



Factors associated with survival in small cell lung cancer: an analysis of real-world national audit, chemotherapy and radiotherapy data

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Background: The mainstay of treatment for small cell lung cancer (SCLC) involves platinum doublet chemotherapy but the optimal duration, 4 *vs.* 6 cycles, is not known. Concurrent thoracic radiotherapy followed by prophylactic cranial irradiation (PCI) is recommended for fit individuals with limited stage. However, outside of clinical trials, the efficacy of sequential thoracic radiotherapy and PCI for extensive stage is uncertain.

Methods: This retrospective, observational, cohort study used English national lung cancer data to determine the factors associated with survival for all people diagnosed with SCLC. More precisely, for individuals who received chemotherapy, we examined survival by the chemotherapy duration, thoracic radiotherapy dose and the use of PCI.

Results: In total 6,438 people were diagnosed with SCLC. We identified that male sex (OR 0.7; 95% CI: 0.62–0.80), increasing age ($P=0.01$) greater comorbidity ($P\leq 0.01$), extensive stage (OR 0.21; 95% CI: 0.19–0.25) and worse performance status (PS2 *vs.* PS0 adjusted OR 0.38 95% CI: 0.31–0.48) were associated with reduced 1-year survival. Receipt of chemotherapy augmented survival. We analysed data for 1,761 people who had received chemotherapy. Thoracic radiotherapy (≥ 30 Gy for extensive stage and ≥ 40 Gy for limited stage) and PCI were independently associated with better survival ($P\leq 0.01$ for each), but 6 cycles of chemotherapy instead of 4 was not (limited stage adjusted OR 0.97; 95% CI: 0.48–1.97) extensive stage adjusted OR 1.34; 95% CI: 0.81–2.21).

Conclusions: Extending chemotherapy beyond 4 cycles to 6 does not augment survival. Appropriately prescribed thoracic radiotherapy and PCI can prolong survival in both limited and extensive stage SCLC.

Keywords: Lung neoplasms; small cell lung carcinoma; prognosis; cranial irradiation; platinum

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Introduction

The international consensus for treatment of small cell lung cancer (SCLC) involves platinum doublet

chemotherapy, however, the optimal duration of this (4 or 6 cycles) remains unclear, especially for extensive stage (ED-SCLC) (1-4). Thoracic radiotherapy is an adjunct

to chemotherapy and evidence suggests that a shorter time to chemo-radiation improves survival, especially for limited stage (LD-SCLC) (5,6). Indeed, for individuals with LD-SCLC and performance status (PS) 0-1, concurrent thoracic radiotherapy is recommended within the first 2 chemotherapy cycles. Sequential consolidative thoracic radiotherapy is recommended for patients that have shown response to chemotherapy who are unfit for concurrent irradiation or have ED-SCLC, but the evidence base outside of clinical trials is sparse. Prophylactic cranial irradiation (PCI) is reserved for people whose cancer has not progressed following first line treatment, however its efficacy in chemotherapy responders with ED-SCLC has been refuted by a recent phase III randomised control trial (7). This has prompted the National Institute for health and Care Excellence (NICE) to downgrade the recommendation from “offer” to “consider” (8). The aforementioned therapies are often confined to specialist cancer hospitals and hence there are likely to be geographical variations in their use (9).

Patients with ED-SCLC are often symptomatic at diagnosis. However, the side effects of treatment and the time spent in hospital may pose a significant burden which can lower the limited quality and quantity of life they have. Therefore, it is important that individuals are offered appropriate treatment with a realistic understanding of the survival gains. Hence, the objectives of this study were to: (I) Quantify the patient, treatment and hospital factors associated with 1-year survival in all people diagnosed with SCLC. (II) Determine whether 6 in comparison to 4 chemotherapy cycles, thoracic radiotherapy and PCI augment the odds of 1-year survival for individuals who receive chemotherapy. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/apm-20-1824>).

Methods

Study design

This study was a retrospective analysis of prospectively collected observational cohort data from individuals who were diagnosed with SCLC. The study was conducted in accordance with the declaration of Helsinki (as revised in 2013). We performed a statistical analysis of patient, tumour and treatment factors to assess their impact on 1-year survival in all people diagnosed with SCLC and a sub-analysis in those who received chemotherapy. The details of

this analysis are outlined below.

