
Article:
Spencer, KL orcid.org/0000-0002-6846-4341, Kennedy, MPT, Lummis, KL et al. (5 more authors) (2019) Surgery or radiotherapy for stage I lung cancer? An intention-to-treat analysis. European Respiratory Journal, 53 (6). 1801568. ISSN 0903-1936

https://doi.org/10.1183/13993003.01568-2018

TITLE:

Surgery or radiotherapy for stage I lung cancer? An intention to treat analysis

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Take home message:

No difference was seen in cancer and treatment specific survival following surgery and SABR. Inferior overall survival may reflect unobserved confounding. Further prospective work should assess quality of life outcomes to support shared-decision making.

ABSTRACT:

Introduction:

Surgery is the standard of care for early stage lung cancer, with stereotactic ablative radiotherapy (SABR) a lower morbidity alternative for patients with limited physiological reserve. Comparisons of outcomes between these treatment options are limited by competing co-morbidities and differences in pre-treatment pathological information. This study aims to address both issues by assessing both overall and cancer-specific survival for presumed stage I lung cancer on an intention-to-treat basis.

Methods:

This retrospective intention to treat analysis identified all patients treated for presumed stage I lung cancer within a single large UK centre. Overall survival (OS), cancer-specific survival (CSS) and combined cancer and treatment-related survival (CTRS) were assessed with adjustment for confounding variables using cox proportional hazards and Fine and Gray competing risks analyses.

Results:

468 patients (including 316 surgery, 99 SABR) were included in the study population. Compared to surgery, SABR was associated with inferior OS on multivariable Cox modelling (SABR HR 1.84 (95% CI 1.32-2.57)) but there was no difference in CSS (HR for SABR 1.47 (95% CI 0.80-2.69) or CTRS (HR for SABR 1.27 (95% CI 0.74-2.17)). Cancer and treatment related death was no different between SABR and surgery on Fine and Gray competing risks multivariable modelling (sub-distribution hazard 1.03 (95% CI 0.59-1.81)). Non-cancer death was significantly higher in SABR than surgery (sub-distribution hazard 2.16 (95% CI 1.41-3.32)).

Conclusion:

In this analysis, no difference in cancer-specific survival was observed between SABR and surgery. Further work is needed to define predictors of outcome and help inform treatment decisions.

Introduction:

Lung cancer has the third highest cancer incidence in the UK and the highest mortality.(1) For medically operable patients with stage I disease, surgical resection with mediastinal lymph node sampling is the standard of care. Overall survival (OS) is 54-73% at 5-years(2–6) with 5-6% loco-regional recurrence (5–7) and 17-18% overall recurrence.(5,6) Lung cancer is, however, associated with advanced age and comorbidity.(8) This results in higher perioperative mortality risk,(9) often precluding surgery.(8) Sub-lobar resection can be considered for patients at higher risk of surgical morbidity or mortality.(10)

Radiotherapy is an alternative treatment for medically inoperable patients or those declining surgery. Historical series of conventionally fractionated radiotherapy (CFRT) have shown poorer outcomes than surgical resection. (11–13) Stereotactic ablative radiotherapy (SABR), however, uses much higher biologically equivalent doses than CFRT providing improved OS with lower morbidity in eligible patients.(14,15) Additionally, a large population-based study in Holland, demonstrated an increase in rates of radical treatment, stable surgical resection rates and improved OS for older patients with early-stage NSCLC when SABR was introduced.(16) In England SABR is only commissioned for peripherally located lesions. Whilst more centrally located early stage lung cancers can be treated with SABR there is considerable debate on the optimal dose and the safety of this approach, particularly for “ultra-central” lesions. The full results of the North America NRG Oncology/RTOG 0813 and the Scandinavian HILUS trial are awaited and may provide further information.(17,18)

Surgical patients tend to be younger with less comorbidity than those undergoing SABR or CFRT.(3,19) As such, comparisons between reported outcomes of cohort studies are limited by selection bias and the confounding effect of unobserved characteristics. Additionally information bias may occur; definitive pathological staging is available for a majority of surgical patients, with upstaged patients usually being excluded from comparisons, whilst occult nodal disease may go undetected in the SABR population despite PET-CT and endobronchial ultrasound (EBUS) nodal aspirate based staging. Conversely, there is a risk that un-biopsied benign disease in SABR cohorts may result in better than expected cancer-specific survival. As a consequence, retrospective comparisons are limited by inevitable case selection differences and staging uncertainty. The extent to which survival differences reflect treatment efficacy, has not been definitively demonstrated. Meta-analyses of cohort studies comparing surgery with SABR have found comparable mortality and local control rates when adjusted for medical operability, age and comorbidity.(3,19) Conversely, a recent propensity-matched study, using SEER data, has suggested superior outcomes with surgery compared to SABR for patients with stage IB disease.(20)

