Title: To biopsy or not to biopsy? Outcomes following stereotactic body radiotherapy (SBRT) for biopsy-confirmed versus radiologically-diagnosed primary lung cancer in a single Australian institution

***Running Head: SBRT with and without biopsies for lung cancer***



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No conflict of interests declared. This project is unfunded, and has been approved by the ethics committee of the Olivia Newton John Cancer Research and Wellness Centre, by whom no patient consents were deemed necessary given low risk of project.

## DATA AVAILABILITY STATEMENT

All data used in the generation of this study has not been submitted with this original research article, however they are available upon request.

## ABSTRACT (232/ 250 words)

**Introduction:** Obtaining tissue diagnosis for lung cancer can sometimes be difficult and unsafe. We evaluated outcomes of biopsy-confirmed versus radiologically-diagnosed lung cancer treated with stereotactic body radiotherapy (SBRT).

**Methods:** A single-institutional retrospective cohort of lung cancer patients treated with SBRT between February 2014 and October 2018. Outcomes of interest were: local failure (LF), distant failure (DF), and overall survival (OS). Probability of LF, DF and OS were estimated using the Kaplan-Meier method. Differences in outcomes between biopsy-confirmed vs. radiologically-diagnosed lung cancer were evaluated using the log-rank test.

**Results:** 65 lung lesions in 61 patients were treated with SBRT. Mean age was 75.6 years. 27 patients (44.3%) were ECOG 2-3. 39 patients (64%) were radiologically-diagnosed. There were 5 cases of LF observed at median of 12.8 months post-SBRT and 12-month LF-free survival was 96% (95%CI=86-99%), with no differences between groups (p=0.1). 16 patients developed DF, with 12-month DF-free survival of 84% (95%CI=71-91%), and no difference between groups (p=0.06). 16 deaths were reported at a median of 12.5 months post-SBRT, with 12-month OS of 83% (95%CI=73-92%), and no differences between study groups (p=0.5). No grade 3 toxicities were reported.

**Conclusion:** The oncological outcomes were similar in patients with early lung cancer treated with SBRT with or without biopsy-confirmation. In situations where tissue diagnosis is not feasible or unsafe, it is not unreasonable to offer SBRT based on clinical and radiological suspicion following multidisciplinary discussions.

**KEY WORDS**

Lung cancer, stereotactic radiotherapy, biopsy confirmation, percutaneous, endobronchial ultrasound

**TEXT**

## INTRODUCTION

Establishing a definite diagnosis in patients with lung lesions can be difficult [1, 2], as the risk factors that predispose patients to lung cancer, often make them less ideal candidates for the necessary clinical work-up to obtain tissue diagnosis. The two usual methods by which tissue diagnosis is established are CT guided percutaneous biopsy, and radial endobronchial ultrasound (EBUS). The CT guided approach bear the advantages of being more efficient as a radiological procedure as opposed to a day procedure. In terms of diagnostic accuracy, a retrospective review has suggested that the CT guided percutaneous biopsy has greater diagnostic accuracy [3], but carries a much higher risk of pneumothorax (17.5% vs . 1.3%), and marginally higher risk of bleeding (7.5% vs 5%) [3]. However, another study found the diagnostic accuracy of radial EBUS to be non-inferior to that of a CT guided biopsy as long as the probe was able to locate the lesion[4]. Larger lesion sizes (15mm and above) are also associated with improved diagnostic accuracy [5]. Despite the high accuracy of both percutaneous and EBUS biopsies which studies report to be greater than 90% with 10% or less chances of false negatives [5-7], up to 20% of biopsies return non-diagnostic [4].

In patients with early stage lung cancer, stereotactic body radiotherapy (SBRT) can be safely delivered, with minimal treatment morbidity and mortality [8] and yields excellent local control of 86% at 2 years [8]. The American Society for Radiation Oncology (ASTRO) guideline has therefore recommended that in situations whereby patients refuse a biopsy, have undergone non-diagnostic biopsy, or who are thought to be at prohibitive risk of biopsy, SBRT may be delivered following discussion within a multidisciplinary cancer care team with a consensus

that the lesion is radiographically and clinically consistent with a malignant lesion based on tumour, patient, and environmental risk factors [9].

