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Stereotactic Ablative Radiotherapy for Early-Stage Primary Non Small Cell Lung Cancer

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Abstract

Background and purpose: Stereotactic Ablative Radiotherapy (SART) has been associated with both impressive early responses and high rates of early-stage NSCLC control. This article reviews the overall survival, local control, toxicity and failure of SART in patients with early-stage NSCLC.

Material and methods: The systematic review was performed following PRISMA guidelines. Survival outcomes were evaluated for early-stage NSCLC. Local control and toxicity outcomes were evaluated for any centrally-located lung tumour.

Results: Twenty-four publications met the inclusion criteria, reporting outcomes for 1654 early-stage NSCLC. There was heterogeneity in the planning, prescribing and delivery of SART and the common toxicity criteria used to define toxicities. SART provided 1,3 and 5-year overall survival rates ranged from 74.5% to 94.7%, 23.0% to 84.7% and 17.0% to 69.5% respectively. The 1,3 and 5-year disease-free survival were ranged from 70.2% to 97.0%, 48.3% to 81.0% and 23.0% to 69.0%. The 5-year local control rate ranged from 83.0% to 86.7%. The locoregional recurrence and distant metastases failure after the treatment of SART were the main patterns of failure. Grade 1 or 2 toxicities may be more common following SABR for early-stage NSCLC.

Introduction

Lung cancer is one of the most prevalent cancers and is the leading cause of cancer-related mortality worldwide, with over 1 million deaths every year [1]. Surgery has been the standard of care for early stages (T1N0 and T2N0) or stage I Non-Small Cell Lung Cancer (NSCLC). However, approximately 1 of every 3 patients with early-stage disease do not undergo surgery [2]. In patients older than 75 years of age, even 2 of 3 patients do not undergo surgery [3]. One reason for this is that mortality associated with surgery in patients aged 70 or older range from 5.2% to 7.4% [3,4]. Besides comorbidity, which may increase surgical risk, a decision not to undergo surgery can also be due to a patient's perception of prognosis and racial factors [5].

For these patients, especially for older patients, Stereotactic Ablative Radiotherapy (SART) is one of the most effective treatments available and constitutes a clear standard of care which allows safe treatment with a higher Biological Equivalent Dose (BED) than conventional radiation therapy. SART has been associated with both impressive early responses and high rates of tumor control. In regard to technical aspects, the application of this new technique spares normal tissue, allows for higher radiation doses without increasing toxicity with a potential

for improved disease control and survival as compared with conventional radiotherapy [6–8]. Multiple prospective clinical trials have established the safety and efficacy of SART for the treatment of early stage NSCLC [9–16]. It has been suggested that SART has a potential for achieving disease control and survival comparable to surgery [17]. This article reviews the disease-free survival, local control, toxicity and failure of SART in patients with early-stage NSCLC.

Materials and Methods

A systematic review was performed according to the PRISMA guidelines [18]. We searched for English-language papers based on PubMed electronic data bases published from December 2000 to December 2013. The search strategy was (sart[tw] or SART[tw] or srt[tw] or stereotactic[tw]) and non-small-cell lung cancer[tw] and early-stage[tw]. Two clinicians reviewed these and the reference lists of selected articles to determine which were suitable for inclusion. 203 studies were identified, from which 24 articles were selected. The prescribed tumour doses were converted into a Biologically Equivalent Dose (BED) to enable comparison between studies. The BED was calculated using the assumption that tumour and normal tissue alpha/beta ratios were 3 Gy (BED3). Local control, survival outcomes and toxicity data were restricted to patients with early-stage NSCLC [19]. Case reports and dosimetric studies were not considered.

Results

From these 24 studies, a total of 1654 early-stage NSCLC patients received SART. The radiotherapy details and tumour characters are shown in (Table 1).

Table 1: The baseline radiotherapy details and tumour characters for early stage NSCLC.

