Highlights

- Unclear if tissue diagnosis in poor PS lung cancer patients alters outcomes
- Tissue diagnosis did not affect treatment or survival in most PS 3 or 4 patients
- Those receiving treatment requiring tissue diagnosis had improved survival
- Aids decision whether to pursue tissue in PS 3 or 4 patients.

ORIGINAL ARTICLE

Main title: Obtaining tissue diagnosis in lung cancer patients with poor performance status and its influence on treatment and survival

Running head: Tissue diagnosis in lung cancer with poor PS

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Figures 2

MicroAbstract

Currently there is controversy surrounding whether a tissue diagnosis in patients with lung cancer and poor performance status (PS) affects subsequent management and survival. The findings from this study suggest that the majority of patients with PS 3 or 4 undergo a diagnostic procedure which does not affect further treatment or affect survival. However, those poor PS patients who do have treatment requiring tissue diagnosis have improved survival, the majority of whom have small cell lung cancer.

Abstract

Introduction

25% of patients with lung cancer have performance status 3 or 4. A pragmatic approach to investigative procedures is often adopted based on the risks and benefits in these patients and whether tissue diagnosis is necessary for anticipated future treatment. This cohort study investigated factors influencing a clinician's decision to pursue a tissue diagnosis in patients with lung cancer and performance status 3 and 4 and to examine the association of tissue diagnosis with subsequent management and survival.

Methods

All patients with lung cancer diagnosed in North Glasgow from 2009 to 2012 were prospectively recorded in a registry. We investigated the relationships between achieving a tissue diagnosis, treatment and survival.

Results

Of 2493 patients diagnosed with lung cancer, 490 patients (20%) were PS 3 and 122 patients (5%) were PS 4. Tissue diagnosis was attempted in 60% and 35% patients with PS 3 and PS 4 respectively. Younger age, better performance status and having stage 4 disease were independently associated with a diagnostic procedure being performed.

Only 5% of patients with poor performance status received treatment conventionally requiring a tissue diagnosis. Age, stage and performance status were independent predictors of mortality. Achieving a tissue diagnosis was not associated with

mortality. Receiving treatment requiring tissue diagnosis is associated with survival benefit.

Conclusions

The majority of patients with poor fitness undergo a diagnostic procedure which does not influence further treatment or affect survival. However, the cohort of patients who do undergo therapy determined by tissue diagnosis have improved survival.

1. Introduction

Lung cancer is still the most common cause of cancer death in the UK,(1) and whilst the overall age-standardised incidence of lung cancer in the UK is slowly decreasing,(2) the age-standardised incidence of lung cancer in women over the age of 75 is increasing. Patients over 75 accounted for around half of all patients diagnosed with lung cancer in 2009 to 2011, and with the elderly population continuing to grow due to improved life expectancy, this pattern is likely to continue.(3)

The diagnosis and management of lung cancer in elderly and less physically fit patients is particularly challenging. Procedures that are considered safe and minimally invasive in well individuals are often less well tolerated and may have increased potential risks in patients with poor performance status. In addition, complex comorbidities affect treatment decisions (4) along with a lack of clear evidence for benefit versus risk of palliative therapies, such as chemotherapy, in this population.

In general, tissue confirmation is usually required for radical treatment (surgery or radical radiotherapy) and is mandatory for chemotherapy including targeted therapy, and immunotherapy. The NICE guidelines published in 2011 suggest aiming for histological confirmation in 80% of patients.(5) National Lung Cancer Standards published by NHS Quality Improvement Scotland in 2008 include a minimal standard rate of histological confirmation of 75%.(6) These targets were set for all patients, irrespective of fitness. The National Lung Cancer Audit (NLCA) presented the national figures for tissue diagnosis in the UK in 2013. The median tissue diagnosis rate was 75%.(7) Indeed, in patients with PS 0 or 1 or younger patients with PS 2

there may be a survival advantage in confirming tissue diagnosis.(8) Tissue diagnosis is also required for newer and potentially less toxic treatments such as EGFR TKIs, ALK inhibitors and immunotherapy, but at present these treatments are only suitable for a small minority of patients.

