficult, leaving open the potential that it may be inadequate. Both of these

issues may increase the possibility of higher rates of recurrence [11]. Segmentectomy refers to removal of an entire anatomical bronchial segment. It involves a detailed dissection of the bronchial segment and pulmonary arterial supply [10, 11]. Performing a segmentectomy is more of a technical challenge for surgeons; its benefit is that it allows adequate lymph node sampling while still preserving lung volume and function [11].

In general, lobectomy is considered a superior approach when compared to sublobar resection. However, debate continues on this topic. The discussion has been muddied by numerous and often conflicting studies comparing lobectomy to sublobar resections that did not separate the types of sublobar resections (segmentectomy or wedge resection), and that included high risk patients who underwent sublobar resection because they could not tolerate a lobectomy. To date, there has been a single prospective randomized study comparing lobectomy to sublobar resection for patients with NSCLC. In 1995, the Lung Cancer Study Group (LCSG) showed that in patients with peripheral early stage (T1N0) NSCLC, lobectomy was superior to limited resection, which was defined as wedge resection or segmentectomy [12]. The study included 247 patients. In cases where wedge or segmental resections were performed, there was a 3-fold increase in local recurrence, a 75% increase in combined local and distant recurrence (p=0.02), and a 50% increase in death in comparison to lobectomies, though this did not reach statistical significance (p=0.09). Based on this landmark study, the standard of care for individuals with peripheral early stage NSCLC (T1N0) is lobectomy with lymph node sampling. Subsequent studies have supported the LCSG findings. In a large retrospective review of the Surveillance, Epidemiology and End Results (SEER) database of 10,761 patients, there was a statistically significant difference in 5 year survival for patients who underwent lobectomy versus sublobar resection (61% vs. 44%) in patients with stage IA NSCLC [13]. As with the LCSG study, wedge resection and segmentectomy were combined in this analysis.

Not all studies have concluded that lobectomy is superior to sublobar resction, with some retrospective studies reporting reporting similar survivals in the two groups. In a series of 784 patients who underwent lung resection for stage I NSCLC, no difference in disease-free survival was noted between patients who had wedge resection or segmentectomy compared to lobectomy [14]. While there was a difference in 5-year survival favoring lobectomy, the authors speculated that patients with sublobar resections may have died earlier due to their underlying comorbid diseases, as patients underwent sublobar resection only if they were determined to be high risk candidates for lobectomy due to decreased cardiopulmonary reserve [14]. Other studies of high risk patients who underwent sublobar resection instead of lobectomy have had similar results, with 2- and 5-year survivals comparable between the two groups [15, 16]. Given that these studies have been retrospective, and in light of the inconsistent findings in the literature comparing survival between surgical types, lobectomy with lymph node sampling remains the standard of care in patients who are medically fit for such an operation, with sublobar resections typically reserved for situations where lobectomy is not possible.

In some studies where sublobar resection was further separated into segmentectomy and wedge resection, there have been no statistically significant differences in 5-year survival between segmentectomy and lobectomy [17, 18]. A recent large single-institution retrospective study comparing anatomic segmentectomy to lobectomy for stage I NSCLC showed no difference in operative morbidity or mortality between the two surgical approaches [19]. . Furthermore, there was no difference in overall or disease free survival between the two groups, although the mean follow up time appeared to be limited in the segmentectomy group. Importantly, a surgical margin of 1cm appeared to be important for preventing a local recurrence. In a study evaluating tumor size and survival following various types of surgery, there was no statistical difference between lobectomy and

segmentectomy for tumors between 2.1cm to 3 cm in diameter, with 5-year survival rates of 87% and 85%, respectively [20]. However, for tumors > 3cm, lobectomy had a 5 year survival of 81% compared to 63% with segmentectomy [20]. These findings suggest that segmentectomy may be a reasonable alternative to lobectomy for small early stage tumors, but that lobectomy remains the treatment of choice for larger cancers. However, in the absence of a randomized trial comparing lobectomy to segmentectomy for treatment of early stage NSCLC, lobectomy remains the standard approach.

