



Original Article

Differential Relapse Patterns for Non-small Cell Lung Cancer Subtypes Adenocarcinoma and Squamous Cell Carcinoma: Implications for Radiation Oncology



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Abstract

Aims: Curative-intent (radical) radiotherapy aims to control local disease and cure non-small cell lung cancer (NSCLC). The predominant subtypes of NSCLC are adenocarcinoma and squamous cell carcinoma (SCC). The radiotherapy paradigm offered to patients does not differ according to these two subtypes. Relapse patterns and disease control rates for adenocarcinoma and SCC treated with radical radiotherapy were determined.

Materials and methods: A radical radiotherapy database covering the period from 2004 to June 2016 was examined to determine the first sites of relapse and the actuarial local and distant control rates.

Results: In total, 537 patients with known pathological subtype were treated over the period. In 39 (7%), the site of first relapse was uncertain. Of the remainder, 203 (41%) had adenocarcinoma and 295 (59%) had SCC. At a median follow-up of 16.4 months, 58% had relapsed. There was a difference in relapse patterns (chi-squared test $P < 0.0005$), with a higher rate of first relapse locally in SCC (42% of all patients versus 24%) and a higher rate of first relapse in the brain for adenocarcinoma (14% versus 3%). The actuarial local control rate was worse for SCC (hazard ratio 0.6, 95% confidence interval 0.5–0.9, $P = 0.002$). The brain metastasis-free survival was worse for adenocarcinoma (hazard ratio 4.1, 95% confidence interval 2.2–7.5, $P < 0.0001$).

Conclusion: There is a difference in relapse patterns between NSCLC histological subtypes, indicating that these are distinct entities. This may have implications for follow-up policy and strategies to improve disease control.

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Key Words: Adenocarcinoma; lung cancer; radiotherapy; relapse; squamous cell carcinoma

Introduction

Lung cancer is the leading cause of cancer-related death [1]. Non-small cell lung cancer (NSCLC) accounts for most lung cancer diagnoses [2]. NSCLC can be subtyped further using morphology and immunohistochemistry, with the two most frequent subtypes being adenocarcinoma and squamous cell carcinoma (SCC). These subtypes differ greatly in their molecular make-up [3]. They also differ in their response to systemic therapy [4], with chemotherapeutic treatment strategies chosen based on pathological

subtyping, as well as molecular profile [5]. Relapse patterns differ between the subtypes; adenocarcinoma is known to have a higher rate of brain metastatic failure after surgery and combined modality therapy [6–8]. A higher local failure rate has been noted after stereotactic body radiotherapy in SCC compared with adenocarcinoma [9]. Radiotherapy protocols do not differ substantially according to NSCLC subtype, with similar strategies used for target definition, motion management and dose fractionation [10]. Some have advocated a different margin for microscopic spread [11], but this is not followed universally [12]. Here, the site of first relapse, local control rates and brain metastasis-free control rates for patients treated with radical radiotherapy at a regional cancer centre are presented.

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Materials and Methods

Study Population

Patients from a prospectively collected database of radical lung cancer treatments at a regional cancer centre were included if they had completed a course of curative-intent radiotherapy between January 2004 and June 2016. Histological subtype was determined from pathological reports, which used morphology and immunohistochemistry. Patients routinely underwent positron emission tomography/computed tomography (PET/CT) staging, but baseline brain imaging was not standard practice. The overall survival of the cohort has been previously reported [13]. Stage was recorded according to AJCC 7th edition [14]. Electronic case records and electronic radiology images were assessed to determine the site of first relapse. Local failure was defined as an enlarging mass, new locoregional lymph nodes or a lesion with histological or cytological confirmation on bronchoscopy [15,16]. Local failures were categorised as ‘in-field’ (within the radiotherapy field) or ‘out-of-field’ by reviewing the radiotherapy records.

Radiotherapy

The standard radiotherapy dose and fractionation used over the period was 55 Gy in 20 fractions. Target definition was determined from PET/CT, when available, or computed tomography staging scans. Elective nodal irradiation was not undertaken. Four-dimensional computed tomography was used for motion management from 2010. Image-guided radiotherapy (IGRT) with megavoltage portal images was introduced in 2005, and kilovoltage cone-beam computed tomography in 2012. Stereotactic ablative radiotherapy (SABR) was used for appropriate patients from 2011. Dose fractionation was converted into the equivalent dose in 2 Gy fractions (EQD2) using an alpha/beta ratio of 10 to allow comparison of dose between the adenocarcinoma and SCC groups.