Majority of the studies on treating lung nodules with SBRT without biopsies were performed overseas. Their common verdict is that there are no significant differences in local control and overall survival between patients treated with SBRT with and without biopsies. However, the proportion of patients treated with and without biopsies in individual studies vary, and for several reasons, the practice pattern of delivering SBRT empirically without biopsies vary geographically. Little is known about the practice pattern and outcomes of treating lung nodules empirically with SBRT in Australia. The aim of this study is to compare the oncological and toxicity outcomes early stage lung cancer patients, with and without biopsy confirmation, treated with SBRT in a single Australian institution.

## METHODS

**Study cohort:** This is a retrospective cohort of consecutive adult (≥ 18 years of age) patients with primary lung cancer, who are either biopsy-confirmed or radiologically-diagnosed, and treated with SBRT at Olivia Newton John Cancer Wellness and Research Centre (ONJCWRC), Austin Health from February 2014 to October 2018. Radiologically-diagnosed lung cancer is defined as lung cancer clinically diagnosed based on clinical/radiological traits in the absence of tissue diagnoses. The process of selecting suspicious lung nodules for SBRT was guided by clinical acumen and multidisciplinary consensus. Decisions whether to treat were made on a case-by-case basis. All patients underwent fluorodeoxyglucose positron emission tomography (FDG-PET) as well as diagnostic chest computed tomography (CT). Strong consideration was paid to smoking

status, previous cancer history, nodule size and radiological appearance (ie. Solid/spiculated versus ground glass), degree of FDG uptake, and evolution over time. Although a number of criteria have been proposed for the clinical diagnosis of malignancy and may have been taken into account, no particular one was strictly employed in our practice, and Herder malignancy probabilities were not formally calculated. As a general rule, lesions not deemed suspicious were not treated (eg. Lesions detected for the 1st time on imaging/had not changed over time/small), and continued on observations at short interval (repeat diagnostic chest CT/FDG PET in 2-3 months). Lesions greater than 5cm in maximal dimensions, or lesions with associated suspicious lymphadenopathy were excluded, ie. All treated lesions were clinically stage ≤ cT2N0 (AJCC 8th staging). This study was approved by Austin Human Research Ethics Committee.

**SBRT treatment and technique**: All patients were simulated supine on a personalised immobilisation cradle, with arms raised. 4D planning CT was acquired on Siemens CT scanner (Siemens AG, Munich, Germany) with 2mm slice thickness, from the thoracic inlet to mid-abdomen covering the entire lung volumes. The planning 4DCT was fused with diagnostic FDG-PET to aid delineation. The internal gross target volume (iGTV) was delineated on the average dataset to encompass the full range of tumour motion with respiration. Until late 2016, the planning target volume (PTV) was generated as a 5mm radial margin around the iGTV, except cranio-caudally where a 10mm margin was used. An isotropic 5mm expansion was used thereafter.

Standard prescribed dose was 48Gy in 4 fractions. A modified prescription dose of 50Gy in 5# was used for large tumours, or those closer to central structures if 4 fraction dose constraints were unachievable. A prescription of 54Gy in 3# was used for non-central targets, away from critical organs at risk (OARs). The OARs delineated for all cases included

both lungs, spinal canal, trachea & proximal bronchial tree, chest wall inclusive of ribs & intercostal muscles, heart, and oesophagus. Brachial plexus, great vessels, liver and stomach were delineated if in close proximity to the target.

A 3D conformal planning technique, using 8-10 beams, including non-coplanar angles was used until late 2016, on Xio® software (Elekta AB, Stockholm, Sweden). Thereafter, all patients were planned with dynamic conformal arc (DCAT) or volumetric modulated arc (VMAT) technique on Monaco® planning software (Elekta AB, Stockholm, Sweden). Dose was prescribed to cover 95% of the PTV, with maximum doses within the iGTV of 120-140% of prescription dose. Dose constraints for OARs were respected for all cases, and applied following CHISEL trial [8] protocol until late 2016, following which AAPM guidelines [10] were used.

**SBRT treatment**: All treatments were delivered using Elekta Infinity™ or Versa HD™ linear accelerator (Elekta AB, Stockholm, Sweden), on non-consecutive days. Pre-treatment image guidance was performed using XVI Cone Beam CT (CBCT). Correction was applied to ensure patient position accuracy within 2mm and 3° of planned position. Post-correction and post-treatment imaging was acquired for all fractions.