In contrast to the findings with anatomic segmentectomy, lobectomy has clearly been shown to have a statistically significant 5-year survival advantage when compared to wedge resection [12, 20, 21]. This may be in part due to the fact that surgeons are better able to visualize and remove tumors and lymph nodes with lobectomy than with wedge resection [11]. In comparing anatomic segmentectomy to wedge resection, the literature shows that there is a lower rate of cancer recurrence with the former. In an analysis of patients undergoing sublobar resections for early stage lung cancer, the 5-year survival with segmentectomy for tumors < 2cm was 96% compared to 85% with wedge resection [20]. The difference in 5 year survival was even more evident with tumors between 2.1cm to 3cm in size (85% compared to 40%) [20].

Tumor size thus appears to be an important factor in the choice of surgical approach for the treatment of early stage NSCLC. The survival advantage and decrease in recurrence rate associated with a more extensive resection are likely due to a combination of factors. First, the number of lymph nodes that can be sampled varies with the type of surgery. During a segmentectomy, the dissection of the bronchial tree exposes lymph nodes that are routinely resected. Conversely, these intraparenchymal lymph nodes are not visualized or sampled during wedge resection [22]. A second factor affecting survival with sublobar resection is the width of the surgical resection margin around the removed tumor. A surgical margin greater than 1cm is more likely to be achieved with segmentectomy than with wedge resection [23]. In order to minimize the risk of recurrence, some surgeons advocate that in sublobar resection the surgical margin width should be greater than the tumor diameter [24].

In comparing recurrence rates among patients undergoing various degrees of resection for early stage lung cancer, one must continue to refer back to the LCSG study, which identified a three-fold increase in cancer recurrence with wedge resection and greater than two-fold increase in recurrence with anatomic segmentectomy compared to lobectomy. Other studies have reported recurrence rates of 2–9% with lobectomy, compared to 19–22% with segmentectomy or wedge resection [21][25, 26].

It is also important to consider the contribution of adequate mediastinal lymph node evaluation in interpreting outcomes associated with surgical resection of early stage lung cancer. In patients with stage I NSCLC who underwent sublobar resection (wedge resection or segmentectomy), recurrence rates as high as 50% have been reported in those patients who did not have mediastinal lymphadenectomy compared to 5% in those who did [27]. This highlights the importance of the mediastinal lymph node evaluation in patients undergoing curative surgery for early stage lung cancer [27].

In summary, lobectomy with lymphadenectomy is recommended as optimal curative intent therapy for patients with early stage NSCLC who are appropriate surgical candidates for such a procedure. Sublobar resection, in particular anatomic segmentectomy, should be considered for patients who are suboptimal candidates for lobectomy due to limited pulmonary reserve or other medical comorbidities (see Table 1). Controversies in this area deserve further study. It is still unclear whether lobectomy with lymphadenectomy is indeed superior to anatomic segmentectomy with lymphadenectomy, particularly in patients with

small (T1a) tumors, and this is a topic of current active study. A recent report using the SEER database evaluated survival after lobectomy or limited resection in patients with stage IA NSCLC with tumors 1 cm size, and found no difference in survival between the two procedures [28]. This finding is of particular interest when considering that lung cancer screening with low-dose CT scanning will likely increase the number of these very small cancers that are identified.

VIDEO ASSISTED THORACOSCOPIC SURGERY (VATS)

The past decade has seen an increase in the use of video assisted thoracoscopic surgery (VATS) for early stage lung cancer. In 2006, there were approximately 40,000 lobectomies performed, and VATS was used in only 2000 (5%) of those cases [29]. This percentage has increased yearly since the initial description of VATS in 1992. Initially VATS was used only for wedge resections; however as the technology has advanced, more surgeons are increasingly facile with VATS for lobectomy and segmentectomy.

Despite its increasing popularity, there is still reluctance among many in the surgical community to change their practice patterns, which may reflect the steep learning curve and technical challenges associated with the VATS approach. There is substantial evidence available demonstrating that VATS lobectomy for early stage lung cancer is an equivalent oncological operation to lobectomy by open thoracotomy, with equal long-term survival rates. In addition, numerous studies have suggested that VATS results in decreased morbidity, decreased length of hospitalization, and a more rapid return to baseline functional levels when compared to open procedures. However, definitive evidence that VATS is superior to open lobectomy is lacking, and changes in practice will likely reflect changing generations of surgeons with more familiarity and training in thoracoscopic surgery rather than the accumulation of such evidence.