In the NLCA cohort between 2004 and 2010, median tissue diagnosis rates for patients with performance status 3 and 4 was 55% and 40% respectively.(8) This implies that clinicians deemed that a pragmatic approach was appropriate in those patients where tissue diagnosis was not performed: either they were not fit to undergo a diagnostic procedure, that obtaining a tissue diagnosis would have no significant bearing on the future management of the individual or that the radiological findings were sufficient to make a diagnosis. Alternatively, the patient may elect not to have a diagnostic procedure.

The aims of this study were to investigate factors that influence a clinician's decision to pursue a tissue diagnosis in patients with lung cancer presenting with performance status 3 and 4 and to examine the relationship of tissue diagnosis on subsequent management and survival.

2. Methods

2.1 *Data collection*

Data for all patients diagnosed with lung cancer in North Glasgow between January 2009 and December 2012 were collected prospectively at multidisciplinary team (MDT) meetings across 3 sites (Gartnavel General Hospital, Glasgow Royal Infirmary and Stobhill Hospital) and collated to examine lung cancer demographics for the National Lung Cancer Audit and Information Service Division Scotland. This database has approval from the West of Scotland Regional Ethics Committee. The three hospitals serve a local population for the Northern half of the NHS Greater Glasgow and Clyde Health Board which comprises approximately 600,000 patients.

Patient characteristics collected for the MDT included age, sex, tissue diagnosis, investigations, performance status (PS, World Health organisation classification), stage of cancer (I to IV consistent with the International Association for the Study of Lung Cancer 7th edition) and treatment. Date of diagnosis was the MDT meeting date, which is conducted on a weekly basis for all incident lung cancers that week. Time to survival was measured from the date of diagnosis to date of all-cause mortality. In general, performance status was assessed by the clinician reviewing the patient prior to the MDT. Patients were allocated a deprivation quintile as a marker for socio-economic status according to the Scottish Index of Multiple Deprivation (SIMD), which was identified based on the patient's full postcode.(9) The SIMD combines 38 indicators across 7 domains which are income, employment, health, education, skills and training, housing, geographic access and crime.

2.2 *Statistical analysis*

Summary statistics were described as number of subjects and percentages for all categorical variables. Logistic regression analyses were performed to estimate the odds ratio and 95% confidence intervals (95%CI) for factors related to having a tissue diagnosis. Cox Proportional hazards regression was performed to estimate hazard ratios and 95%CI for factors associated with all-cause mortality. For both logistic regression and cox regression, initial univariate analysis was performed using relevant variables and those with an association yielding a p-value of less than 0.1 were put into the final models. SPSS version 22.0 was used for analysis and the graphs generated using GraphPad Prism 6.0.

3. Results

There were 2493 patients diagnosed with lung cancer between 2009 and 2012. The mean age was 71 with an even gender split (male sex 49%; Table 1). The majority of patients had stage 3B or 4 lung cancer at diagnosis (64%). The median follow up period was 43 months (minimum 17, maximum 70) and 98% of patients were followed up to death or 2 years.

Performance status was documented in 93% of patients. Pathological tissue diagnosis was confirmed in 96% of PS 0 and 1 patients and 80% in PS 2. There were 490 patients (20%) with PS 3 and 122 patients (5%) with PS 4 (Table 2). These less fit patients were older (all patients mean age 71; PS 3 and 4 mean age 76) and had a female preponderance (all patient male sex 49%; PS 3 and 4 45%). Tissue diagnosis was attempted in 60% and 35% and was successful in 50% and 27% of patients with PS 3 and PS 4 respectively. 62% of PS3 and 83% of PS4 patients had stage 4 lung cancer. 9% of PS3 and 7% of PS 4 patients had more than one procedure.

Logistic regression was performed to assess whether specific patient characteristics influenced clinicians' decisions regarding attempting tissue diagnosis (Table 3). As expected, younger age and better performance status were independently associated with a diagnostic procedure being performed. Additionally, patients with either stage 1 or stage 4 disease were more likely to undergo a diagnostic procedure than those with stage 2 or 3.

Subsequent treatment of lung cancer is shown in Table 2 and Figure 1. 8 (2%) patients of performance status 3 underwent radical radiotherapy, 25 (5%) had chemotherapy,

118 (24%) had palliative radiotherapy, 339 (69%) had best supportive care. Thus, only 7% of patients with PS3 received treatment that conventionally requires a tissue diagnosis. No patients of performance status 4 underwent radical radiotherapy or chemotherapy, 6 (5%) had palliative radiotherapy and 116 (95%) had best supportive care.