**Follow-up**: All patients underwent routine follow-up 2-3 weeks post-SBRT for review of any acute SBRT-related toxicities, based on the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Patients were restaged with a FDG-PET scan 3 months post SBRT to assess treatment response. Patients with complete metabolic response on the 3-month post-SBRT FDG-PET scan were followed up with staging CT chest scan 3-monthly in the first year following SBRT, 6-monthly in the second year and annually thereafter. Patients yet to

achieve complete metabolic responses in their 3-month post-SBRT FDG-PET scan would return for a further FDG-PET scan in 3 months, and proceed to 3-monthly follow-up with CT chest scan once complete metabolic response is achieved.

**Covariates of interest**: All patient-, tumour-, treatment-related data were retrospectively collected from our institutional electronic medical records. *Patient factors* collected were: age, sex, and ECOG performance status at diagnosis. *Tumour factors* collected included: number of lesions treated, location of lung lesions (central vs. peripheral), and distance from the chest wall. Central lesions were defined as those within 2 cm of proximal bronchial tree (carina, main bronchi) and/or major vessels (aorta, upper mediastinal vessels, pulmonary artery) and/or critical structures eg. heart, oesophagus. *Treatment factors* included: the dose and fractionation regimen, and the biologically effective dose (BED), which was calculated based on the linear quadratic formula, using an alpha-beta ratio of 10. This was dichotomised to BED of ≤100Gy vs. >100Gy.

**Endpoint definition**: The oncology endpoint of interests were: local failure (LF), distant failure (DF), and overall survival (OS). LF was defined as any enlargement of the SBRT-treated lung lesion demonstrated on CT that is accompanied by new FDG uptake further to documented PET-response post SBRT. All structural enlargements of SBRT-treated lesions detected on CT were followed up with FDG-PETs and discussed in MDMs during which consensus is sought on diagnosing local failure in addition to deciding further management. DF was defined as radiological evidence of disease progression beyond the SBRT-treated lung lesions, regardless of whether it is on the ipsilateral or contralateral lung, or any other extra-thoracic progression for each *individual patient*. OS included any reported death. The toxicity endpoints included toxicities graded based on CTCAE v4.0, and severe toxicities

were defined as any grade 3 and above toxicities reported at any stage during or following completion of treatment.

**Statistical analyses**: Differences in characteristics between patients who had biopsy-confirmed vs. radiologically-diagnosed lung cancer were evaluated using the Student's t-test (or Mann-Whitney U-test as appropriate) for continuous variables and Pearson's chi-squared test for categorical variables. The LF, DF, and OS were estimated using the Kaplan Meier methods. The time-to-event was defined as the time between completion of SBRT to the date of events of interest. The LF was estimated for individual SBRT-treated lesions. For patients who had multiple SBRT treatments, the time-to-events for DF, and OS were estimated from the date of completion of first SBRT treatment. Patients who did not develop the event of interest were censored on the date of last follow-up. Differences in outcomes of interest between patients who had biopsy-confirmed vs. radiologically-diagnosed lung cancer were assessed using the log-rank test. A two-sided $p<0.05$ was considered statistically significant. All statistical analyses were performed using STATA I/C 13 (STATA Corp, College Station, TX, USA).

## RESULTS

A total of 61 patients were included in this study (Table-1). The mean age of the study cohort was 75.6 years (SD=8.3). There were 35 males (57%) and 26 females (43%). More than half of the patients had ECOG performance statuses of 0-1 at the time of SBRT. Approximately two-thirds of patients (39/61) were radiologically-diagnosed without biopsy confirmation. There were multiple reasons for the lack of biopsy confirmation including patient refusal, and failure of previous biopsy attempt(s) to yield a conclusive result. There were no significant

differences in characteristics between patients who were radiologically diagnosed vs. biopsy-confirmed (Table-1).

Of the total of 65 SBRT-treated lung lesions, 12 lesions (18%) were located centrally and 53 (82%) were located in the peripheral region. The majority of the lung lesions were treated to 48Gy in 4 fractions (BED=105.6Gy) (n=46, 70.7%); whereas 9 (13.8%) received 54Gy in 3 fractions (BED=151.2Gy), 7 (10.7%) received 50Gy in 5 fractions (BED=100Gy), 2 (3.1%) received 40Gy in 5 fractions (BED=72Gy, of which one patient ceased after 32Gy in 4 fractions), and 1 (1.5%) received 20Gy in 1 fraction (BED=60Gy). Patients who did not have biopsy confirmation received higher doses; 93% were treated to a BED of >100Gy, compared to 68% of patients who had biopsy confirmation (P<0.009).