There does not appear to be a difference between VATS and open procedures in 5-year survival for surgically resected early stage NSCLC. In the current largest review of a single center experience that included 1100 patients, McKenna and colleagues found that their 5-year survival rate with VATS for early stage NSCLC was comparable to most contemporary series of patient undergoing open lobectomy [29]. Other single institution reviews have also shown similar 5-year survival rates between VATS and open lobectomy [30–33]. In a multicenter review performed in Japan, the 5-year survival rate for patients with early stage NSCLC was not statistically significant between the two groups: 97% with open lobectomy versus 96% with VATS [34]. Other studies have reported no statistically significant differences in locoregional recurrence with VATS compared to conventional lobectomy [29, 34, 35].

The perioperative mortality rates with VATS and conventional open thoracotomy are similar [35, 36]. Initially skeptics of VATS questioned whether an adequate lymph node dissection could be performed, but it is clear that lymph node dissection performed via VATS can be performed as thoroughly as with an open approach [37, 38]. Shortly after the initiation of VATS, a randomized study was done that compared VATS lobectomy to open lobectomy and found no difference in duration of chest tube drainage, length of hospital stay, recovery time, or a decrease in post thoracotomy pain [39]. However since that time, a number of studies have reported significantly shorter hospital length of stay, less post-operative pain and pain medication use, fewer hospital re-admissions, shorter recuperation time, shorter chest tube drainage duration, and better preservation of pre-operative performance status with VATS [40, 41]. [34, 42] [43]. The procedure is associated with smaller chest wall incisions and consequently less inflammation, which may contribute to diminished post-

operative discomfort and shorter length of stay [34]. VATS causes fewer inflammatory markers to be released compared to conventional open lobectomies [37, 44].

All of the above should be considered in choosing the type of surgery to perform for early stage NSCLC. This may be of particular importance in patients who are anticipated to have treatment with post-operative chemotherapy, as recuperation after surgery will often impact the timing of adjuvant therapy. Petersen and colleagues demonstrated that patients undergoing VATS resections had fewer delays in the delivery of adjuvant chemotherapy, and additionally that these patients were more often able to tolerate the prescribed dose of chemotherapy without interruption [45].

VATS is more likely to be performed in large academic centers with higher surgical volume and dedicated thoracic surgeons [36, 46]. The Society of Thoracic Surgeons (STS) is comprised of predominantly board-certified thoracic surgeons (220 of the 225 members). In a review of the STS database, it was noted that 22% of all lobectomies in 2004 were performed via VATS, with that percentage increasing to 32% in 2006 [47]. Of note, 36% of all thoracic surgeries in the United States are performed by general surgeons, who typically do not have extensive training or experience with VATS [48]. It has been demonstrated that thoracic surgical procedures performed by general surgeons are associated with higher mortality, morbidity, and length of stay than are observed with specialty trained thoracic surgeons [49, 50]. The reasons for these differences are likely multifactorial. General surgeons have less exposure and perform fewer thoracic surgeries during their training. In addition, a lower postoperative mortality with lung cancer resection is observed in centers performing a higher volume of cases [47, 51]. Both factors likely contribute to the lower mortality and morbidity seen in high volume centers with specialty trained thoracic surgeons [36, 47, 51].

Tumor location and size factor into whether VATS can be feasibly performed. Large tumors (> 6 cm in diameter) may necessitate an open approach because of the challenge of manipulating such a bulky tumor with VATS instruments, and also due to the practical consideration that a larger incision will be required to get a large tumor out of the chest. While a central tumor location is not necessarily a barrier to a VATS approach, these tumors are often approached with an open thoracotomy because a tactile approach may be needed to ensure adequate surgical margins.

In summary, substantial evidence demonstrates that VATS lobectomy is an appropriate alternative to open lobectomy when performed by experienced hands in centers with adequate thoracic surgical volume. VATS appears to have equivalent oncologic outcomes when compared with open thoracotomy. The decision of which procedure should be chosen for curative intent surgery for early stage NSCLC should be based on the experience of the individual surgeon, the experience of the operating institution, and patient anatomic considerations.