Three randomised controlled trials comparing surgery and SABR in higher risk medically operable patients have, unfortunately, failed to recruit (SABR: ROSEL (NCT00687986), STARS (NCT00840749), ASOSOG-RTOG (NCT01336894)) and the results of the feasibility SABRTooth trial are awaited (NCT02629458). An intention-to-treat analysis of pooled data from ROSEL and STARS demonstrated superior 3-year OS with SABR, although small sample size and short follow-up mean these results should be interpreted with caution.(21) Further randomised studies (including STABLE-MATES (NCT02468024), POSTIIV (NCT01753414) and VALOR (NCT0298476) are ongoing.

Given the clear challenges faced in randomising patients in this situation,(22) this study aims to analyse the outcomes following radical treatment of presumed stage I lung cancer in order to assess cancer specific mortality and treatment effect within an intention to treat population.

Materials and methods:

This single centre retrospective cohort study included all consecutive patients diagnosed and treated with curative intent for presumed stage I lung cancer at Leeds Teaching Hospitals NHS Trust (LTHT) between January 2008 and May 2013. All patients who received radical lung cancer treatment were identified using an automated search of the local electronic health record. Pre-treatment stage was confirmed using radiology and multi-disciplinary team (MDT) records using the 7th edition of TNM staging for lung cancer. Manual review of records identified additional patients treated surgically for presumed stage I lung cancer, but subsequently diagnosed with benign pathology. All patients underwent PET-CT staging. All patients with presumed stage I disease pre-treatment were included in the study cohort. Patients without histological confirmation needed to a have (1) a PET positive lesion and/or serial growth on imaging; (2) a contra-indication to, or a failed biopsy; and (3) MDT consensus supporting a lung cancer diagnosis before having radiotherapy. Demographic and baseline clinical data (including performance status) were collected. Co-morbidity and physiological reserve, however, were not systematically recorded and therefore were not considered within this analysis.

Leeds Teaching Hospitals NHS Trust (LTHT) is a large publically funded UK teaching hospital. It has a local catchment population of 780,000 and is the regional referral centre for a further 2.7 million for both surgery and radiotherapy. All patients are managed by a lung cancer specific MDT in line with national guidelines. Prior to May 2009, CFRT was the standard non-surgical treatment for stage I lung cancer in LTHT. At this time, SABR was

implemented as the standard of care for patients with medically inoperable peripheral stage I disease.(23,24) CFRT remained the standard of care for more central lesions.

Standard follow-up after radical treatment of lung cancer during this period included clinic review with chest radiograph three monthly in year one, 6 monthly in year two and annually in years three to five.(25) Recurrence was defined on radiological or clinical grounds, and either pathologically confirmed or clinically accepted by lung cancer MDT review. New primary lung cancers, diagnosed on the basis of histological subtype, immunohistochemistry or clinically, were not considered recurrences.(26,27) The site of recurrence was recorded as local, nodal or metastatic. Local recurrence included recurrence at the resection margin following surgical resection or within the lung parenchyma of the same lobe following sub-lobar resection or radiotherapy (i.e. potentially >2-3cm from the gross tumour volume). Nodal recurrence included all intra-thoracic lymph nodes. Extra-thoracic lymph nodes, different ipsilateral lobe, contralateral lung, pleural effusions or distant organ recurrence were considered metastatic. Date and cause of death were recorded. The latter was determined through retrospective case-note review by two independent investigating doctors and defined as treatment-related, cancer-related (death following diagnosis of recurrent cancer) or due to co-morbidity (death without recurrent cancer). No inter-observer disagreement occurred.

All analyses were based on delivered treatment modality (surgery, SABR or CFRT). Baseline characteristics of the treatment groups were compared using the chi-squared test and two-sided t-test for age. OS, cancer-specific survival (CSS) and combined cancer and treatment-related survival (CTRS) were determined and Kaplan-Meier Survival curves produced. Censoring was at the point of data collection for OS; at data collection, death due to co-morbidity or treatment related death for CSS; and at data collection or death due to co-morbidity for CTRS. CSS therefore encompasses deaths following cancer recurrence only, while CTRS encompasses deaths due to either cancer treatment or recurrence.(28) The factors associated with these outcomes were considered using univariable and multivariable cox proportional hazards models. Histological subtype was excluded from multivariable models due to collinearity of the unknown subgroup with the radiotherapy treatment arms. Heterogeneity of treatment effect on CTRS with age and performance status was assessed using interaction terms and by examining separate treatment cohorts

To address possible concerns about the suitability of Cox modelling in a situation where censoring differs widely between cohorts, the multivariable analysis was replicated using a Fine and Gray competing risks model.(29) The cumulative incidence function of death due to varying causes was plotted.