**Follow-up**: The median follow-up for the cohort was 15 months (range: 0.2-67 months).

**Local failure:** Of the 65 SBRT-treated lung lesions, there were 6 (9%) local failures observed at a median of 16 months post-SBRT (range: 7.3-34 months). The estimated 12-month and 24-month LF free survival were 96% (95%CI=86-99%) and 85% (95%CI=67-94%) respectively (Figure-1A). When stratified by biopsy confirmation, the 12-month LF free survival was 97% (95%CI=82-99%) for biopsy-confirmed lesions and 95% (95%CI=71-99%) for lesions without biopsy-confirmation (p=0.1) (Figure-1B). Of the 7 lesions with LF, only 1 was treated radically with a salvage lobectomy, while the rest were observed.

**Distant failure**: Of the 61 patients, 16 (26%) patients had DFs at a median of 8.8 months post SBRT (range: 2.3-32.9 months). The estimated 12-month and 24-month DF free

survival was 84% (95%CI=71-91%) and 68% (95%CI=50-81%) respectively (Figure-2A). When stratified by biopsy confirmation, the estimated 12-month DF free survival was 85% (95%CI=60-95%) for patients who had biopsies compared to 83% (95%CI=66-92%) for patients without biopsies (p=0.06) (Figure-2B). Of the 16 patients who had DF, 3 (30%) had salvage SBRT, 5 (50%) were treated with systemic therapy, while 2 (20%) were observed clinically.

**Overall survival:** At last follow-up, there were 16 deaths reported at a median of 12.5 months post-SBRT (range: 0.2-42.3 months) – 7 (32%) patients with biopsy-confirmed lung cancer, and 9 (23%) patients with radiologically-diagnosed lung cancer. The estimated 12-month and 24-month OS was 85% (95%CI=73-92%) and 70% (95%CI=54-81%) respectively (Figure-3A). When stratified by biopsy confirmation, the estimated 12-month OS was 80% (95%CI=54-92%) for patients who had biopsy confirmation, compared to 89% (95%CI=73-96%) for patients who did not have biopsy confirmation (P=0.5) (Figure-3B).

**Toxicity outcomes**: No grade 3 or above toxicities were reported. A small proportion of patients experienced grade 2 toxicities; cough (2%), pneumonitis (2%), dyspnoea (3%), hypoxia (2%), and oesophagitis (2%).

## DISCUSSION

In our single institutional cohort, approximately two-thirds of patients with early lung cancer did not have biopsy confirmation prior to SBRT. Although the ASTRO guidelines endorse the treatment of early lung cancer with SBRT in situations where biopsy-confirmation is not feasible or unsafe, the practice of SBRT without biopsy confirmation varies internationally. In

Europe, 65% (188/288) of patients in the first UK cohort of SBRT for early lung cancer were treated without biopsy confirmation [11], and similarly, in a large Dutch single institutional cohort, 65% (441/676) did not have biopsy confirmation prior to SBRT [12]. This is in contrast to the practice in North America, whereby only 15% (131/878) of patients in a large single institutional cohort in Canada [13], and 35% (33/94) in a single institution in the US [14], did not have biopsy confirmation prior to SBRT for early lung cancer. While this study is based on a single institutional cohort, to the best of our knowledge, it is the first Australian study that serves to fill the gap in our understanding of the pattern of practice of biopsy confirmation prior to SBRT for early lung cancer in Australia.

In terms of outcomes following SBRT, we did not observe differences in local control between patients who had biopsy-confirmed and radiologically-diagnosed lung cancer. This is consistent with multiple earlier international series [11-17]. In a matched group analyses of 131 patients without biopsies and 131 patients with biopsies in Canada, Dautruche et al reported a 3-year local control of 80% and 85% in those with and without biopsies respectively (p=0.8) [13]. In the Dutch single institutional study, Verstegen reported a 3-year local control of 91% in a historical cohort of 382 patients without biopsy confirmation, as compared to 90% in a more contemporary series of 209 patients with biopsy confirmation (p=0.9) [16]. In a single US institutional study, Fischer-Valuck reported a 3-yr local control of 93% in 65 patients with biopsy confirmation and 94% in 23 patients without biopsies (p=0.9) [17].