TUMOR SIZE AND SURVIVAL AFTER RESECTION

There is an increased risk of lung cancer mortality with larger tumors, even in patients undergoing successful resection [52]. Since its inception, TNM staging has served to provide a common descriptive language as well as important prognostic information for patients with solid tumors, including NSCLC [53, 54]. Over the past decade, there has been a great deal of interest in the effect of tumor size, even within the same stage, as there is an association between tumor size and survival [4, 55–57]. Patients with resected small tumors (<2cm) are well described as having a better 5-year survival than patients whose tumors measure 2.1cm to 3cm [13]. This effect of tumor size on survival was one of the driving forces for change in the lung cancer staging system. The current 7th edition of the TNM

staging classification for lung cancer identified new cut points for the size of the primary tumor at 2cm, 3cm, 5cm, and 7cm. Goldstraw and colleagues reclassified over 13,000 cases of tumors originally staged by the previous 6th edition of the staging system, and demonstrated that median 5-year survival was affected by placement in a different stage [4]. For example, patients who had tumors of 6cm and no lymph node involvement were classified as T2N0, stage IB in the old system, with a group 5-year survival of 54%. However in the new system these were reclassified as T2bN0, stage IIA with a group projected 5-year survival of 46%. Ttumors > 7 cm in diameter with ipsilateral hilar lymph node involvement were staged T2N1, stage IIB in the 6th edition, with a 5 year survival of 38%. In the 7th edition, these tumors would be classified as T3N1 (stage IIIA) with a 5 year survival of 24%. The new changes in the T descriptor in addition to other changes in the staging classification system represent a major advance in lung cancer management, and should enhance our ability to more accurately group and characterize patients based on the anatomic description of their cancers.

AGE AND SURVIVAL AFTER RESECTION

Traditionally, lung cancer operations have been avoided in the older geriatric population due to concern related to the likelihood of increased morbidity and mortality. Some studies have shown a higher mortality rate in elderly patients undergoing surgery for early stage NSCLC, suggesting that age is an independent predictor of survival [13, 58]. However, other studies have demonstrated that lung cancer surgery for elderly patients is a reasonably safe and viable option. As is true for all patients, lung cancer surgical outcomes in older individuals are dependent on their performance status and comorbid conditions [59, 60]. It has been repeatedly demonstrated that elderly patients with good performance status and no comorbid conditions have similar postoperative outcomes as their younger counterparts. For example, there was no difference in 5-year survival in 133 Japanese elderly patients (age greater than 75) who underwent either lobectomy or sublobar surgery for stage I NSCLC, and also no difference in the postoperative complication rate [61, 62]. Similarly, a study in the Netherlands analyzed nearly 2,000 patients over the age of 80 who were diagnosed with stage I or II NSCLC over a period of 15 years, of whom 6% (124 patients) underwent surgical intervention. The survival rate in the resected patients after 1 year was 83% and after 5 years was 47%, which is comparable to outcomes of surgery in other age demographics in the Netherlands [63]. It is of note that only a small minority of the elderly patients in this study were treated surgically. The fact that they did so well emphasizes the fact that appropriate patient selection is important in optimizing outcomes, but also raises the question as to whether more of the elderly patients in that cohort might have benefited from a surgical approach.

Based on these and other studies, there should be no absolute age cut off for surgery in patients with early stage NSCLC. This recommendation is clear in the American College of Chest Physicians (ACCP) evidence-based guidelines for lung cancer [64]. Each case should be individualized, and the patient's comorbidities, functional status, and personal beliefs taken into account prior to deciding whether or not surgery is an appropriate recommendation..

SMALL CELL LUNG CANCER

Approximately 13% of all lung cancers diagnosed are SCLC histology [66]. Over the past ten years, the philosophy of treatment of limited stage small cell cancer (SCLC) has changed. (See also the article in this issue by Neal, Gubens, and Wakelee, Advances in the Management of Small Cell Lung Cancer.) SCLC tends to progress rapidly and is typically diagnosed after it has metastasized to other sites [65]. Like NSCLC, SCLC is staged by the

TNM paradigm, but the traditional classification as "limited" or "extensive" stage continues to have practical utility. Limited stage SCLC is defined as disease confined to one hemothorax, the mediastinum, and supraclavicular lymph nodes, with the entire extent of disease able to be included in one radiotherapy field. SCLC beyond limited stage is defined as extensive disease. Traditionally, the treatment for limited stage SCLC has been combination chemotherapy and radiation therapy [67]. While current guidelines state that there is not enough evidence to categorically offer surgery to limited stage SCLC patients, consideration is often given to resection with adjuvant chemotherapy for patients who have small tumors and are node negative. In these cases, patients should undergo a thorough evaluation to confirm that disease is truly confined to the primary site, typically with mediastinoscopy, brain imaging, abdominal imaging and bone scan prior to surgery [68].