Author	N/median year	TS	ETL	TDG/F	OS(%)	LC(%)	AS/LS(%)
Haidar [41]	55/78	I/II	Any	48/4, 56/5	1y, 83.0 2y, 65.0	1y, 91.0	8.7/13.0
Shibamoto [29]	180/77	I	Any	44, 48, 52/4	5y, 52.0	5y, 85.0	Grade ≥ II 20/0
Jeppesen [43]	100/78	T1-2N0M0	Any	45, 66/3	5y, 34.0	5y, 61.0	No side effects
Fujino [44]	87/74	T1-2N0M0	Any	45, 72.5/3, 10	5y, 69.5	5y, 86.7	Grade ≥ II 1.1/0
Lagerwaard [40]	177/76	T1-2N0M0	Any	60/3, 5, 8	1y, 94.7 3y, 84.7	1y, 98.0 3y, 93.0	Grade ≥ III 5.0/0
Haasbeek [21]	63/-	I	Any	60/8	3y, 64.3	3y, 92.6	grade III 0/6.3
Turzer [45]	36/74	I	Any	45/3	1y, 83	3y < 3 cm 86.0; >3 cm 73.0	Grade I 52.7/8.0
Taremi [9]	108/-	I	Peripheral central	48/4; 54, 60/3	1,3,5y, 79.0,38.0,17.0	1y, 92.0 4y, 89.0	Grade < III 49.1/0
Asashi Koto [46]	57/75	IA /IB	Any	45/3	3y,71.7;5y,48.9	3y, T1 77.9 T2 40.0	Grade III 21.0/-
Bral [16]	40/66	T1-3N0M0	Any	60/3, 4	3y, 57.1	1y, 97.0 2y, 84.0	2.5 died/0
Timmerman [6]	59/72	T1-2N0M0	Any	54/3	3y, 55.8	3y, 97.6	Grade III, IV 16.3/0
Bradley [10]	91/-	T1-2N0M0	Any	54/3	-	2y, 86.0	-/-
Brown [55]	67/-	T1-2N0M0	Any	60, 67.5/3–5	1y, 93.6;3y83.5	1y, 93.2 4.5y, 85.8	7.4/0
Stephans [26]	69/73	I	Any	50/5, 60/3	1y, 83.1	1y, 97.3	Grade < II 12.2/10.0
Ricardi [11]	62/73.7	IA/IB	Any	45/3	3y, 57.1	3y, 87.8	-/-
Fakiris [5]	70/-	T1-2N0M0	Any	60, 66/3	3y, 42.7	3y, 81.7	Grade III–V peripheral 10.4 or central 27.3/0
Salazar [20]	60/75	IA/IB	Any	62.5/7	3y, 23.0	5y, 70.0	Grade I–II 19.0/ Grade II 3.0
Scorsetti [31]	43/75.5	IA/IB	Any	30.5/1–4	2y, 53.0	1y, 93.0 2y, 53.0	Grade I–II 20.9/ Grade I–II 16.1
Hof [30]	42/-	IA/IB	Any	19-30/1	1,3y, 74.5, 37.4	1,3y, 89.5, 67.9	-/-
Brown [47]	31/-	T1-2N0M0	Any	48/12	3y, 42.0	3y, 76.0	-/-
Hiraoka [23]	32/-	T1-2N0M0	Any	48/4	3y, 83.0	-	No grade II
Timmerman [32]	70/70	T1-2N0M0	Any	60, 66/3	2y, 54.7	2y, 95.0	Grade III–V 20.0/0
Hof [48]	10/-	I	Any	19–26/1	1y, 80.0 2y, 64.0	1y, 88.9 2y, 71.1	Grade III 28.3/0
Nagata [3]	45/-	T1N0M0	Any	48/4	3y, 76.0	3y, 68.5	No grade III

TS: Tumour stage; TL: Tumour locations; TDG/F: Total dose gray/fractions;OS: overall survival; LCR: Local control rate; AS/LS: acute side effects/ late side effects.

Survival: The survival after SART treatment when considered for early-stage NSCLC of different studies is shown in (Table 1). In almost all studies, the median survival varied between 13.8 and 61.5 months, the 1,3 and 5-year overall survival rates ranged from 74.5%–94.7%, 23.0%–84.7% and 17.0%–69.5%, respectively. The 1,3 and 5-year disease-free survival were ranged from 70.2%–97.0%, 48.3%–81.0% and 23.0%–69.0%. When evaluating the factors effects the survival, the importance of tumour size was analyzed with respect to survival. The local progression-free survival for patients with T1 was longer than for those with T2 tumours (P = 0.006) [9,20]. The 1-year local progression-free survival estimate dropped below 80% for lesions with a diameter of more than 4 cm [21]. In patients with tumors ≤ 20 mm, overall survival was significantly higher than that in patients with tumors > 20 mm [23]. Simon, et al. [22] documented a significant difference in survival between patients with large (> 3 cm) and small (≤ 3 cm) tumours (P < 0.002). There was, however, no significant relationship between T-stage and overall survival in one study [22]. Therefore, it is hard to draw firm conclusions on the exact importance of tumour size for survival.