Our reported OS in patients with biopsy-confirmed and radiological-diagnosed lung cancer was also not dissimilar to earlier studies, and again, there were no significant differences in OS between patients with or without biopsy-confirmation in most of the earlier studies [12-16], except in the UK series [11]. In the study by Murray et al, patients who had biopsy-

confirmation had improved OS (HR=05.4, p=0.03) following SBRT compared to those without biopsy confirmation [11]. It is however, interesting to note that patients who did not have biopsy confirmation had worse Medical Research Council (MRC) breathlessness scores, which may reflect their underlying comorbidities which preclude them from having potentially high-risk biopsies, rather than the biopsy confirmation itself impacting on OS.

One patient in our cohort treated with SBRT without tissue diagnosis was found to have metastatic small cell lung cancer (SCLC) upon biopsy of a subsequent liver metastasis. Had SCLC been discovered on biopsy at initial presentation, systemic therapy would have been recommended as part of her initial management which might possibly have improved her long-term disease outcome/survival. Hence, accurate diagnosis is important for treatment selection, and it is important to obtain tissue biopsies whenever safe enough to do so.

As expected, we observed minimal toxicities with SBRT and reported no grade three or four toxicities. This is consistent with other studies [18, 19], and highlights the feasibility of SBRT as a curative option in frail patients.

All patients in this study population were staged with FDG-PET. As seen in NLST trial, the rate of false positivity of lung nodules detected on CT reaches as high as 96% [20]. Other studies which involved utilising FDG-PETs in the workup for lung nodules show an assuringly lower rate of false positives [21], suggesting that FDG-PETs are useful in avoiding unneccessary treatment to patients. Unlike Asian populations where there exists endemic benign differentials for FDG-avid lung nodules such as tuberculosis, that is generally not the case in our Australian population. For the above reasons, we are comfortable with our approach of basing our patient-selection for treatment on serial FDG-PETs.

We acknowledge the inherent limitations of this study, being single institutional and retrospective, flawed by potential inconsistencies in classification of variables such as performance status. The lack of a standardised decision-making process with clinical tools such as the British Thoracic Society p-nodule risk app where biopsies were not obtained is not ideal and may have subjected us to inconsistencies in practice. However being an audit, changes are not able to be made with regards to this in a retrospective manner.

Documentation on medical records was not always clear on the reasons which precluded successful tissue diagnosis, and that information was not collected. Another limitation is the relatively short follow-up period (median follow-up of 15 months) compared to other larger international series. Nonetheless, earlier studies have consistently showed that even with longer follow-up, there were no differences in oncological outcomes between those with or without biopsy confirmation.

The understanding of the Australian current practice of SBRT for early lung cancer with or without biopsy, and the evaluation of the associated outcomes is especially important in the current climate whereby the government is exploring the prospect of a national lung cancer screening program. It is likely that we will be seeing increasing number of incidental lung lesions on screening low-dose chest CTs especially among high risk patients, and these are precisely the patients in whom obtaining biopsy confirmation may be particularly risky given their underlying comorbidities due to smoking.

In conclusion, our single institutional experience showed that only one third of our patients underwent biopsies prior SBRT, and outcomes were comparable between patients with or without biopsy confirmation. Although there are situations where the risks of biopsies

outweigh the benefits where it is not unreasonable to offer SBRT empirically based on clinical and radiological suspicion following multidisciplinary discussion, we would advocate maximal efforts to obtain tissue biopsies within safe limits in the interest of ensuring that every patient receives the most clinically appropriate treatment for their diagnoses.



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Table 1 | Baseline characteristics of the study cohort, and details of treated lesions

| | | Radiologically diagnosed | Biopsy confirmed | p-value |
|---|---|---|---|---|
| **Patient characteristics (n=61)** | | N=39 | N=22 | |
| **Sex** | **Male (n=35)** | 20 (57%) | 15 (43%) | 0.2 |
| | **Female (n=26)** | 19 (73%) | 7 (27%) | |
| **Age** | **Mean (SD)** | 75.1 (7.5) | 76.5 (9.6) | 0.5 |
| | **Median (range)** | 76.8 (57.6-89.1) | 77.5 (52.1-89.6) | |
| **ECOG** | **0-1 (n=34)** | 18 (53%) | 16 (47%) | 0.05 |
| | **2-3 (n=27)** | 21 (78%) | 6 (22%) | |
| **Number of SBRT lesion(s) treated per patient** | **1 (n=57)** | 36 (63%) | 21 (37%) | 0.6 |
| | **2 (n=4)** | 3 (75%) | 1 (25%) | |
| **Characteristics of treated lesions (n=65)** | | N=43 | N=22 | |
| **Location of lesion** | **Central (n=12)** | 7 (58%) | 5 (42%) | 0.5 |
| | **Peripheral (n=53)** | 36 (68%) | 17 (32%) | |
| **Distance from chest wall (mm)** | **Median (IQR)** | 9 (4-17) | 7 (0-15) | 0.3 |
| **BED of SBRT treatment** | **≤100Gy** | 3 (30%) | 7 (70%) | 0.009 |