Statistics

Categorical data, such as stage and Eastern Cooperative Oncology Group performance status, were compared between adenocarcinoma and SCC groups using the chi-squared test. Continuous data, such as age and EQD2, were compared using Student’s *t*-test. Actuarial survival was taken from the start of radiotherapy or the start of sequential chemotherapy if this was sooner. Univariate analysis was undertaken for factors known to affect survival – stage, gender, age, performance status, PET/CT staging, pathological subtype – and radiotherapy technique factors of dose in EQD2, image guidance (IGRT) method and respiratory motion compensation technique.

Local Protocol

The recommended follow-up policy was to review 3–4 monthly for years 1–3, 6 monthly for years 4 and 5 and consideration was given to discharge at 5 years. Clinical practice at the time was to request chest radiographs (CXR) at each review, and to request computed tomography of the chest and abdomen where there was clinical concern about relapse. Where required, PET/CT was used to differentiate between local relapse within the radiotherapy field (in-field) and radiotherapy scarring. Brain imaging was requested solely to exclude brain metastases in the presence of suggestive symptoms.

Results

Study Group

In total, 797 patients were treated radically over 15.5 years. Of these, 537 (67%) were diagnosed with the adenocarcinoma or SCC subtype. The site of first relapse was uncertain in 39 (7%) due to incomplete imaging, providing a study population of 498 (adenocarcinoma $n = 203$ and SCC $n = 295$) (Figure 1). Baseline demographics of the adenocarcinoma and SCC study groups are shown in Table 1. Ninety-three per cent of patients were PET/CT staged. There were more male patients in the SCC group (67% compared with 44%, $P < 0.00001$). Although there was no difference in the distribution of performance status, there was a difference in disease stage ($P = 0.02$). Patients in the SCC group were more likely to be treated for stage III disease (55% compared with 45%).

Radiotherapy

The type of treatment delivered differed ($P = 0.01$), with more chemoradiation, either sequential or concurrent, given in the SCC group. Patients with stage I disease were more likely to receive SABR in the adenocarcinoma group (38% versus 17%, $P = 0.001$), whereas access to concurrent chemoradiation was 16% in the adenocarcinoma group compared with 13% in the SCC group. More of those in the adenocarcinoma group received advanced radiotherapy techniques, such as four-dimensional computed tomography (55% versus 44%, $P = 0.004$) and kilovoltage IGRT (46% versus 37%, $P = 0.004$). The average dose was also higher in the adenocarcinoma group (64 Gy versus 62 Gy, $P = 0.007$). Across the entire study population, 70% of treatments were given in 20 fractions, 9% as SABR fractionations, 19% with 2 Gy fractionation and 1% alternative dose fractionation. A more detailed breakdown is given in Table 2.

Relapse Patterns

With a median follow-up of 16.4 months, 207 (42%) of the study population had not relapsed; 65 had died of other causes and 142 were disease free at the last follow-up. Of