Analyses were repeated excluding patients without histological confirmation prior to treatment.

All statistical analyses were carried out in STATA IC 14. This study was approved as a local evaluation of treatment outcomes by LTHT Research and Innovation department.

Results:

3201 patients diagnosed with lung cancer at LTHT, commenced treatment between January 2008 and May 2013. Of these, 463 were treated with curative intent for presumed stage I lung cancer (pre-treatment stage). A further 5 patients underwent surgery for presumed stage I NSCLC with subsequent benign histology. The final study population consisted of 468 patients. 316 individuals underwent surgical resection (67.4%), 99 (21.2%) SABR and 53 (11.3%) CFRT (Figure 1). Of the surgically resected patients 268 (84.8%) patients underwent lobectomy or pneumonectomy, 48 (15.2%) sub-lobar resection (of which 7 anatomical segmentectomy (14.6%)). Median follow-up was 4.9, 3.8 and 4.7 years following surgery, SABR and CFRT respectively.

Compared to the SABR cohort, the surgically treated patients were younger ($p<0.001$) with better WHO performance status ($p<0.001$) (Table 1). Pre-treatment confirmation of malignancy was available in 56 (56.6%) patients treated with SABR and 34 (62.3%) treated with CFRT. Six patients included within the surgical cohort were found to have small-cell lung cancer (SCLC) at histological review.

Median OS for all radically treated patients was 4.7 years (95% CI 4.0-5.6). Figure 2a shows OS by treatment cohort. Two year OS was 79.8% (95% CI 74.9-83.8)), 58.6% (95% CI 48.3-67.6) and 54.7% (95% CI 40.5-66.9) for the surgery, SABR and CFRT cohorts respectively. Compared to surgery, SABR and CFRT were associated with significantly worse OS on both univariable and multivariable analyses (HRs for multivariable analyses were 1.840 (95% CI 1.317-2.570) for SABR and 2.278 (95% CI 1.539-3.372) for CFRT). In addition, increasing age, male sex, poor performance status, higher stage and unknown histology were all associated with worse OS in univariable analysis. Sex and age retained this significance on multivariable analysis (Table 2). Excluding patients who did not have a confirmed malignancy prior to treatment resulted in a HR for SABR compared to surgery of 1.696 (95% CI 1.130-2.545). A similar but lesser effect was seen in CFRT (HR 2.232 (95% CI 1.385-3.598))(See Table 4s).Compared to surgery, CFRT was associated with significantly worse CSS on both univariable and multivariable analyses (multivariable HR was 2.281 (95% CI 1.204-4.319)). CSS following SABR, however, was not significantly different from surgery on either univariable or multivariable analysis (multivariable HR 1.469 (95% CI 0.802-2.688). In

addition, increasing age and higher stage were associated with worse CSS in univariable analyses, but only higher stage retained this on multivariable analysis (Table 1s and Table 5s).

There were no treatment-related deaths in the SABR cohort; 10 (3.2%) were seen in the surgical cohort and 1 (1.9%) following CFRT (p=0.073). Median time to post-surgical death was 20 days with only one individual dying more than 90 days after surgery. CFRT was associated with a significantly worse CTRS than surgery on both univariable and multivariable analyses (HR for multivariable analysis 2.133 (95% CI 1.208-3.767), while CTRS following SABR was not significantly different to surgery on either univariable or multivariable analysis (HR for multivariable 1.271 (95% CI 0.744-2.170) (Table 3). Excluding patients without histological confirmation prior to surgery resulted in a slight change in the HR of both SABR and CFRT (HR 1.370 (95% CI 0.733-2.561) and HR 2.018 (95% CI 1.004-4.055) respectively)(see Table 6s). No significant interaction between the impact of age or performance status and treatment modality was demonstrated in the multivariable CTRS Cox model although the univariable relationship with age and performance status varied between interventions (Table 4 and 2s).

Fine and Gray competing risks analysis confirmed the CTRS analysis findings; SABR outcomes were no different to surgery on multivariable analysis (Sub-distribution hazard (SHR) 1.030 (95% CI 0.585-1.814)) (Table 5). The cumulative incidence of death due to treatment, cancer or other causes by treatment cohorts is shown in Figure 3. The SHR was 1.149 (95% CI 0.587-2.250) when patients without histological confirmation were excluded (Table 7s).