As anticipated, age, performance status and stage were independent predictors of mortality (Table 4). Although having a tissue diagnosis was not was associated with improved survival (hazard ratio 1.08 [95% CI 0.91-1.26], p=0.38; Table 4, Figure 2A) receiving treatment requiring a tissue diagnosis was (HR 0.63 [95% CI 0.44-0.92], p=0.01; median 86 days vs 38 days; Figure 2B). The majority of these patients had small cell lung cancer (Table 5).

4. Discussion

Almost all randomised controlled trials evaluating therapy in patients with lung cancer recruit patients of good performance status (PS).(10) However, a significant minority of patients in clinical practice are of PS 3 and 4. In the UK Lung Cancer audit between 2004 and 2010, patients of PS 3 and 4 accounted for 24% of patients at presentation with lung cancer, where PS was recorded.(8)

In a cohort of patients with a poor PS, we have looked at which patients undergo a diagnostic procedure and its influence on treatment and mortality. In our large cohort, 25% of patients had poor PS. 60% and 35% of patients with PS 3 and 4 underwent a diagnostic procedure respectively. We found that younger age and better performance status were independently associated with the performance of a diagnostic procedure, but not sex or socio-economic status. In a study of patients diagnosed with lung cancer in England and Wales from 2004 to 2010, younger age, better performance status, stage, comorbidity and deprivation all affected pathological confirmation.(8) Interestingly, stage 1 and stage 4 patients were more likely to have a diagnostic procedure than those with stage 2 and 3 at presentation. It is likely that that those with early stage lung cancer are more likely to have a diagnostic procedure as an alternative diagnosis is more likely than in those with more advanced disease. Furthermore, these patients are more likely to be eligible for radical treatment. Those with stage 4 cancer are more likely to have a diagnostic procedure as their extent of disease will make tissue diagnosis easier.

The recommendations of the 2011 NICE guideline development group and the 2008 Healthcare Improvement Scotland National Lung Cancer Standards were that trusts increase their tissue diagnosis rates towards the national average of 75% for all patients, irrespective of general fitness. It is clear that this will differ depending on PS. It may be more appropriate to suggest the tissue diagnosis rates are higher than 90% in patients with PS 0 to 2. This would leave clinicians free to make pragmatic decisions on whether to perform invasive, unpleasant and potentially hazardous tests depending on the need to confirm the diagnosis or direct treatment. Traditionally respiratory physicians perform the tests necessary to confirm diagnosis in patients with lung cancer, prior to review by the oncologists who then decide on fitness for treatment after a multidisciplinary meeting. A change in this approach might be required to assess fitness for treatment requiring a tissue diagnosis prior to performing any diagnostic test.

There are a number of reasons for choosing to obtain a tissue diagnosis in patients with lung cancer. Firstly it is used to confirm the diagnosis. However, two-thirds of patients of poor performance status have radiologically confirmed stage 4 lung cancer and thus pathological confirmation is less likely to be essential to secure a diagnosis. In some patients, tissue diagnosis is obtained as part of a therapeutic procedure to improve symptoms, such as aspiration of a pleural effusion. Pleural aspiration is less invasive than bronchoscopy or lung biopsy. The higher proportional rate of pleural aspirate as a diagnostic procedure in our PS 3 and 4 patients may reflect this (Table 2).

An alternative reason for performing a diagnostic procedure is to direct therapy. Historically, patients with PS 3 and 4 would not be considered for systemic treatment. The risks of side effects and toxicity were thought to outweigh the benefits. However, there is evidence that palliative chemotherapy in patients with Karnofsky PS 60-70 (equivalent to WHO PS 2 or 3) may derive symptomatic benefit, even without improving survival.(13) In addition, new, molecular directed therapies such as tyrosine kinase inhibitors (TKIs) and ALK inhibitors are better tolerated than standard chemotherapy regimens and have been shown in Japan to improve survival even in unfit patients.(14) Indeed, performance status is influenced by cancer as well as age and comorbidity. Acute decline in performance status due to cancer activity may be improved with systemic therapy, although there is limited evidence that chemotherapy in patients of PS3 and 4 is beneficial. A previous reported series in small cell lung cancer show very poor survival even with systemic therapy.(15) In this study, 27% of patients with PS 4 had a tissue diagnosis. However, none of these patients received treatment that required confirmation of tissue type ie radical radiotherapy or chemotherapy. Furthermore, their median survival was 12 days.