Study population

This was a retrospective cohort study that used English National Lung Cancer Audit (NLCA) data to identify people diagnosed with SCLC from 1st January 2015 to 21st September 2016 based on their histological code. We linked these data with Systemic Anti-Cancer Therapies (SACT), National RadioTherapy DataSet (RTDS) and Hospital Episode Statistics (HES) data. All were prospectively collected via clinical coding or electronic records/prescriptions. These data are held by Public health England, with whom we had a data-sharing agreement. The data are routinely collected National health service hospital data and consent is assumed unless the patient specifically withdraws this. The data are pseudonymised. Ethical approval was obtained from the NHS Health Research Authority (16/LO/0503).

One-year survival

Date of death was derived from the Office of National Statistics records. The most recent update to this record was 21st September 2017, therefore each patient had follow up for at least 1-year from their date of diagnosis. 1-year survival was defined as survival greater than or equal to 365 days from the date of diagnosis.

Therapies

An individual was defined as receiving chemotherapy if there was a record of administration within 6 months after SCLC diagnosis. If no date was present or it was beyond 6 months of diagnosis chemotherapy was classed as not given. The chemotherapy regimens were grouped according to the first chemotherapy drugs that were given except “other”. This consisted of drugs given in small quantities e.g., gemcitabine + cisplatin. Chemotherapy regimens that differed to the initial prescription were classed as a second-line treatment and not were analysed. Chemotherapy regimen was classed as “missing” if the administration date was present but drug details were not given. Prior to administering the first chemotherapy cycle the prescriber has to input the planned cycle duration. We used this information for the planned cycle duration. We used the consecutive dates recorded for when a patient received a chemotherapy dose to determine how many cycles of chemotherapy they actually received.

Radiotherapy was classed as given if an administration date was present after diagnosis. Thoracic radiotherapy was stratified by the maximal dose prescribed. For LS-SCLC this was “radical intent” (≥ 40 Gy) and “palliative” (< 40 Gy), whereas for ED-SCLC it was “consolidative” (≥ 40 Gy) and “palliative” (< 40 Gy). This dose threshold was chosen as it aligned with the Royal College of Radiologists recommendations (10). In addition, we conducted a sensitivity analysis with a dose threshold at ≥ 30 Gy for radical/consolidative intent. We did not examine whether radiotherapy was fractionated to once or twice daily. Prophylactic Cranial Irradiation (PCI) was defined as radiotherapy given to the skull or with prophylactic intent following chemotherapy at 20 or 25 Gy in 5 or 10 fractions for people with ED-SCLC and 25 Gy in 10 fractions for people with LD-SCLC.

Covariates

Socioeconomic status was calculated from postcode of residence (Townsend index of deprivation 1-least deprived to 5-most deprived). Performance Status (PS) was classed according to World Health Organisation criteria. A patient's pre-treatment Tumour Node Metastases (TNM) records were used to classify stage into limited and extensive, similar to Veteran Administration Lung Cancer Study Group (VALSG) criteria. ED-SCLC was any T or N with M1a/b spread (11). Stage was “missing” if TNM was not recorded. Charlson index of co-morbidities was categorised as 0, 1, 2–3 and ≥ 4 . It was calculated from previous diagnoses (excluding lung cancer) recorded at hospital admissions up to the date of SCLC diagnosis (12,13). Individuals with no prior admissions or comorbidities were assigned a score of 0. Any variables that had $> 50\%$ missing data were not included in our analysis, e.g., smoking status and forced expiratory volume in 1 second. These were assumed to be missing at random.

Statistical analysis

All analyses were completed using Stata V15 (Stat Corp, TX USA). We described the whole cohort of people diagnosed from 1st January 2015 to 21st September 2016 and performed univariate and multivariable logistic regression for the odds of 1-year survival. Our multivariable model for 1-year survival included factors that were *a priori* or significant on univariate testing ($P \leq 0.05$). These factors were age, sex, socioeconomic status, PS, stage, co-

morbidities and chemotherapy. This method reduces the effect of selection bias and confounding. We conducted a similar sub-analysis in the 2016 population that received chemotherapy as our radiotherapy data were limited to this time. The multivariable logistic regression model in this sub-analysis included receipt of radiotherapy, PCI and chemotherapy cycles in addition to the previously mentioned factors. We assessed the significance of each variable using the likelihood ratio test.