Second primary cancers were diagnosed in 13 (7.0%) surgical patients and 6 (6.1%) SABR patients, none were seen following CFRT. Diagnosis of recurrence was predominantly clinical in the SABR cohort (83%) and histological in the surgical cohort (62%). Recurrence was predominantly distant in all cohorts (Figure 1s). SABR and CFRT had an increased proportion of local recurrences compared to surgery. Further analysis is limited by the differing rates of non-cancer death between the cohorts.

The significantly inferior OS seen following radiotherapy was further assessed by reversal of the competing risks analysis; with death due to co-morbidity considered an event and cancer or treatment-related deaths competing risks. Despite adjustment in multivariable models SABR and CFRT were associated with significantly greater non-cancer mortality (SHR 2.161 (95% CI 1.408-3.315, p<0.001) and SHR 1.868 (95%CI 1.075-3.243, p=0.027) respectively) (Supplementary Table 3s).

Discussion:

Randomised controlled trials aiming to compare survival following radical treatment of early stage lung cancer with surgical resection and SABR have, unfortunately, struggled to recruit. Previous studies have addressed the question of comparative treatment efficacy using observational data. In these studies, however, comparisons are often biased by selection, unobserved confounding and information bias. To our knowledge, this is the only study to deliver an intention-to-treat analysis of patients receiving radical treatment for presumed stage I lung cancer considering separately overall, treatment and cancer-specific survival outcomes.

The OS in this study was comparable to published data,(2–6) with the best outcomes observed following surgical resection. SABR and CFRT were associated with inferior OS compared to surgery despite adjustment for available baseline characteristics. While CFRT was associated with worse CSS and CTRS than surgery, no significant difference in either CSS or CTRS was observed between surgery and SABR. That reversal of the competing risks model, considering cancer-related death the competing risk, identified significantly increased non-cancer mortality in the radiotherapy treatment arms supports the hypothesis that the OS analysis is likely to be biased by unobserved confounding e.g. due to respiratory function and co-morbidity.

Cox modelling of CTRS attempts to assess treatment effect in a theoretical population where death due to other causes is not possible and hence with limited, although not absent, potential for confounding due to co-morbidity. Unfortunately, this situation does not reflect the real world and censoring individuals at death due to other causes, is open to criticism.(30,31) It is assumed that those who are censored are represented by the remaining population and unequal censoring between the treatment arms may result in over-estimation of the hazard in the more heavily censored (radiotherapy treatment) arms, risking biased estimates of effect.(31) Fine and Gray competing risks analysis provides a means to address this. Notably, however, the risk of cancer recurrence beyond co-morbid death remains unobserved. Given the controversy over the optimum methodology results from both are shown allowing the reader to review the outcomes. Both methods demonstrate no difference in cancer and treatment related outcomes between surgery and SABR, while CFRT was associated with inferior CTRS on Cox modelling. These outcomes were unchanged when only individuals with confirmed malignancy prior to treatment were included.

Leeds Cancer Centre has a well-established thoracic surgical service, with six dedicated thoracic surgeons, a dedicated thoracic surgical theatre and high dependency unit (HDU),

thoracic surgery nurse specialists and an enhanced recovery program. The post-operative mortality in this cohort (3.2%) is in line with national outcomes. The recent Lung Cancer clinical outcomes publication from the UK National Lung Cancer Audit and the Society for Cardiothoracic Surgery in Great Britain and Ireland has reported a 3.8% 90-day mortality rate after lung cancer resection following 5,657 operations in 2014.(8,32) In this population, with average operative mortality, no difference is seen in combined cancer and treatment related survival following SABR. It is notable that the surgically treated population predominantly underwent lobectomy in this cohort. If trials investigating the role of anatomical segmentectomy change current practise, it is not possible to assess the impact this might have on the current results.(33,34)

In order to further assess the factors associated with the outcomes observed, the treatment specific effects of performance status and age were considered, revealing heterogeneity in treatment effect. CTRS following surgery appears worse in the older and frailer populations, whilst these factors had no significant association with survival following radiotherapy. Caution is required in these comparisons; the different sizes of the investigated cohorts makes identification of significant differences more likely in the larger surgical cohort than in the radiotherapy cohorts, although the hazard ratios demonstrated in the radiotherapy cohorts show no suggestion of demonstrating similar effects. Previous studies have identified multiple predictors of surgical mortality and morbidity, including sex, age, co-morbidity, baseline pulmonary function and baseline patient reported global health, amongst others.(35,36) These findings are also supported by the recent findings of Stokes et al who demonstrate a significant interaction between age and treatment modality upon the risk of early mortality in a large population based cohort.(37) With the effect of post-operative mortality potentially having a major impact upon the optimal treatment strategy, careful case selection is critical; future research efforts should focus upon helping to predict individual outcomes.