Despite 50% of PS3 patients having tissue diagnosis confirmed, in only 13% of these patients did this influence further treatment. Overall, there was no difference in mortality between patients with and without a tissue diagnosis, even after adjusting for other factors which may affect survival including age and stage. However, receiving treatment requiring tissue confirmation was independently associated with survival, independent of age and stage. This subset was younger, had a female predominance and more likely to have a diagnosis of small cell lung cancer. These findings back up the traditional opinion that patients should undergo a diagnostic

procedure as the pathology may confirm small cell lung cancer which is more likely to have a favourable response to chemotherapy. This is likely to extend to non-small cell lung cancers that are EGFR or ALK positive and thus amenable to TKIs and ALK inhibitors that are better tolerated with a lesser side-effect profile, but at present this only represents a small minority of patients.

We recognise that rates of treatment with chemotherapy in patients with PS 3 and 4 vary between centres, and this may be higher in some specialist centres treating highly selected patients in comparison to our unselected cohort. All patients in this study were discussed at a MDT in the presence of three consultant lung cancer oncologists and, along with performance status, other factors such as co-morbidities, patient's wishes, expectation and deprivation level may have been relevant in the decision not to give systemic treatment.

5. Limitations

This cohort of patients is from the North Glasgow area. While a significant proportion of the patients are of lower socioeconomic status, there is a reasonable distribution. This distribution will be similar to many other industrial towns and cities with high prevalence of cigarette smoking and similar rates of lung cancer, and thus the findings are relevant and applicable to other areas of the UK and overseas.

It is possible that the patients who underwent treatment directed by their tissue diagnosis had been misclassified as PS3. While a useful measure of general fitness, this scale is subjective. Indeed in a study of 100 consecutive cancer patients from Denmark, overall there was only moderate agreement between three oncologists recording performance status (overall Kappa 0.55).(18) However, in our cohort, performance status is independently associated with mortality and thus likely to be accurate in the majority of cases.

6. Conclusion

Thus in this cohort, many patients of performance status 4 undergo a diagnostic procedure which does not influence further treatment or affect survival. However, some patients of performance status 3 received treatment determined by tissue diagnosis and this is associated with improved survival. Therefore, patients with performance status 3 who would be considered for chemotherapy, including biological or targeted therapy, should be offered a tissue diagnosis.

7. Clinical Practice Points

- It is currently not known whether a tissue diagnosis in patients with lung cancer and poor performance status (PS) affects subsequent management and survival.
- The majority of patients with PS 3 or 4 underwent a diagnostic procedure which did not affect further treatment or affect survival.
- However, those patients who did have treatment requiring tissue diagnosis had improved survival – the majority of these had small cell lung cancer.
- This manuscript will aid clinicians in making decisions regarding whether or not to obtain histological confirmation in the 25% of patients who are performance status 3 or 4.

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9. Tables

Table 1: Patient characteristics

	Entire cohort	Performance status 3		Performance status 4	
		Tissue diagnosis attempted	Tissue diagnosis not attempted	Tissue diagnosis attempted	Tissue diagnosis not attempted
N	2493	295 (60)	195 (40)	43 (35)	79 (65)
Male sex	1232 (49)	133 (45)	84 (43)	22 (51)	38 (48)
Mean age (SD)	71 (10)	73 (9)	79 (8)	74 (8)	78 (10)
Stage					
1	399 (16)	19 (7)	24 (12)	2 (3)	0
2	167 (7)	9 (3)	21 (11)	2 (3)	0
3	660 (26)	80 (27)	34 (17)	8 (10)	9 (21)
4	1266 (51)	187 (63)	116 (60)	67 (85)	34 (79)
Scottish Index of Multiple Deprivation					
Most deprived 1	1352 (54)	179 (61)	111 (57)	26 (61)	44 (55)
2	468 (19)	54 (18)	38 (20)	7 (16)	19 (24)
3	246 (10)	26 (9)	15 (8)	2 (5)	4 (5)
4	206 (8)	18 (6)	16 (8)	3 (7)	3 (4)
Least deprived 5	221 (9)	18 (6)	15 (8)	5 (12)	9 (11)

All data presented as n (%) except mean age (standard deviation)
* 1 patient not staged due concurrent pulmonary inflammatory disease process. SD: standard deviation.