Results

Whole SCLC cohort

There were 6,438 people diagnosed with SCLC whose demographics are summarised in *Table 1*. Approximately 51.3% ($n=3,303$) were male and the median age was 70 years (IQR 63–76). The majority of individuals had ED-SCLC [$n=4,264$ (66.2%)]. We found that 1,860 (28.9%) people survived 1-year. For people with LD-SCLC 1-year survival was 53.8% ($n=1,068$) in contrast to ED-SCLC where this was 17.0% ($n=725$). A total of 1,578 (84.8%) people who survived 1-year received chemotherapy. Chemotherapy was mostly carboplatin + etoposide ($n=1,170$) or cisplatin + etoposide ($n=274$).

One-year survival

After adjusting for age, sex, socioeconomic status, PS, comorbidities, stage and chemotherapy the multivariable analysis showed significant differences in the odds of 1-year survival by patient factors (*Table 1*). Males were less likely to survive compared with females (males adjusted OR 0.70 95% CI: 0.62–0.80). Similarly, increasing age was associated with poorer survival (LR trend $P=0.01$). Individuals with worse PS were less likely to survive 1-year (PS 2 *vs.* PS 0 adjusted OR 0.38 95% CI: 0.31–0.48) as were people with more co-morbidities (Charlson index ≥ 4 *vs.* 0 adjusted OR 0.62 95% CI: 0.52–0.74). Individuals with ED-SCLC were less likely to survive 1-year in comparison to LD-SCLC (adjusted OR 0.21 95% CI: 0.19–0.25). There was significant variation in 1-year survival by receipt of chemotherapy. Individuals who did not receive chemotherapy were less likely to survive than those who were given carboplatin + etoposide (adjusted OR 0.28 95% CI: 0.24–0.33). In contrast, people receiving cisplatin + etoposide were more likely to survive (*vs.* carboplatin + etoposide adjusted OR 1.57 95% CI: 1.23–1.99) however,

Table 1 Features of patients diagnosed with SCLC and people that survived 1-year from diagnosis with odds ratios for 1-year survival

Factor	Total population		Survived one year		OR 1-year survival	95% CI	Adjusted OR* 1-year survival	95% CI	P value (LR test)
	n=6,438	%	N=1,860	%					
Sex									
Female	3,135	48.7	1,043	33.3	1		1		0.01
Male	3,303	51.3	817	24.7	0.66	0.59–0.73	0.70	0.62–0.80	
Age group									
<60	997	15.5	381	38.2	1.48	1.28–1.71	1.25	1.06–1.49	0.01 [¥]
60–79	4,527	70.3	1,335	29.5	1		1		
≥80	914	14.2	144	15.8	0.48	0.37–0.54	0.66	0.53–0.82	
Townsend Quintile									
Least deprived-1	806	12.5	243	30.2	1		1		
2	1,117	17.4	334	29.9	0.99	0.81–1.20	1.06	0.83–1.32	0.79
3	1,268	19.7	345	27.2	0.87	0.71–1.05	0.92	0.73–1.15	
4	1,516	23.6	444	29.3	0.96	0.80–1.16	0.92	0.74–1.14	
Most deprived-5	1,731	26.9	494	28.5	0.93	0.77–1.11	0.92	0.74–1.14	
Performance status									
0	869	13.5	442	50.9	1		1		<0.01
1	1,918	29.8	742	38.7	0.61	0.52–0.72	0.69	0.57–0.83	
2	1,286	20.0	274	21.3	0.26	0.22–0.32	0.38	0.31–0.48	
3	806	12.5	65	8.1	0.08	0.06–0.11	0.19	0.14–0.26	
4	234	3.6	3	1.3	0.01	0.00–0.04	0.04	0.01–0.14	
Missing	1,325	20.6	334	25.2	0.33	0.27–0.39	0.55	0.45–0.68	
Charlson comorbidity index									
0	1,822	28.3	659	36.2	1		1		<0.01
1	1,306	20.3	514	39.4	1.15	0.99–1.33	1.15	0.97–1.37	
2–3	1,227	19.1	340	27.7	0.68	0.58–0.79	0.76	0.63–0.92	
≥4	2,083	32.4	347	16.7	0.35	0.30–0.41	0.62	0.52–0.74	
Stage									
Limited	1,984	30.8	1,068	53.8	1		1		<0.01
Extensive	4,264	66.2	725	17.0	0.18	0.16–0.20	0.21	0.19–0.25	
Missing	190	3.0	67	35.3	0.47	0.34–0.64	0.60	0.42–0.85	
Chemotherapy									
Did not have chemotherapy	2,443	37.9	282	11.5	0.21	0.18–0.24	0.28	0.24–0.33	<0.01
Carboplatin + etoposide	3,040	47.2	1,170	38.5	1		1		
Cisplatin + etoposide	416	6.5	274	65.9	3.08	2.49–3.83	1.57	1.23–1.99	
CAV	24	0.4	3	12.5	0.23	0.07–0.77	0.26	0.07–0.86	
Other chemo	83	1.3	26	31.3	0.73	0.46–1.17	0.73	0.43–1.19	
Single platinum	273	4.2	45	16.5	0.32	0.23–0.44	0.42	0.30–0.61	
Missing drug name	159	2.5	60	37.7	0.97	0.70–1.35	0.86	0.55–1.15	