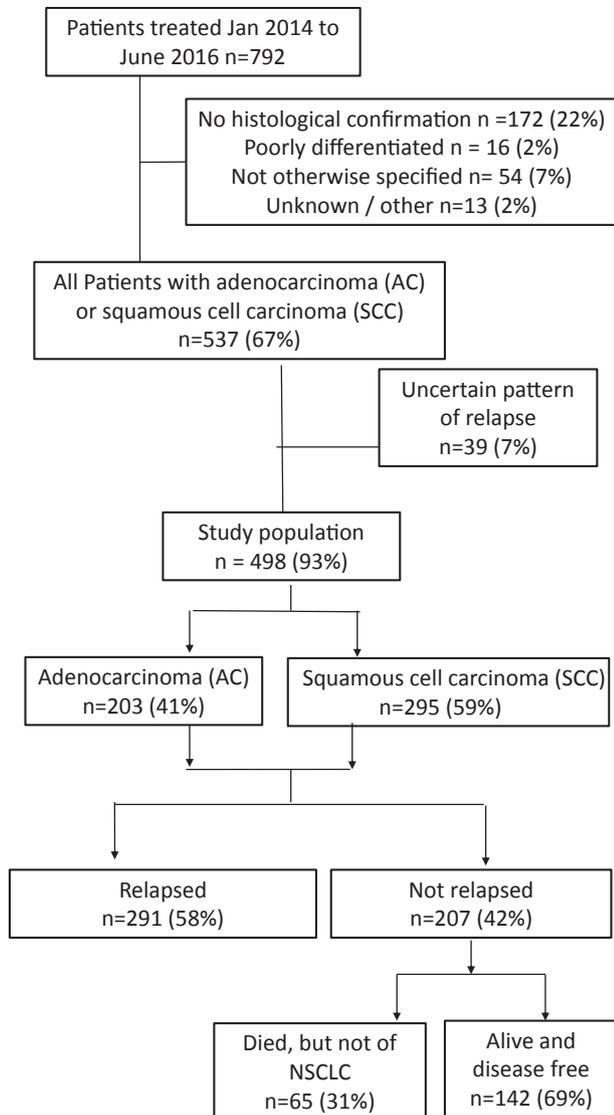


Fig 1. CONSORT diagram for patient selection.

those who had relapsed, 115 (40%) had adenocarcinoma and 176 (60%) had SCC. For those who had relapsed, 16% were re-staged with PET/CT, 79% with computed tomography, 4% with CXR and 21% had brain imaging. For those who had relapsed in the brain, lung staging was undertaken by PET/CT (7%), computed tomography (79%) and CXR alone (14%).

A difference in relapse rate between SCC and adenocarcinoma groups was observed in the study population (chi-squared test $P < 0.0005$ and [Figure 2](#)). There was a higher rate of first relapse in the brain for adenocarcinoma (14% versus 3%) and there was a higher rate of first relapse locally in the SCC group (42% versus 24%). The same pattern was seen for stage I alone ($P = 0.04$) and stage III alone ($P = 0.0005$).

Survival Outcomes

Overall survival and disease-free survival were similar for the two groups ([Figure 3](#)). However, the local control

rate was worse for SCC (hazard ratio 0.6, 95% confidence interval 0.5–0.9, $P = 0.002$), whereas there was a better brain metastasis-free survival for SCC (hazard ratio 4.1, 95% confidence interval 2.2–7.5, $P < 0.0001$) and a trend to better metastasis-free survival (hazard ratio 1.2, 95% confidence interval 0.9–1.7 $P = 0.12$). NSCLC pathological subtype remained predictive of local control and brain metastasis-free survival in multivariate models using other factors predictive of survival ([Tables 3 and 4](#)).

Analysis of In-field and Out-of-field Relapse by Pathological Subtype

The patterns of local relapses were different for the pathological subtypes: 84% (111 of 132) of the local relapses in the SCC group were solely within the radiotherapy portal compared with 41 (65%) of the 63 local relapses in the adenocarcinoma group ($P = 0.0023$). Out-of-field regional and supraclavicular fossa (SCF) lymph node relapses accounted for 21% and 8% of adenocarcinoma local relapses, respectively, as opposed to 10% and 1% in the SCC group. The remainder of the relapses were out-of-field lung nodules (6% of adenocarcinoma and 5% SCC).

Discussion

The presented single-centre study population is comparable with national audit data according to baseline characteristics and the hypofractionated schedule 55 Gy in 20 fractions is commonly used in UK centres [12]. Survival outcomes have been reported previously [13] and are similar to other UK [15,17] and European centres [13]. We conclude that this study is representative of patients selected for curative-intent radiotherapy for NSCLC. Demographics features between the adenocarcinoma and SCC groups differed. Adenocarcinoma is known to be more frequent among women [18]. Patients in the SCC group were of more advanced stage and were more likely to receive combined chemoradiation treatments, as these are advocated for patients of advanced stage [19]. There was a higher percentage of the adenocarcinoma group receiving SABR. SABR is delivered with a much higher EQD2 dose than conventional radiotherapy and in our centre four-dimensional computed tomography and cone-beam IGRT were first introduced for this group of patients. The adenocarcinoma group had a higher average dose delivered and more access to four-dimensional computed tomography and cone-beam IGRT. These factors were accounted for in the multivariate analyses of survival.