As for the location of tumour, previous studies found central (*vs.* peripheral) location did impact survival on both univariate and multivariate analyses [14,21,24]. The largest retrospective cohort found the 3-year overall survival for central and peripheral early-stage NSCLC was statistically not different (64% *vs.* 51%) [25], while another study found tumour location did not impact survival on univariate analysis for early-stage NSCLC [12].

Total radiation dose is another important prognostic factor for early stage NSCLC. Hiraoka M [26] reported that the overall survival of patients was significant positively correlated with the doses which they received the BED was less than 100 Gy, respectively. Overall survival at 3 years was 42% when the BED was less than 100 Gy, and 46% when it was over l00 Gy. In tumors, which received a BED of more than 100 Gy, overall survival at 3 years was 91% for operable patients, and 50% for inoperable patients [27]. Onishi, et al. [28] found improved overall survival rates with BED ≥ 100 Gy. They reported the most benefit in those with medically operable tumours, treated with BED ≥ 100 Gy. Patients with early stage NSCLC received radiation doses 10 Gy × 5 experienced a survival at 1 years in approximately 83.1% compared with 76.9% for patients receiving 20 Gy × 3 [29].

Local control: SART seems to be a safe and effective treatment for early stage NSCLC, which got high local control (Table 1). Among them, the 5-year local control rate (LCR), ranged from 83.0% to 86.7% [12,30]. The 3-year and 2-year LCR ranged from 40.0% to 97.6% and 53% to 95% [10,31–33]. With respect to local control, achieving a BED > 100 seems to be very important. The actuarial 2-years local tumor control was 85% for tumors treated with a BED > 100 Gy compared to 60% for tumors treated with a BED ≤ 100 Gy [34]. Onishi, et al. [28] found improved local control with BED ≥ 100 Gy. Stephans, et al. [25] reported that for the 10 Gy × 5 and 20 Gy × 3 cohorts at 1-year, local control was 97.3% *vs.* 100%. For patients with resectable early-stage NSCLC, 5-year actuarial local control rates were 84% for patients receiving a BED of 100 Gy or more and 37% for those receiving less than 100 Gy. Timmerman, et al. [10] reported a 3-year local control rate of 97.6%. Taken together the data indicated that better local control was obtained with the higher doses used in these studies. The local recurrence rate was 20% when the BED was less than 100 Gy and 6.5% when the BED was over 100 Gy. These data are support for better local control when total dose is increased [34].

Tumour size is one of the most important factors affecting both locoregional and distant control. In one of the studies it was seen that T2 lesions when compared with T1 lesions had significantly increased chances of local, regional and distant failures [35]. A similar study by Dunlap, et al. [36] concluded that SART for T2 NSCLC had a higher local recurrence rate. Hence, tumour size is an important predictor of response in SART. McGarry RC, et al. [37] found that excellent local control was achieved at higher dose cohorts. Patients with early stage NSCLC received radiation doses 10 Gy × 5 experienced a local control at 1 year in approximately 97.3% compared with 100% for patients receiving 20 Gy × 3 [29].

Patterns of failure: The patterns of failure after the treatment of SART include locoregional recurrence and distant metastases (Table 1). In early stage of NSCLC, distant metastases were the most common reason for treatment failure with SART [10,16,34,38]. In contrast, the frequency of locoregional recurrence was less, but varied considerably according to different reports [39,40]. The locoregional recurrence rate had ranged between 8.7%–37% and the distant metastasis rate of 8%–20% after a period of 1–2 years follow up [24,31,41,42]. On the basis of follow up after SART, median time to relapse varied from 21 to 30 months. The majority of recurrences occurred within 3 years after treatment. Thus, a 3-year follow-up is needed to estimate the recurrence rate after SART of early stage NSCLC. In our review of SART for early stage NSCLC studies, we found that the main pattern of failure was distant metastasis. This occurred in 9.7% to 29% of patients in studies with at least 30 months follow-up [41,43]. Nodal recurrences occurred in approximately 10% of patients [43]. Recurrences were associated with increased tumour size [44].