Table 2: Survival, tissue typing and treatment

	All	Performance status 3	Performance status 4
n	2493	490	122
Dead	2195 (88)	481 (98)	122 (100)
Median survival (IQR), days	167 (45-460)	55 (22-153)	12 (3-36)
Tissue diagnosis attempted	2023 (81)	295 (60)	43 (35)
Tissue diagnosis achieved	1887 (76)	245 (50)	33 (27)
Number of procedures			
0	469 (19)	195 (40)	79 (65)
1	1608 (65)	250 (51)	34 (28)
2	346 (14)	39 (8)	6 (5)
3 or more	70 (3)	6 (1)	3 (2)
1st procedure			
Bronchoscopy	875 (35)	123 (25)	15 (12)
EBUS	386 (16)	43 (9)	4 (3)
CT biopsy	260 (10)	23 (5)	4 (3)
US biopsy node	186 (7)	24 (5)	1 (1)
Pleural aspirate	133 (5)	39 (8)	13 (11)
Tissue type			
NSCLC	1515 (61)	190 (39)	27 (21)
SCLC	371 (15)	55 (11)	7 (6)
Unknown	606 (24)	245 (50)	89 (73)
Treatment			
Any active treatment	1102 (67)	151 (31)	6 (5%
Surgery	287 (12)	0	0
Radical XRT +/- chemotherapy	252 (10)	8 (2)	0
Chemotherapy +/- Palliative XRT NSCLC	287 (12)	5 (1)	0
Chemotherapy +/- Palliative XRT SCLC	276 (11)	20 (4)	0
Palliative XRT	541 (22)	118 (24)	6 (5)
Best supportive care	827 (33)	339 (69)	116 (95)

All data presented as n (%) except median survival (interquartile range)

IQR: interquartile range; EBUS: endobronchial ultrasound; SCLC: small cell lung cancer; NSCLC: non small cell lung cancer; XRT: radiotherapy.

Table 3: Logistic regression of likelihood of attempting a tissue diagnosis in patients of performance status 3 and 4

	Odds ratio	95% confidence interval	p-value
Age	0.92	0.90-0.94	<0.001
Male sex	0.79	0.55-1.13	0.20
Performance status 4	0.31	0.20-0-49	<0.001
Stage*			<0.001
1	1		
2	0.54	0.28-1.04	0.06
3	0.26	0.11-0.59	0.001
4	1.79	1.14-2.80	0.01
Socioeconomic status**			0.99

*Reference category Stage 1
**Scottish index of multiple deprivation

Table 4: Cox regression of survival in patients of performance status 3 and 4

	Hazard ratio	95% confidence interval	p-value
Age	0.99	0.98-1.0	0.006
Male sex	1.17	0.98-1.37	0.07
Performance status 4	2.09	1.70-2.57	<0.001
Stage*			
1	1		
2	1.07	0.66-1.73	0.78
3	1.65	1.15-2.36	0.01
4	2.96	2.11-4.17	<0.001
Treatment needing tissue	0.63	0.44-0.92	0.01

Variables excluded from model on univariate testing: socioeconomic status and tissue diagnosis achieved
*Reference category Stage 1

Table 5: Comparison of patients who underwent treatment for lung cancer that required tissue diagnosis with those who did not have treatment requiring tissue diagnosis

	Had treatment requiring tissue	Did not have treatment requiring tissue
n	33	563
Male sex	26%	52%
Age	70	73
Stage		
1	5 (15)	40 (7)
2	1 (3)	31 (5)
3	8 (24)	123 (21)
4	19 (57)	385 (67)
Performance status		
3	7)	93)
4	0)	100)
Tissue type		
*No tissue diagnosis**	3 (9)	331 (57)
SCLC	9 (64)	41 (7)
NSCLC	21 (27)	207 36)
Median survival (IQR), days	75 (45-369)	39 (14-106)
Treatment		
Radical XRT	8 (24)	
Chemotherapy for SCLC	20 (61)	
Chemotherapy for NSCLC	5 (15)	