This study has a number of limitations. First, it is a single centre study, although with a large and diverse population this effect is minimised. Second, despite covering a prolonged time period the cohort remains limited in size, this might limit the potential to identify significant differences in treatment effect, although it is notable that despite this the reverse competing risks analysis identified a significantly higher cumulative incidence of death due to co-morbidity in the non-surgical cohorts. Third, cause of death was identified through retrospective case-note review. Primary care records and those from other secondary care centres were not available to support this analysis. It is also acknowledged that this can be challenging prospectively and certainly has limitations retrospectively. All individuals with recurrence were presumed to have died of cancer whilst conversely it could be argued that

some individuals may have had recurrence which went unrecognised prior to death. The impact of this cannot be assessed but the two factors may balance each other out. Local recurrence is particularly difficult to identify accurately following SABR. If present, false positives might be worsening the CSS and CTRS following SABR and are therefore unlikely to change the outcome of this study. Fourthly, the higher non-cancer mortality in the radiotherapy cohorts might be masking increased risk of subsequent cancer recurrence, this remains unobserved. Finally, this study only addresses survival outcomes. The lack of difference in cancer and treatment related survival outcomes following SABR and surgery demonstrated here make assessment of quality of life outcomes a high priority; this information being of even greater importance to the shared-decision making process where cancer outcomes are similar. Further work is needed, assessing these additional outcomes in larger cohorts and with greater numbers of patients considered eligible for either treatment option.

The data presented in this study demonstrate comparable OS,(2–6) recurrence rates (5–7) and peri-operative mortality to published UK data.(8) In this population significant differences were observed in non-cancer deaths but no difference in combined cancer and treatment related survival following SABR and surgery. This finding, however, appears to be masking significant heterogeneity of treatment effect. There is now a pressing need to investigate this further. Randomised trials would be ideal, however, given the challenges of recruitment, high quality prospective data collection, assessing not only survival but also quality of life are urgently required to help guide the shared-decision making process.

Acknowledgements:

This work uses data provided by patients and collected by the NHS as part of their care and support. We are grateful to Mark Rutherford (University of Leicester) for his review and statistical advice. KS was supported by a Wellcome Trust grant and Medical Research Council fellowship (MR/N021339/1) during this project.

Table 1 – Baseline characteristics of the treated cohorts. Histological subtype was not significantly different between the cohorts when those without histological confirmation were excluded (p=0.379). p values represent the comparison between surgery and SABR.

	Surgery		SABR		CFRT		p
Age							
Median	69.9		76.7		76.5		
Inter-quartile range	(57.12-82.7)		(63.5-90.0)		(63.8-89.3)		
Age groups	(n)	(%)	(n)	(%)	(n)	(%)	
30-59	47	14.87	4	4.04	0	0.00	<0.001
60-69	112	35.44	21	21.21	12	22.64	
70-79	127	40.19	42	42.42	20	37.74	
≥80	30	9.49	32	32.32	21	39.62	
Sex							
Female	176	55.70	44	44.44	30	56.60	0.050
Histology							
Squamous cell	95	30.06	21	21.21	16	30.19	<0.001
Other	215	68.04	35	35.35	17	32.08	
Benign	5	1.58	0	0.00	0	0.00	
Unknown	1	0.32	43	43.43	20	37.74	
Pre-op stage							
IA	197	62.34	68	68.69	23	43.40	0.252
Post-op stage							
IA	140	44.30					
IB	107	33.86					
IIA	36	11.39					
IIB	17	5.38					
IIIA	9	2.85					
IIIB	1	0.32					
IV	1	0.32					
Benign	5	1.58					
Performance status							
0-1	263	83.23	41	41.41	17	32.08	<0.001
2	45	14.24	29	29.29	20	37.74	
3-4	8	2.53	29	29.29	16	30.19	
Year							
2008	55	17.41	0	0.00	9	16.98	<0.001
2009	51	16.14	8	8.08	6	11.32	
2010	46	14.56	19	19.19	13	24.53	
2011	54	17.09	30	30.30	7	13.21	
2012	72	22.78	28	28.28	14	26.42	
2013	38	12.03	14	14.14	4	7.55	
Total	**316**		**99**		**53**		

Table 2: Univariable and multivariable cox proportional hazards for overall survival.