Our study showed an increased rate of relapse in the brain for patients with adenocarcinoma. A retrospective case series [6] of 177 resected patients with stage IIIA (of whom most had preoperative radiotherapy) showed a 3-year brain metastasis-free survival of 56% in non-squamous pathology versus 68% in patients with SCC. The 3-year rate in our study was 73% for adenocarcinoma compared with 95% for SCC. The difference observed may be due to the higher stage in the surgical cohort [8]. In a study

Table 1
Baseline demographics of the study population

Patients with relapse	Adenocarcinoma	Squamous	P value
Number	195	292	
Gender; % male	45%	66%	$P < 0.00001$
Average age (\pm standard deviation)	70 years (± 10)	70 years (± 9)	$P = 0.8$
Year of treatment			$P = 0.18$
2004	1 (1%)	6 (2%)	
2005	8 (4%)	11 (4%)	
2006	5 (3%)	7 (2%)	
2007	4 (2%)	19 (7%)	
2008	7 (4%)	17 (6%)	
2009	5 (3%)	14 (5%)	
2010	16 (8%)	21 (7%)	
2011	18 (9%)	25 (9%)	
2012	19 (10%)	37 (13%)	
2013	30 (15%)	40 (14%)	
2014	33 (17%)	35 (12%)	
2015	29 (15%)	44 (15%)	
2016	20 (10%)	16 (5%)	
ECOG PS			$P = 0.37$
0	31 (16%)	48 (16%)	
1	99 (51%)	135 (46%)	
2	52 (27%)	82 (28%)	
3	9 (5%)	11 (4%)	
x	4 (2%)	16 (5%)	
% PET/CT staged	95%	95%	$P = NS$
Disease stage			$P = 0.02$
I	76 (37%)	84 (28%)	
II	24 (12%)	44 (15%)	
IIIA	78 (38%)	121 (41%)	
IIIB	15 (7%)	41 (14%)	
IV (separate primary)	9 (4%)	4 (1%)	
x	1 (0.5%)	1 (0.5%)	
Treatment paradigm			$P = 0.01$
Radiotherapy alone	100 (51%)	165 (57%)	
SABR	30 (15%)	18 (6%)	
Sequential chemoradiation	46 (24%)	86 (29%)	
CRT	19 (10%)	23 (8%)	
Treatment access			
% stage I receiving SABR	38%	17%	$P = 0.002$
% stage III receiving CRT	16%	13%	$P = 0.58$
4DCT planning	107 (55%)	129 (44%)	$P = 0.005$
Cone-beam IGRT	91 (47%)	106 (36%)	$P = 0.005$
Average dose (EQD2, α/β 10)	64 Gy	62 Gy	$P = 0.003$

4DCT, four-dimensional computed tomography; CRT, concurrent chemoradiation; ECOG PS, Eastern Cooperative Oncology Group performance status; EQD2, equivalent dose in 2 Gy fractions; IGRT, image-guided radiotherapy; PET/CT, positron emission tomography/computed tomography; SABR, stereotactic ablative radiotherapy.

of 455 patients treated with primary radiotherapy, 3.7% developed symptomatic brain metastases within 6 months [20]. This is less than in the current study, but only 18% were classified as adenocarcinoma. Trials of prophylactic cranial

irradiation have shown a reduction in brain metastases in NSCLC patients, but without an improvement in overall survival [21] and a decline in neurocognitive function [22]. Hippocampal sparing may reduce the toxicity from

Table 2
Dose fractionations received

Treatment paradigm	Concurrent	Sequential	Radiotherapy alone	SABR	
20 fractions	65%	59%	88%	3 fractions	4%
2 Gy fractions	35%	40%	11%	5 fractions	56%
Alternative fractions	1%	1%	1%	8 + fractions	42%

SABR, stereotactic ablative radiotherapy.