Yu and colleagues reviewed 1560 patients with SCLC from the SEER database, of whom 247 underwent lobectomy for Stage I disease (primary tumor < 3 cm diameter without other disease) [69]. Of those, 205 patients did not undergo radiation therapy, with 3- and 5-year survivals of 58% and 50%, respectively. There was no difference in survival when compared to patients who did undergo post operative radiation therapy (p=0.90) [69]. The median survival of patients who underwent surgery for localized SCLC (defined as T1–T2 NX-N0) was an impressive 65 months, with a 5-year overall survival of 52% [67]. These results suggest that patient with early localized SCLC may benefit from curative intent surgery with adjuvant chemotherapy, with or without radiation therapy [66].

CHEMOTHERAPY

Treatment regimens involving early stage NSCLC concentrate on surgical removal of the tumor. In recent years there have been numerous trials published on the role of adjuvant chemotherapy (4–8 weeks after surgery) for early stage NSCLC. (See also the article in this issue by Gettinger and Lynch, A Decade of Advances in the Treatment of Advanced Stage Lung Cancer.) Prior to the use of platinum-based chemotherapy there was no survival advantage to adjuvant chemotherapy, and so it was not routinely used. However, more recent studies with the use of platinum-based adjuvant chemotherapy, particularly cisplatin, research appear to demonstrate a reduction in mortality [70].

There have been four large trials published in the past decade that have confirmed the utility of adjuvant chemotherapy in early stage NSCLC. All of the trials incorporated cisplatin-based chemotherapy regimens. The survival benefit seen in these studies was observed predominantly in stage II lung cancer, as opposed to stages IA or IB. The LACE trial (Lung Adjuvant Cisplatin Evaluation) was a meta-analysis of these trials, inclusive of 4500 patients. The LACE trial showed that patients with Stage II NSCLC who received adjuvant chemotherapy had a 5% decrease in risk of death at five years compared to patients who received no chemotherapy. In contrast, patients with stage IA disease who received chemotherapy had worse outcomes than those who did not receive chemotherapy, and there was no survival advantage in patients with stage IB disease who received chemotherapy [71].

The ANITA trial (Adjuvant Navelbine International Trialist Association) examined the impact of adjuvant chemotherapy in patients with Stages IB, II, and III NSCLC [72]. Stage II and III patients who received adjuvant chemotherapy demonstrated improved survival (66 months compared to 44 months), with an 8.6% increase in overall survival at 5 years compared to those who received no chemotherapy [72]. This study showed that there was no benefit in using adjuvant chemotherapy in patient with stage IB disease [72].

Two other trials, the JBR trial and IALT (International Adjuvant Lung Trial), showed that similar results. Both studies demonstrated a survival advantage in patients with stage II

disease who received adjuvant chemotherapy as opposed to no chemotherapy [73, 74]. In the JBR trial, patients with Stage II disease who received adjuvant chemotherapy had a 5-year survival of 59%, compared to 44% in those who received no chemotherapy [73].

Based on these results, the standard of care in patients with stage II disease is surgical resection followed by adjuvant chemotherapy [75]. The role of adjuvant chemotherapy in stage IB lung cancer remains controversial. None of the aforementioned trials found a survival advantage in patients with stage IB who received adjuvant chemotherapy [71–74]. However another landmark trial, CALGB 9633, which examined patients solely with stage IB disease, initially showed a survival advantage in patients who had resection and adjuvant chemotherapy [8], and on the basis of this advantage the trial was stopped early. However after the ANITA, JBR, and IALT trials failed to confirm this benefit, CALGB 9633 was reviewed with more longitudinal data, and no statistical significance in survival after 74 months (i.e. beyond the original 5-year survival benchmark) was observed in patients who received chemotherapy compared to those that did not [8]. Of note, a subgroup analysis noted that in patients with tumors > 4cm in size (Stage IB), a 31% increase in disease-free survival in patients who received adjuvant chemotherapy compared to those who did not was identified [8].