Side effects of radiotherapy: Published reports of SART for lung cancer describe a very low acute and late toxicity rate, with rates for grade 3 or higher toxicity being typically less than 4% [31–33,37,41,42,44–51]. In general, the common side-effects are mild to moderate (grade 1 to 2) and transient. The reported rate of grade ≥ 3 late toxicity was less than 10% in most studies. Most of the accumulated grade 5 events have occurred when patients received high-dose SART to centrally located tumours adjacent to meditational organs [9,52,53]. Timmerman, et al. [10] reported a rate of 12.7% grade 3 adverse events, 3.6% grade 4 adverse events, whereas Fakiris, et al. [9] reported that grade 3 to 5 toxicity

occurred in 5 of 48 patients with peripheral lung tumors (10.4%) and in 6 of 22 patients (27.3%) with central tumors. Lagerwaard, et al. [41] found the toxicity was mild, with grade ≥ 3 radiation pneumonitis and rib fractures in 2% and 3%, respectively. Finally, there were other toxicities, such as oesophagitis, skin reactions, chest wall pain and general malaise such as fatigue [54].

Discussion

Although surgery provides the standard of care for early stages stage I NSCLC, patients with a clinical diagnosis of early stage NSCLC have a 5-year survival of only 43%–50% [55]. Surgery is less likely to be recommended for the elderly and those with comorbidities [56,57]. For these patients, SART has been a replacement therapy method to improve overall survival [3,57]. We carried out a review of published studies on SART in patients with early stage NSCLC, which identified 24 studies reporting clinical outcomes for 1654 patients. Our main endings were that the overall survival, local control, patterns of failure and side effects of radiotherapy reported following SART for early-stage NSCLC was different in most studies. Furthermore, we analyzed the factors on affecting the results of survival, local control, patterns of failure and side effects.

Firstly, tumour size and location were the most important determinants of outcome of SART for early stage NSCLC. The local progression-free survival was related with T stage [9,20]. In patients with tumors ≤ 20 mm, overall survival was significantly higher than in patients with tumors > 20 mm [23]. Simon [22] has proved that there was a significant difference in survival between patients with large (> 3 cm) and small (≤ 3 cm) tumours. The location of tumour affected the results of SART for early stage NSCLC, there were sufficient clinical data to prove that tumour location did impact the overall survival [12,14,21,24]. However, there were opposite result that tumour location did not impact survival on univariate analysis for early-stage NSCLC [12]. Tumour size also affected the locoregional and distant control, it was seen that T2 lesions when compared with T1 lesions had significantly increased chances of local, regional and distant failures [35]. Therefore, tumour size is an important predictor of response in SART [35,36]. Previous study has proved that recurrences were associated with increased tumour size, which determines the amount of normal tissue irradiated and affects the side effects of radiation radiotherapy. There is sufficient clinical information available to relate tumour size to toxicity [43]. Tumour location also affects the side effects of radiotherapy. The use of SART in centrally located early-stage NSCLC has been associated with increased toxicity. Therefore, care needs to be taken with organ at risk doses, particularly when treating central lesions and those close to the spinal cord.

Secondly, dose fractionation and total dose also affect the results of SART for early stage NSCLC. In previous published studies, many different dose fractionation and total dose were used. The most common dose-fractionation schedules used were ≤ 20 Gy per fraction with a total of three fractions. Therefore, in order to compare the results of different studies, the relative efficacy of radiotherapy fractionation schemes can be predicted and compared by calculating the BED. Multiple studies have found a correlation between clinical outcomes and the BED. The present analysis indicates that patients with early stage NSCLC, treated by SART should receive LQED2 doses higher than 100 Gy. Overall survival at 3 years was 42% when the BED was less than 100 Gy, and 46% when it was over l00 Gy [27]. With respect to local control, achieving a BED > 100 Gy seems to be very important. Previous study demonstrates that the 2-years local tumor control was 85% for tumors treated with a BED > 100 Gy compared to 60% for tumors treated with a BED ≤ 100 Gy [34]. Taken together the data indicate that better local control was obtained with the higher doses used in these studies.

In summary, this systemic review suggests SART offers a safe and effective curative treatment for patients with early stage NSCLC.

Conclusions

SART offers a safe and effective curative treatment for patients with early-stage NSCLC.

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Conflict of interest

There is no conflict of interests regarding the publication of this article.

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