	Univariable				Multivariable			
	Hazard ratio	p	Lower 95% CI	Upper 95% CI	Hazard ratio	p	Lower 95% CI	Upper 95% CI
Age								
<60	1.000	-	-	-	1.000	-	-	-
60-69	1.559	0.111	0.903	2.692	1.369	0.264	0.790	2.372
70-79	2.317	0.002	1.372	3.913	1.954	0.013	1.150	3.319
≥80	3.063	<0.001	1.758	5.336	1.897	0.030	1.064	3.380
Sex								
Female	1.000	-	-	-	1.000	-	-	-
Male	1.614	<0.001	1.260	2.068	1.670	<0.001	1.296	2.152
Histology								
Squamous	1.000	-	-	-	-	-	-	-
Other	0.730	0.031	0.548	0.971	-	-	-	-
Benign	0.555	0.412	0.136	2.263	-	-	-	-
Unknown	1.951	<0.001	1.365	2.788	-	-	-	-
Pre-op stage								
IA	1.000	-	-	-	1.000	-	-	-
IB	1.392	0.009	1.084	1.786	1.276	0.063	0.987	1.650
Performance status								
0-1	1.000	-	-	-	1.000	-	-	-
2	1.697	<0.001	1.261	2.283	1.306	0.098	0.952	1.793
3-4	2.244	<0.001	1.569	3.209	1.328	0.171	0.885	1.992
Treatment								
Surgery	1.000	-	-	-	1.000	-	-	-
SABR	2.389	<0.001	1.787	3.192	1.840	<0.001	1.317	2.570
CFRT	2.831	<0.001	1.999	4.008	2.278	<0.001	1.539	3.372

Table 3: Univariable and multivariable cox proportional hazards model for combined cancer and treatment related survival.

	Univariable				Multivariable			
	Hazard ratio	**p**	**Lower 95% CI**	**Upper 95% CI**	**Hazard ratio**	**p**	**Lower 95% CI**	**Upper 95% CI**
Age								
<60	1.000	-	-	-	1.000	-	-	-
60-69	1.826	0.147	0.810	4.120	1.670	0.219	0.738	3.783
70-79	2.279	0.041	1.034	5.024	1.993	0.090	0.898	4.428
≥80	2.332	0.053	0.990	5.493	1.645	0.274	0.674	4.013
Sex								
Female	1.000	-	-	-	1.000	-	-	-
Male	1.387	0.082	0.959	2.007	1.386	0.090	0.950	2.022
Histology								
Squamous	1.000	-	-	-	-	-	-	-
Other	0.887	0.577	0.583	1.351	-	-	-	-
Benign	0.000	-	-	-	-	-	-	-
Unknown	1.302	0.388	0.715	2.369	-	-	-	-
Pre-op stage								
IA	1.000	-	-	-	1.000	-	-	-
IB	1.870	0.001	1.293	2.705	1.744	0.004	1.193	2.550
Performance status								
0-1	1.000	-	-	-	1.000	-	-	-
2	1.485	0.076	0.960	2.296	1.281	0.302	0.801	2.047
3-4	1.232	0.519	0.653	2.326	0.841	0.629	0.416	1.699
Treatment								
Surgery	1.000	-	-	-	1.000	-	-	-
SABR	1.309	0.272	0.809	2.118	1.271	0.380	0.744	2.170
CFRT	2.426	0.001	1.472	3.997	2.133	0.009	1.208	3.767

Table 4: Treatment specific univariable combined cancer and treatment related survival models for performance status and age upon. Univariable outcomes for each treatment and co-variable were modelled separately.

	HR	p	Lower 95% CI	Upper 95% CI
Surgery				
Performance status				
0-1	1.000	-	-	-
2	1.050	0.887	0.536	2.057
3	2.911	0.039	1.055	8.028
Age				
<60	1.000	-	-	-
60-69	1.575	0.324	0.639	3.885
70-79	2.347	0.054	0.987	5.581
≥80	2.353	0.113	0.816	6.785
SABR				
Performance status				
0-1	1.000	-	-	-
2	1.082	0.869	0.425	2.756
3	0.642	0.456	0.201	2.056
Age				
<60	1.000	-	-	-
60-69	1.608	0.661	0.193	13.383
70-79	0.868	0.895	0.107	7.037
≥80	0.655	0.704	0.074	5.782
CFRT				
Performance status				
0-1	1.000	-	-	-
2	1.553	0.385	0.575	4.199
3	0.560	0.402	0.144	2.174
Age				
<60	-	-	-	-
60-69	1.000	-	-	-
70-79	1.249	0.707	0.392	3.977
≥80	1.099	0.870	0.357	3.387

Table 5. Fine and Gray uni-variable and multi-variable competing risks models assessing death due to cancer or treatment with death due to other causes considered a competing risk. SHR – Sub-distribution hazard ratio.