To summarize, the recommendation that adjuvant chemotherapy is recommended for patients with Stage II NSCLC does represent a substantive change in practice over the past decade. In contrast, the treatment approach for patients with stage IB lung cancer has not changed. The American Society of Clinical Oncology does not recommend adjuvant chemotherapy in these patients [75]. However, based on the results of the CALGB 9633 trial, there may be a role for adjuvant chemotherapy in select patients with stage IB NSCLC with large tumors (> 4cm). Further, the new staging system adds a further level of complexity as patients with tumors >5cm in diameter with no lymph node involvement are now classified as stage IIA; whether they might benefit from adjuvant chemotherapy is a subject for future study.

ADVANCES IN CHEST RADIOTHERAPY

Approximately 25% of all patients with early stage NSCLC are medically inoperable [76]. As most patients diagnosed with lung cancer are current or former smokers, many have chronic obstructive pulmonary disease as well as other medical comorbidities. These patients may be deemed medically inoperable because of projected high rates of complications and death. Patients also may be considered inoperable due to severe heart disease and poor performance status. Patients further may simply decline surgery for personal reasons; these patients are typically treated as if they were medically inoperable. Follow up of these patients through the SEER database demonstrates that they have a median survival of 14 months [77]. The 5-year survival rate of patients treated with supportive care alone is less than 10% [78].

In the past, the only option for patients who declined surgery or who were medically inoperable was radiation therapy. These patients were given 1–3 Gray (Gy)/fraction for 4–7 weeks for a total dose of 20–80 Gy [79]. The local recurrence rate (i.e. tumor recurrence at the site that was irradiated) varied from 6.4–70% [79]. The 3 year recurrence rate was in the range of 60–67% [79], while 5-year survival varied from 0–42% [80, 81]. Given these statistics, it is evident that conventional radiation therapy for early stage NSCLC has a high local relapse rate and a low 5-year survival [78]. The patients who benefit most from conventional radiation therapy are those with smaller tumors and those who receive higher doses of radiation to the tumor [80].

Perhaps the greatest advancement in the last ten years for early stage NSCLC has been the use of stereotactic body radiation therapy (SBRT) in patients who are deemed medically inoperable or refuse surgery. SBRT is a method where high doses of radiation (greater than 15Gy per fraction) are delivered to a tumor in five or fewer sessions over one to two weeks [80]. The radiation is transported via six to twelve radiation beams that all converge onto the tumor, which allows the targeting of a greater amount of radiation to the tumor while sparing the skin and normal surrounding lung tissue [82].

The Radiation Therapy Oncology Group (RTOG) recently published 3 year results on 55 patients with early stage NSCLC treated with SBRT [83]. They demonstrated that local control at 3 years was 90%, with a 3 year disease-free survival rate of 48%. The 3 year primary tumor control in this study was an impressive 97%, which is two-fold greater than that of conventional radiation therapy [83]. There are some limitations to the use of SBRT. It is a newer treatment option that is not available in all centers and can only be done in tumors up to 5cm, as the radiation dose becomes rate limiting. Further, there is limited information on the relapse rate after 3 years. The largest trial to date has follow up only out to 3 years [78, 83]. Another limitation is that SBRT cannot be used in centrally located tumors due to an 11-fold risk of developing severe radiation toxicity and increased risk of life threatening bleeding, as compared to its relative safety in peripheral tumors [84].

Most studies that have been completed for SBRT for lung cancer have been performed in patients who are medically inoperable. Given the impressive short term SBRT results in patients with early stage NSCLC, there is growing interest in studying its use in patients who are surgical candidates. There is an ongoing trial in the Netherlands randomizing patients to either surgery or SBRT for Stage I NSCLC that will examine local and regional control at 2 and 5 years. There is hope that this study will build on work already completed in Japan, in which a subgroup analysis showed that patients who were medically operable or refused surgery, and who were treated with SBRT, had a 5-year survival of 71% [85, 86].