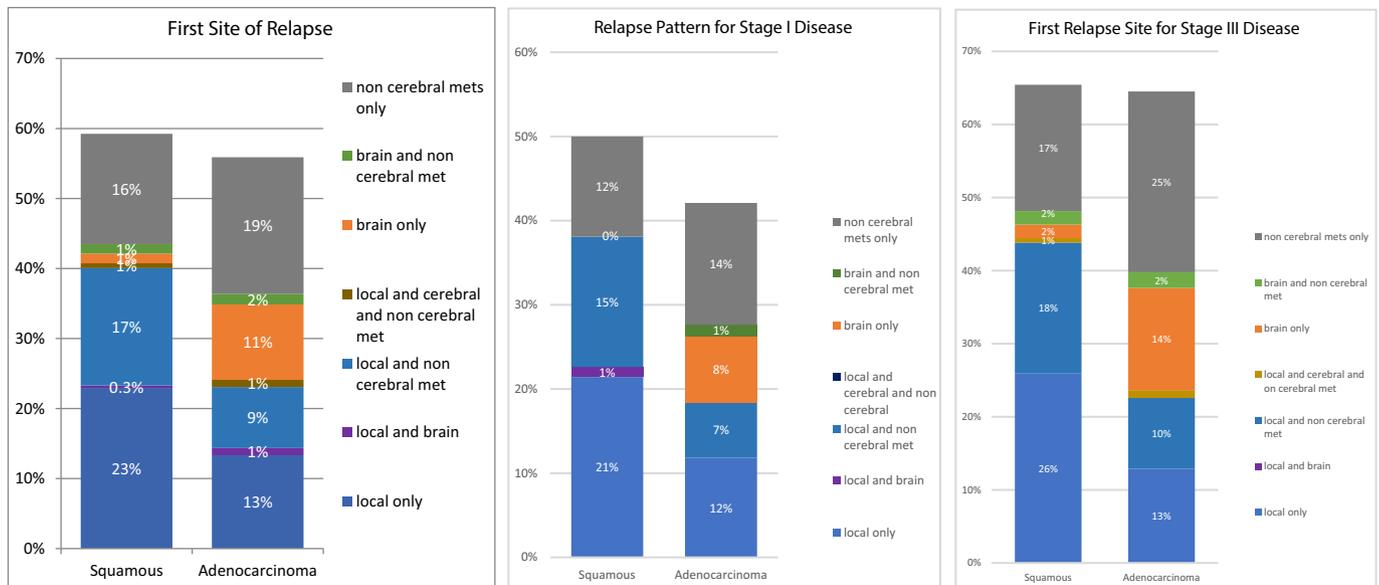


Fig 2. First site of relapse by pathological subtype and stage.

prophylactic cranial irradiation and provide a better therapeutic index [23].

We have shown a higher rate of local relapse among patients with SCC. A study of local control after stereotactic lung radiotherapy showed a higher local relapse rate in SCC compared with adenocarcinoma [9]. This study examined 740 patients with early stage NSCLC treated with SABR and showed a 3-year local failure rate of 19% in SCC compared with 9% in adenocarcinoma. The current study aligns with this finding in patients treated with a wider range of stages and treatments, including conventional and SABR fractionations.

Two studies comparing hyperfractionated accelerated radiotherapy showed less improvement in local control in patients with non-squamous compared with SCC [24,25]. A study of 13 306 patients treated in the USA [26] found that patients with SCC treated with SABR derived more benefit in survival compared with patients with adenocarcinoma and concluded that this may be due to a difference in metastatic potential between the two histological subtypes. More aggressive local therapy may be more effective in SCC, given its propensity to relapse locally.

Recent attempts to build risk prediction tools for local and distant failure for patients with locally advanced NSCLC incorporated histopathology [27]. The authors of this competing risks analysis retrospectively reviewed 251 patients and found similar patterns of relapse in adenocarcinoma (more distant) and SCC (more local) as identified in the presented study. These tools await external validation.

In addition, our study found a difference in the pattern of local relapse between adenocarcinoma and SCC, with more adenocarcinoma relapsing in out-of-field lymph nodes. Several surgical studies [28,29] of PET/CT-staged patients found that those with adenocarcinoma had a higher rate of occult lymph nodes not detected on preoperative imaging. Whereas modern radiotherapy trials omit elective nodal

irradiation of uninvolved lymph node stations with a low rate of failure in these stations [30], retrospective surgical series of occult lymph nodes recommend caution [31]. High incidental nodal irradiation may go some way to account for this and may obscure differences between adenocarcinoma and SCC [32]. Further investigation in prospective studies would be of benefit. Although there is variation in the follow-up strategies proposed by agencies for NSCLC [33,34], there is no differentiation between adenocarcinoma and SCC. Close follow-up has been advocated for patients in whom salvage therapy may affect overall survival [35], with a recognition that there is increasing availability of salvage therapy [36]. The higher rate of cerebral relapse among patients with adenocarcinoma may warrant a lower threshold for cerebral follow-up scans.

With the rising eminence of aggressive local therapy of oligometastatic disease, early detection of relapse has increasing importance [37]. Increased access to SABR has enabled clinicians to offer radical doses of radiotherapy in the non-curative setting to provide sustained disease control across tumour sites, including NSCLC [38]. In order to optimise available resources for delivery of this novel treatment paradigm, it would be prudent that stratification is applied to follow-up for lung cancer patients using available prognostic biomarkers for relapse.