| | | | | |
|---|---|---|---|---|
| | **(n=10)** | | | |
| | **>100Gy (n=55)** | 40 (73%) | 15 (27%) | |

SBRT = stereotactic body radiotherapy; BED = biologically effective dose; SD = standard deviation; IQR = Interquartile range

Figure 1 | Local failure following stereotactic body radiotherapy (SBRT) for (a) all treated lesions, (b) lesions stratified by tissue confirmation

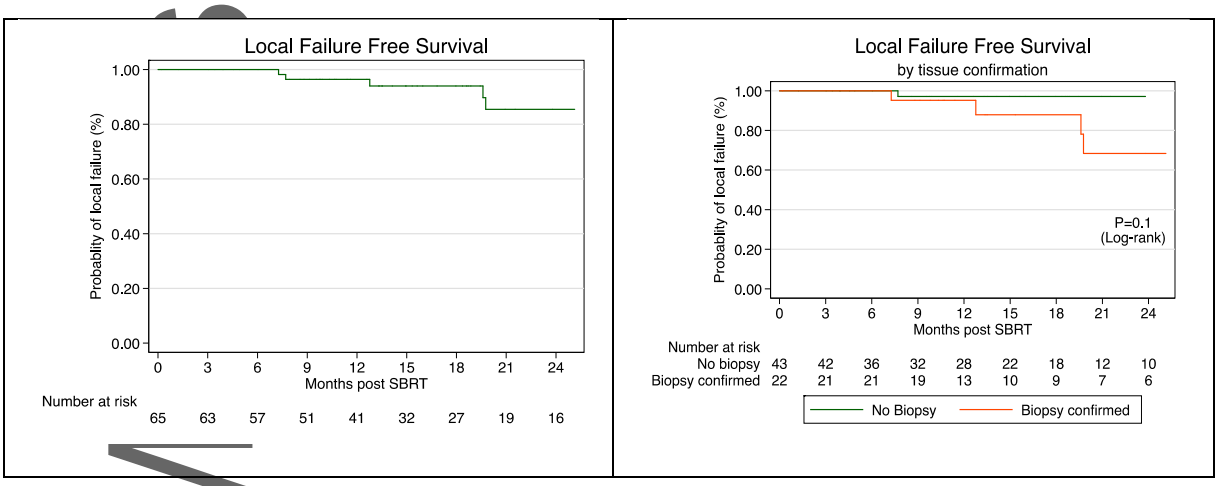



Figure 2 | Distant failure following stereotactic body radiotherapy (SBRT) for (a) all patients, (b) patients stratified by tissue confirmation