	Univariable				Multivariable			
	SHR	**p**	**Lower 95% CI**	**Upper 95% CI**	**SHR**	**p**	**Lower 95% CI**	**Upper 95% CI**
Age								
<60	1.000	-	-	-	-	-	-	-
60-69	1.799	0.158	0.797	4.064	1.747	0.186	0.764	3.990
70-79	2.105	0.064	0.956	4.632	1.914	0.121	0.842	4.355
≥80	1.929	0.130	0.824	4.517	1.590	0.315	0.644	3.928
Sex								
Female	1.000	-	-	-	-	-	-	-
Male	1.267	0.208	0.876	1.831	1.230	0.292	0.837	1.805
Pre-op Stage								
IA	1.000	-	-	-	1.000	-	-	-
IB	1.819	0.001	1.259	2.628	1.712	0.006	1.166	2.515
Performance status								
0-1	1.000	-	-	-	-	-	-	-
2	1.369	0.156	0.887	2.113	1.256	0.329	0.794	1.987
3-4	0.912	0.779	0.482	1.728	0.741	0.446	0.342	1.604
Treatment								
Surgery	1.000	-	-	-	1.000	-	-	-
SABR	1.000	0.999	0.621	1.610	1.030	0.919	0.585	1.814
CFRT	1.848	0.014	1.130	3.023	1.654	0.097	0.913	2.996

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Supplementary material:

Table 1s: Univariable and multivariable cox proportional hazards for cancer specific survival.

	Univariable				Multivariable			
	HR	**p**	**L95% CI**	**U 95% CI**	**HR**	**p**	**L95% CI**	**U 95% CI**
Age								
<60	1.000	-	-	-	1.000	-	-	-
60-69	2.351	0.076	0.914	6.045	1.980	0.159	0.765	5.126
70-79	2.927	0.023	1.162	7.370	2.254	0.087	0.889	5.716
>=80	3.192	0.020	1.196	8.516	1.837	0.239	0.668	5.054
Sex								
Female	1.000	-	-	-	1.000	-	-	-
Male	1.335	0.145	0.905	1.969	1.357	0.135	0.909	2.026
Performance status								
0-1	1.000	-	-	-	1.000	-	-	-
2	1.685	0.023	1.073	2.646	1.457	0.134	0.891	2.382
3-4	1.479	0.232	0.779	2.808	0.906	0.787	0.442	1.856
Stage								
IA	1.000	-	-	-	1.000	-	-	-
IB	2.015	<0.001	1.366	2.972	2.006	0.001	1.335	3.014
Histology								
Squamous	1.000	-	-	-	1.000	-	-	-
Other	0.939	0.786	0.598	1.475	1.221	0.399	0.768	1.941
Benign	-	-	-	-	-	-	-	-
Unknown	1.587	0.141	0.857	2.938	1.181	0.638	0.591	2.359
Treatment								
Surgery	1.000	-	-	-				
SABR	1.579	0.068	0.967	2.580	1.469	0.213	0.802	2.688
CFRT	2.806	<0.001	1.672	4.712	2.281	0.011	1.204	4.319

Table 2s. Cox multivariable cancer and treatment related survival model assessing a possible interaction between treatment type and performance status.

	HR	p	Lower 95% CI	Upper 95% CI
Age				
<60	1.000	-	-	-
60-69	1.620	0.250	0.712	3.687
70-79	1.941	0.106	0.869	4.337
≥80	1.612	0.298	0.657	3.956
Sex				
Female	1.000	-	-	-
Male	1.385	0.092	0.948	2.024
Histology				
Adenocarcinoma	-	-	-	-
Squamous cell	-	-	-	-
Other	-	-	-	-
Unknown	-	-	-	-
Pre-op stage				
IA	1.000	-	-	-
IB	1.727	0.005	1.178	2.530
Performance status				
0-1	1.000	-	-	-
2	1.103	0.777	0.559	2.177
3	2.716	0.056	0.975	7.568
Treatment				
Surgery	1.000	-	-	-
SABR	1.370	0.372	0.686	2.733
CFRT	2.300	0.042	1.029	5.141
PS-Treatment interaction				
PS 2 – SABR	1.165	0.796	0.367	3.697
PS 3 – SABR	0.231	0.063	0.049	1.086
PS 2 – CFRT	1.262	0.700	0.386	4.132
PS 3 – CFRT	0.188	0.053	0.035	1.025

Table 3s. Fine and Gray competing risks model for non-cancer death with death due to cancer and treatment considered competing risks.