Our study had a number of potential weaknesses. Histopathological classification was based on the histopathologist's morphological and immunohistochemical report at the time of diagnosis and cell blocks were not reviewed as part of this study, meaning variation in pathology reporting techniques and standards observed during the study period are not accounted for in this analysis. Furthermore, routine computed tomography scans were not used in the follow-up. However, patients suspected of relapse by clinical assessment and routine CXR had further tests organised, which led to 96% having computed tomography or PET/CT.

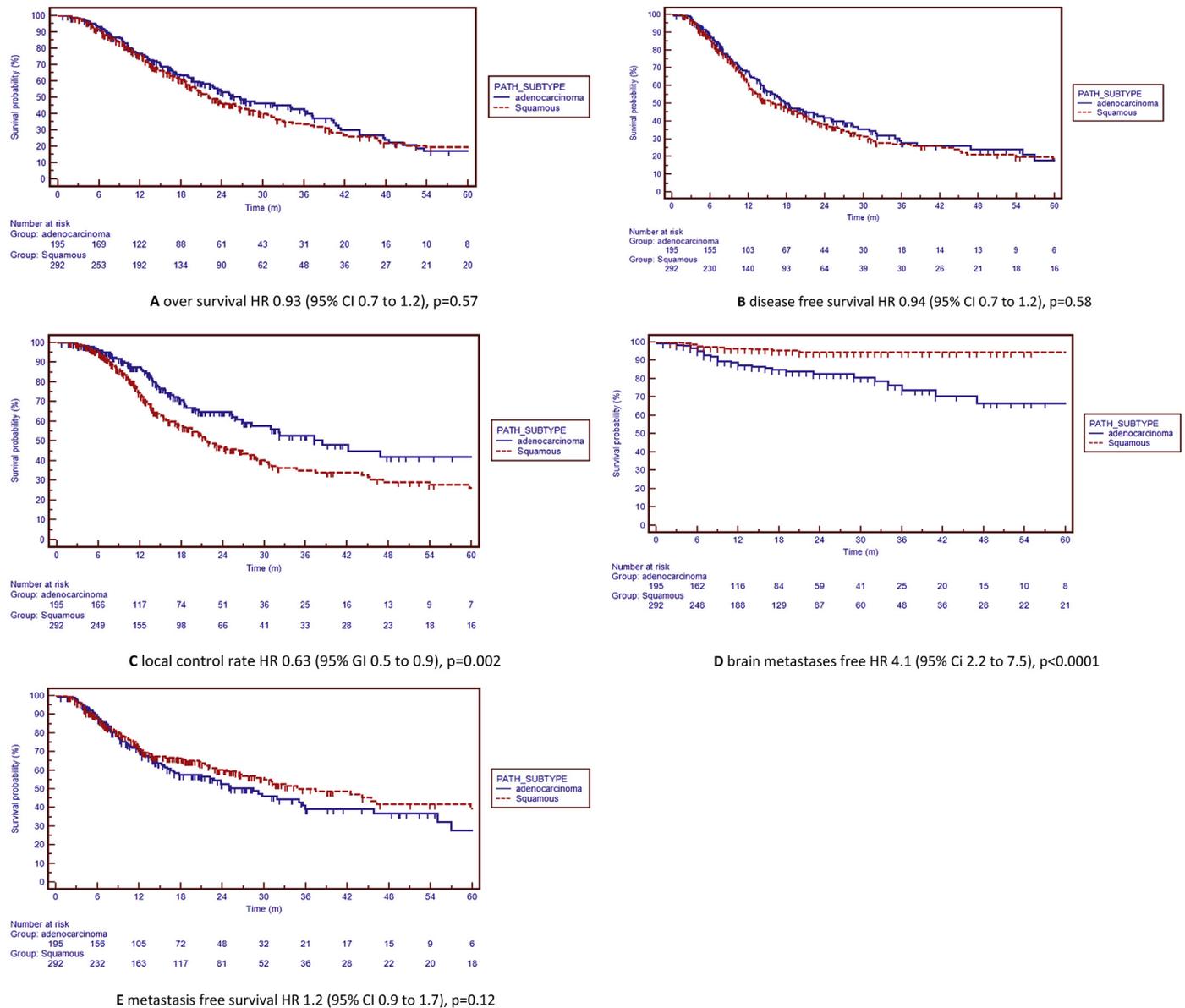


Fig 3. Actuarial survival curves by histological subtype.