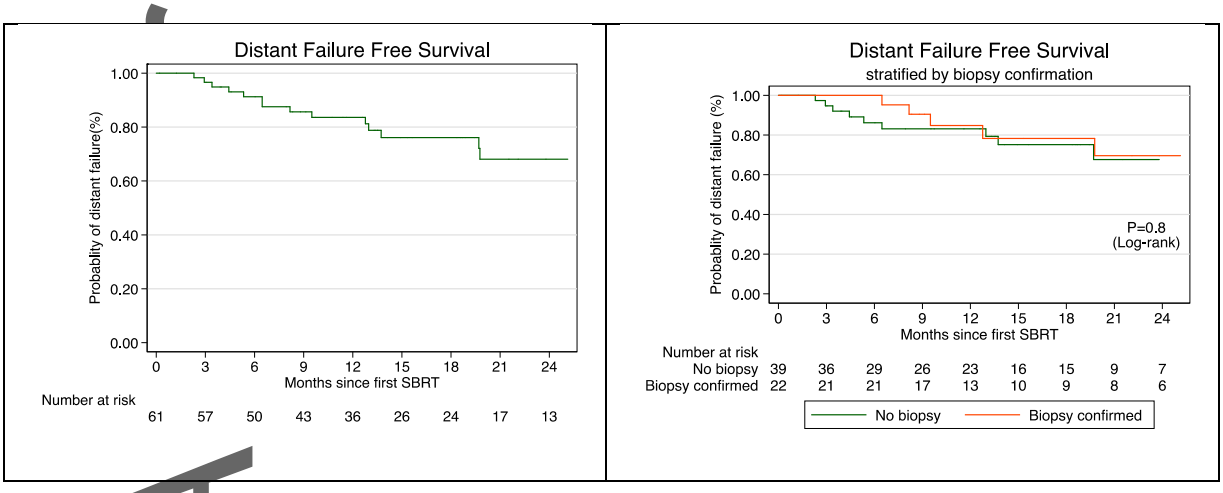
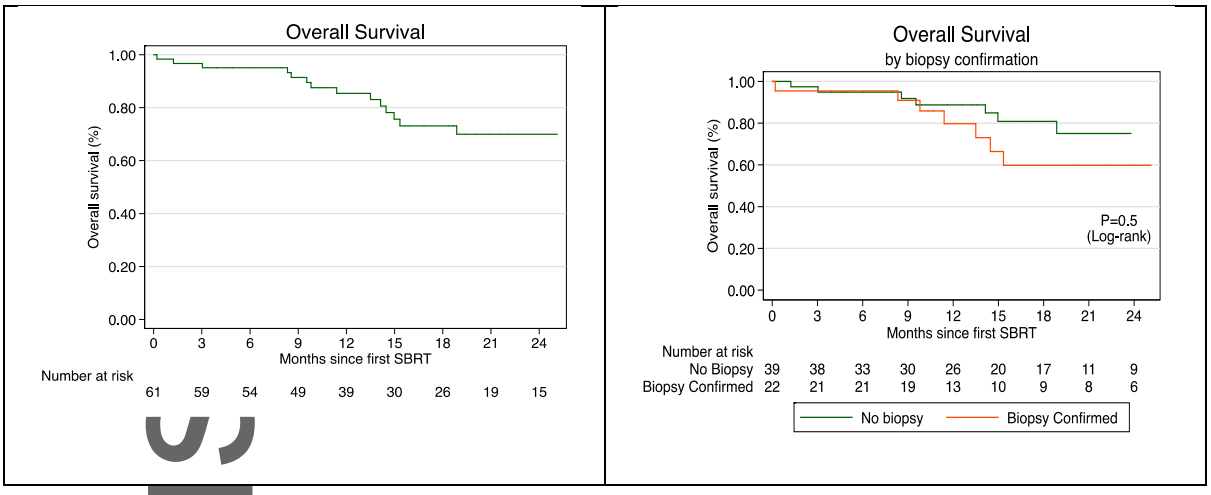
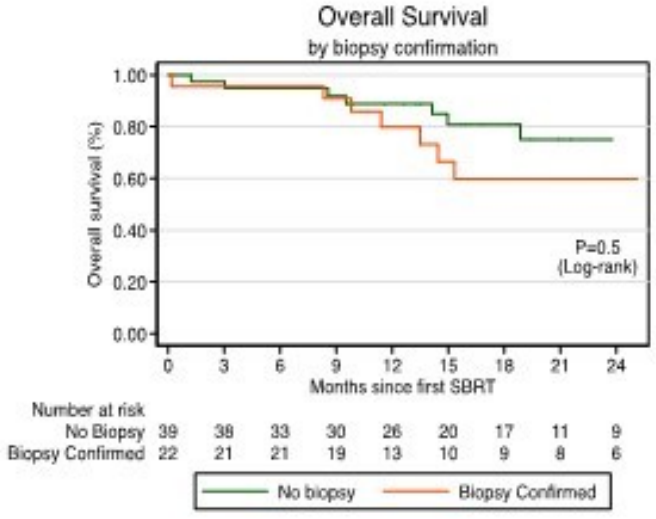


Figure 3 | Overall survival following stereotactic body radiotherapy (SBRT) for (a) all patients, (b) patients stratified by tissue confirmation




## Graphical Abstract Text




Establishing a definite diagnosis of lung lesions can be difficult. This study reveals similar oncological outcomes between patients with early primary lung cancer treated with stereotactic body radiotherapy (SBRT) with or without biopsy-confirmation. However, clinicians should strive to obtain tissue diagnoses wherever safe, to ensure that the most diagnosis-appropriate treatment recommendations are made.