		Subdistribution hazard ratio	p	Lower 95% CI	Upper 95% CI
Age					
	<60	1.000	-	-	-
	60-69	0.958	0.914	0.437	2.097
	70-79	1.563	0.233	0.750	3.256
	≥80	1.793	0.152	0.807	3.984
Sex					
	Female	1.000	-	-	-
	Male	1.682	0.003	1.189	2.381
Pre-op Stage					
	IA	1.000	-	-	-
	IB	0.834	0.317	0.584	1.190
Performance status					
	0-1	1.000	-	-	-
	2	1.130	0.578	0.734	1.741
	3-4	1.753	0.034	1.045	2.942
Treatment					
	Surgery	1.000	-	-	-
	SABR	2.161	<0.001	1.408	3.315
	CFRT	1.868	0.027	1.075	3.243

Table 4s. Multivariable cox proportional hazards model for overall survival in patients with pathologically confirmed lung cancer.

	Hazard ratio	p	Lower 95% CI	Upper 95% CI
Age				
<60	1.000	-	-	-
60-69	1.524	0.161	0.845	2.748
70-79	2.232	0.005	1.267	3.933
>=80	1.993	0.033	1.058	3.756
Sex				
Female	1.000	-	-	-
Male	1.762	<0.001	1.324	2.345
Pre-op stage				
IA	1.000	-	-	-
IB	1.404	0.020	1.055	1.868
Performance status				
0-1	1.000	-	-	-
2	1.363	0.090	0.953	1.950
3-4	1.076	0.794	0.619	1.871
Treatment				
Surgery	1.000	-	-	-
SABR	1.696	0.011	1.130	2.545
CFRT	2.232	0.001	1.385	3.598

Table 5s. Multivariable cox proportional hazards model for cancer-specific survival in patients with pathologically confirmed lung cancer.

	HR	p	Lower 95% CI	Upper 95% CI
Age				
<60	1.000	-	-	-
60-69	2.625	0.072	0.917	7.512
70-79	2.928	0.041	1.043	8.218
>=80	1.706	0.367	0.534	5.452
Sex				
Female	1.000	-	-	-
Male	1.412	0.124	0.909	2.193
Performance status				
0-1	1.000	-	-	-
2	1.483	0.169	0.845	2.603
3-4	1.041	0.926	0.447	2.425
Stage				
IA	1.000	-	-	-
IB	2.110	0.001	1.350	3.296
Histology				
Squamous	1.000	-	-	-
Other	1.251	0.347	0.784	1.996
Treatment				
Surgery	1.000	-	-	-
SABR	1.634	0.133	0.861	3.099
CFRT	2.144	0.044	1.021	4.502

Table 6s. Multivariable cox proportional hazards model for cancer and treatment-related survival in patients with pathologically confirmed lung cancer.

	HR	p	Lower 95% CI	Upper 95% CI
Age				
<60	1.000	-	-	-
60-69	2.027	0.113	0.845	4.862
70-79	2.386	0.047	1.014	5.619
≥80	1.490	0.436	0.547	4.059
Sex				
Female	1.000	-	-	-
Male	1.443	0.080	0.958	2.176
Pre-op stage				
1A	1.000	-	-	-
1B	1.762	0.007	1.169	2.657
Performance status				
0-1	1.000	-	-	-
2	1.235	0.438	0.724	2.106
3	0.962	0.926	0.422	2.189
Treatment				
Surgery	1.000	-	-	-
SABR	1.370	0.324	0.733	2.561
CFRT	2.018	0.049	1.004	4.055

Table 7s. Multivariable Fine and Gray competing risks model for cancer or treatment related death with death due to other causes considered a competing risk. Including only patients with pathologically confirmed lung cancer.

	SHR	p	Lower 95% CI	Upper 95% CI
Age				
<60	1.000	-	-	-
60-69	2.059	0.109	0.851	4.983
70-79	2.264	0.070	0.937	5.472
>=80	1.419	0.503	0.510	3.951
Sex				
Female	1.000	-	-	-
Male	1.290	0.253	0.834	1.995
Pre-op Stage				
IA	1.000	-	-	-
IB	1.707	0.013	1.120	2.600
Performance status				
0-1	1.000	-	-	-
2	1.189	0.517	0.704	2.006
3-4	1.018	0.970	0.408	2.538
Treatment				
Surgery	1.000	-	-	-
SABR	1.149	0.685	0.587	2.250
CFRT	1.464	0.321	0.690	3.106

Figure 1s. Sites of recurrence at 2 years post-treatment as a proportion of all patients experiencing recurrence by treatment cohort.