Fibrosis within the radiotherapy field can make it difficult to determine local relapse [39]. A combination of computed tomography and PET/CT features has been used to determine relapse. In a review of 1390 patients, local failure was associated with overall survival, defined as enlargement of greater than 25%, the development of severe tumour-related complications such as post-obstructive pneumonia or haemoptysis not attributable to radiotherapy toxicity or intercurrent disease, the appearance of a new lesion within the radiotherapy field or biopsy-proven recurrence [36]. A review of 26 studies investigated how to determine local relapse after SABR [40]. Computed tomography features associated with relapse were enlargement of at least 20%, bulging margin, disappearance of air bronchograms, linear margin disappearance, lymph node enlargement or

ipsilateral effusion. PET/CT showing an $SUV_{max} > 5$, or greater than pre-treatment, were also associated with local failure.

In our study, we used increasing primary tumour size, biopsy confirmation and PET/CT scan features to determine relapse. It is possible that cerebral relapses may have been missed because brain imaging was only requested if there were worrying symptoms; overall 21% of patients had a brain scan. The median survival after local failure was 6.7 months and it might be expected that occult cerebral disease may have become symptomatic in that time frame, precipitating a scan and diagnosis. Although local relapses may be difficult to distinguish from radiotherapy fibrosis, we have used recognised criteria to determine local failure [16].

Table 3
Univariate and multivariate analysis of local control

Univariate analysis of local control			
Factor	P value	Hazard ratio	95% confidence interval
Gender	0.2	1.2	0.9–1.6
Age	0.03	0.98	0.97–1.0
PET/CT staging	0.36	0.77	0.44–1.34
Disease stage	0.0001	1.37	1.17–1.61
No. pathological lymph nodes	0.012	1.18	1.04–1.34
Pathological subtype	0.0029	0.64	0.47–0.86
Performance status	0.62	0.95	0.80–1.14
Chemotherapy given	<0.0001	1.9	1.39–2.53
Year of treatment	0.19	1.03	0.99–1.09
EQD2 (dose)	0.0035	0.98	0.96–0.99
Respiratory motion	0.11	0.91	0.82–1.02
IGRT	0.08	0.77	0.57–1.03
Multivariate analysis			
Age			0.64
Disease stage			0.25
Chemotherapy given			0.25
Pathological subtype			0.005
EQD2 (dose)			0.02
No. pathological lymph nodes			0.82

EQD2, equivalent dose in 2 Gy fractions; IGRT, image-guided radiotherapy; PET/CT, positron emission tomography/computed tomography.

Table 4
Univariate and multivariate analysis of brain metastasis-free survival

Factor	P value	Hazard ratio	95% confidence interval
Univariate analysis of brain metastasis-free survival			
Gender	0.08	0.58	0.32–1.07
Age	0.0001	0.95	0.92–0.97
PET/CT staging	0.08	0.43	0.18–1.02
Stage	0.0015	1.75	1.20–2.50
No. pathological lymph nodes	0.0014	1.53	1.20–1.95
Pathological subtype	<0.0001	4.5	2.34–8.7
Performance status	0.25	0.8	0.56–1.17
Chemotherapy given	0.005	2.5	1.30–4.81
Year of treatment	0.13	1.08	0.98–1.20
EQD2 (dose)	0.59	0.99	0.96–1.02
Respiratory motion	0.91	1.01	0.80–1.27
IGRT	0.23	1.45	0.80–2.64
Multivariate analysis of brain metastasis-free survival			
Age	0.35		
Stage	0.17		
No. pathological lymph nodes	0.21		
Chemotherapy given	0.91		
Pathological subtype	0.0007		

EQD2, equivalent dose in 2 Gy fractions; IGRT, image-guided radiotherapy; PET/CT, positron emission tomography/computed tomography.

Conclusions

We have confirmed a higher rate of cerebral relapse in patients with adenocarcinoma. We have shown a higher rate of local relapse in patients with SCC. The type of local relapse also differed, with the adenocarcinoma group having more out-of-field locoregional relapses in lymph nodes.

This supports the evidence that these subtypes are clinically distinct. This should be taken into account in radiotherapy clinical trial design and follow-up policies.

Conflict of Interest

The authors report no conflicts of interest.

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