Radiotherapy advances over the past decade also include the use of radiofrequency ablation (RFA) for treatment of lung tumors (see Table 2 for a comparison of radiation therapy modalities). Despite the fact there are no controlled studies that compare lung ablation to surgery or radiation, RFA has become more accepted. Performing RFA is similar to performing a CT guided lung biopsy. Patients are placed in a CT scanner, sedated, and an RFA probe is placed into the tumor. The probe contains stainless steel electrodes that protrude outwards into the tumor; heat is transmitted to the tumor for a set amount of time (dependent on the size of the tumor) to achieve coagulation necrosis. Once the electrodes have cooled, the probe is removed and the track from the tumor to the skin is ablated in order to prevent bleeding and tumor cell dissemination [87]. Results depend on the size of the tumor, with 64% 2-year local control in tumors < 3cm in size, but only 25% in tumors > 3cm [84]. Although data are limited to small series, the overall survival with RFA at all stages at one year is 70% and at two years is 48%, both of which are superior to conventional radiation therapy [87]. The disadvantage of RFA is an approximately 30% rate of pneumothorax [89, 90], related to the trocar and probe passing through normal lung tissue to reach the tumor. RFA is also limited by tumor size and location; tumors located within 1 cm of hilar structures are associated with increased risk of incomplete ablation and damage to bronchovascular structures, potentially leading to hemothorax [91]. These considerations contribute to limited use of RFA for the treatment of NSCLC.

CONCLUSION

As we emerge from the last decade, there has been a diversification of options for the treatment of early stage lung cancer (Table 3). VATS is now more widely performed, with

oncologic outcomes equivalent to open thoracotomy. While lobectomy remains the standard approach to surgical resection, lesser resections such as segmentectomy and wedge resection are considerations for some patients. Advances in surgical, radiation, and medical therapies continue to evolve. Future research questions will focus on comparing long term outcomes with these modalities, including survival as well as patient-centered endpoints such as quality of life.

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Table 1

Advantages and Disadvantages of surgeries for early stage lung cancer

Surgery	Advantages	Disadvantages
1) Lobectomy	• Lowest recurrence rate • Entire tumor and lymph nodes removed	• Greater loss of lung function • More extensive and lengthier procedure
2) Segmentectomy	• Preservation of lung function • Low recurrence rate • Better tolerated in patients with comorbid medical conditions • Greater number of lymph node dissected than wedge resection • Better surgical margin compared to wedge resection	• Technically challenging • Recurrence rate not clearly equal to lobectomy
3) Wedge Resection	• Preservation of lung function • Better tolerated in patients with comorbid medical conditions • Shorter operative time	• Highest recurrence rate • Lung tissue removed with disregard to anatomy • Surgical margins may be less sufficient • Cannot remove intrapulmonary (N1) lymph nodes • Mediastinal lymph node dissection often limited or not performed

Table 2

Advantages and Disadvantages of Radiotherapy for early stage lung cancer

Radiotherapy	Advantages	Disadvantages
1) Conventional Radiation Therapy	• Widely available	• High relapse rate • Low 5 year survival • Requires 4–7 weeks for compleetion
2) Stereotactic Body Radiation Therapy	• Completed within a few treatments • Good local control at 3 years • Can perform in patient with comorbid conditions • Can perform in patients who decline surgery • Can perform in tumors up to 5 cm in size	• Limited data available on relapse rates after 3–5 yrs • Limited availability • Cannot perform in centrally located tumors
3) Radiofrequency Ablation	• Completed in one session • Good local control at 2 years • Can perform in patients with comorbid conditions • Can perform in patients who decline surgery	• Limited data available on relapse rates after 3–5 yrs • Limited availability • Best for tumors <3cm in size • Cannot perform in centrally located tumors • High rate of pneumothorax

Table 3

5-year survival and locoregional relapse rate after various therapies for early stage non-small cell lung cancer

Treatment modality	5 year survival	Locoregional relapse rate
Lobectomy	47–90%[92]	2–28%[26,14]
Segmentectomy	57–85%[17,20]	8–29%[92,14]
Wedge Resection	27–84%[17,20]	15–55%[92,22]
Conventional Radiotherapy	0–42%[81]	60–67%[79]
Stereotactic Body Radiation Therapy	48–71% at 3 years[83,85]	22% at 3 years[83]
Radiofrequency Ablation	48–70% at 2 years[87]	25–64% at 2 years[87]