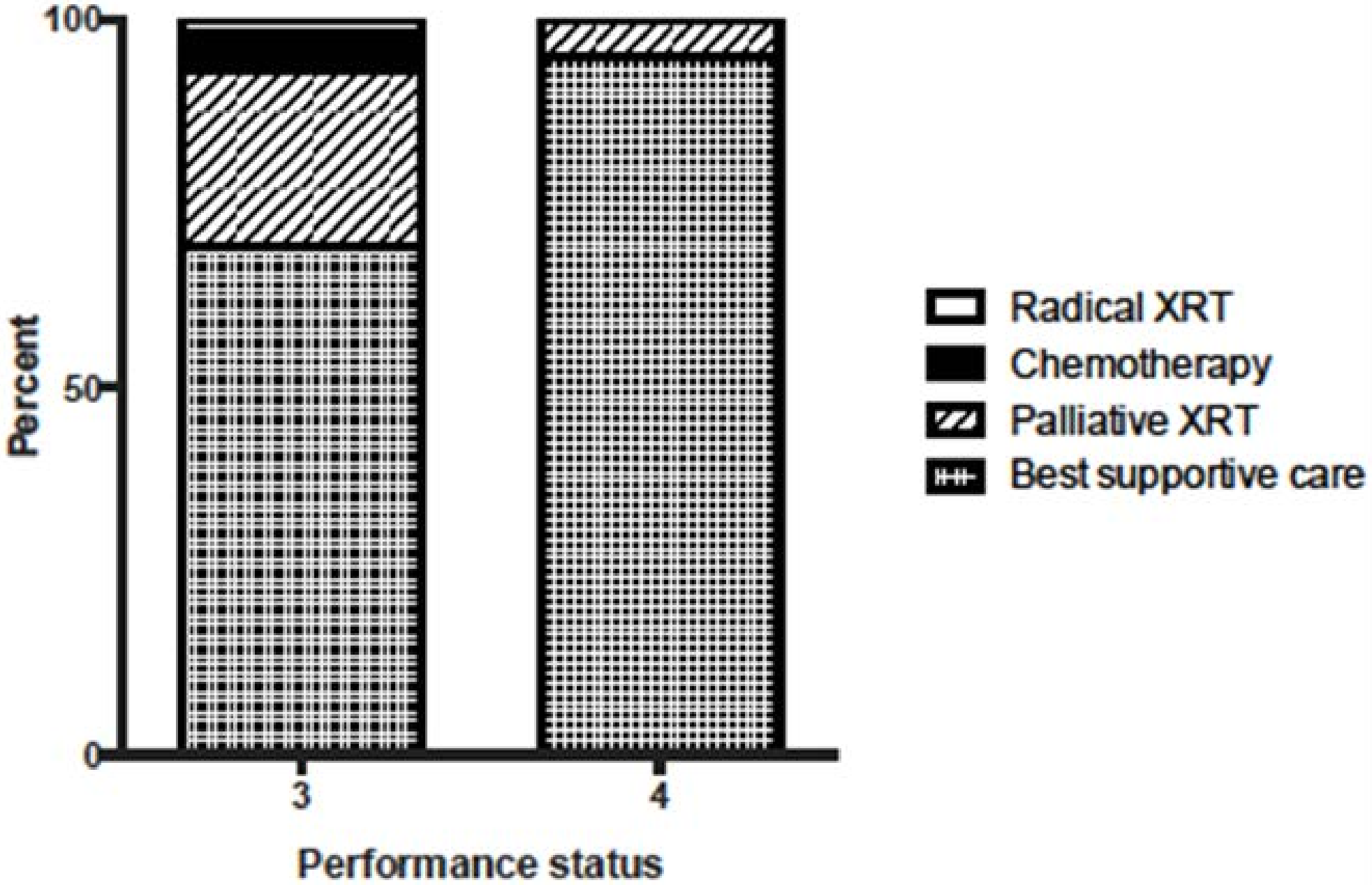
All data presented as n(%) except median survival (interquartile range)

*3 patients received radical radiotherapy based on radiological appearances alone.
SCLC: small cell lung cancer; NSCLC: non small cell lung cancer; XRT: radiotherapy.

10. Figure legends

Figure 1: Treatment administered in patients of poor performance status

Figure 2: Panel **A** Survival curves of patients with poor performance status by whether or not a tissue diagnosis was established Panel **B** Survival curves of patients with poor performance status in whom treatment requiring a tissue diagnosis was and was not administered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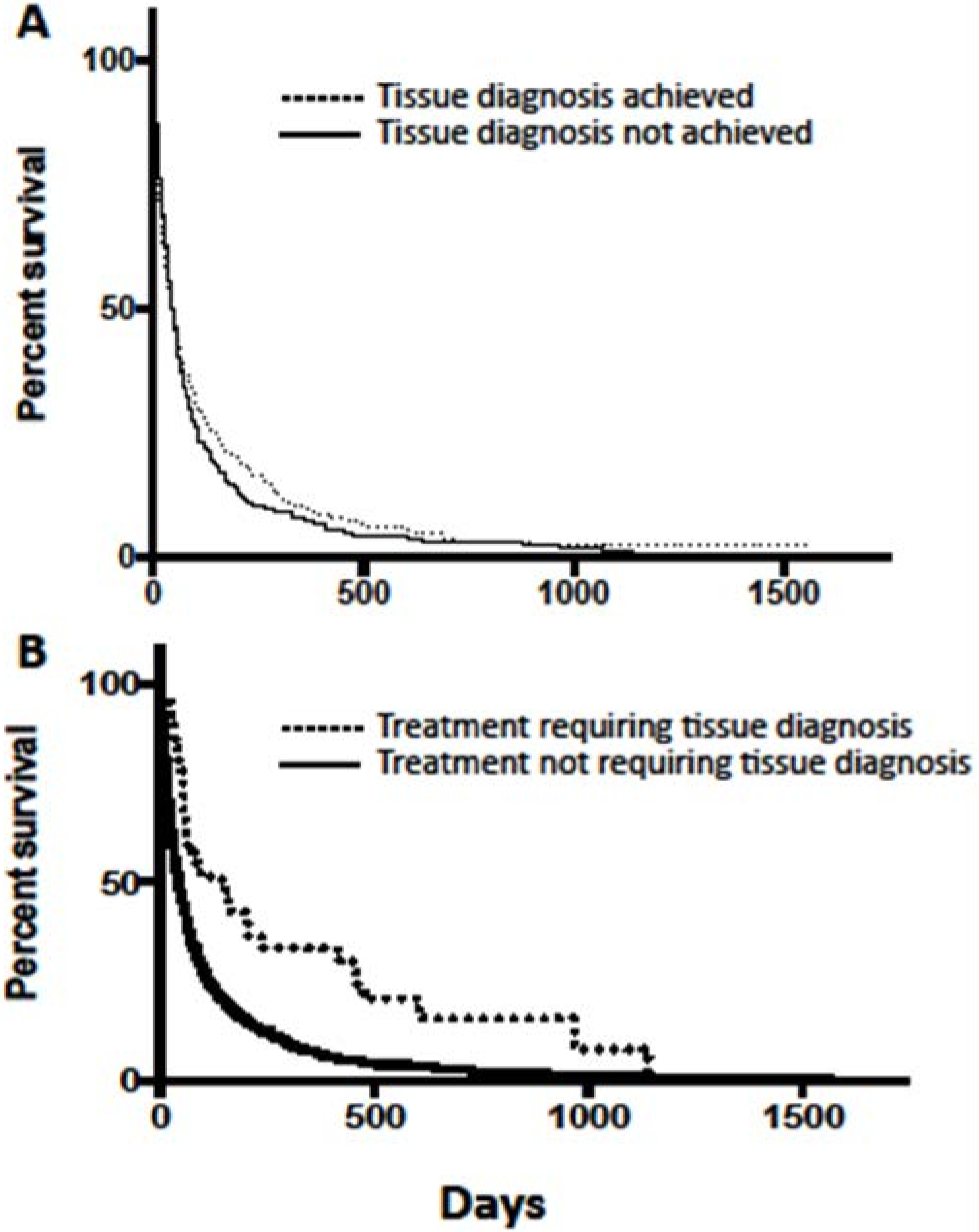
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