LR, likelihood ratio test. *Adjusted for all other variables in table; ¥, LR test trend.

PS, comorbidities and stage were confounders to this. Receipt of a single platinum drug conferred poorer survival (*vs.* carboplatin + etoposide adjusted OR 0.42 95% CI: 0.30–0.61). Socioeconomic status was not associated with survival ($P=0.79$).

Survival following receipt of chemotherapy

We identified 1,761 individuals who were diagnosed in 2016 and received chemotherapy. Of these, 695 (39.5%) survived 1-year. Survival varied considerably by stage, hence our results are presented by LD-SCLC and ED-SCLC separately (combined stage survival can be found in [Table S1](#)).

Limited stage

The 1-year survival for people with LD-SCLC who received chemotherapy was 60.7% ($n=381$). The following results are shown in [Table 2](#). After adjustment for patient, tumour, chemotherapy and radiotherapy 1-year survival was associated with PS (PS 3–4 *vs.* PS 0 adjusted OR 0.32 95% CI: 0.13–0.77). Individuals who were given cisplatin + etoposide were more likely to survive 1-year compared with carboplatin + etoposide (adjusted OR 2.09 95% CI: 1.17–3.74), but PS was a confounding factor. Receipt of radical radiotherapy was associated with better survival in comparison to not receiving radiotherapy (radical adjusted OR 3.32 95% CI: 2.07–5.31). This association remained, although less pronounced, when the radical threshold total radiotherapy dose was set to 30Gy (*vs.* nil radiotherapy adjusted OR 2.83 95% CI: 1.84–4.34, [Table S2](#)). PCI augmented the odds of 1-year survival (adjusted OR 2.42 95% CI: 1.33–4.39). There was no independent association between survival and age ($P=0.59$), sex ($P=0.07$), co-morbidity score ($P=0.32$) and the number of chemotherapy cycles administered ($P=0.53$). We conducted a sub analysis of the characteristics of the patients who received 4 *vs.* 6 chemotherapy cycles and have included these results in [Table S3](#). Both groups were evenly matched.

Extensive stage

Fewer people survived 1-year with ED-SCLC than LD-SCLC (26.2% $n=286$). The associated patient factors differed to LD-SCLC (shown in [Table 3](#)), in particular sex (male *vs.* female adjusted OR 0.53 95% CI: 0.39–0.73) and

co-morbidity (co-morbidity score ≥ 4 *vs.* 0 adjusted OR 0.64 95% CI: 0.43–0.94). PS was a significant prognostic factor ($P\leq 0.01$) whereas socioeconomic status ($P=0.16$) and age (P trend=0.30) were not. The odds of survival differed by the chemotherapy cycles received. Individuals receiving less than the planned amount of cycles (mean 3 cycles received) were less likely to survive 1-year (*vs.* 4 cycles adjusted OR 0.37 95% CI: 0.23–0.61). Similarly, people that received a planned amount of chemotherapy that was fewer than 4 cycles in length (mean 2 cycles) were less likely to survive (*vs.* 4 cycles adjusted OR 0.27 95% CI: 0.09–0.76). Six chemotherapy cycles did not augment survival in comparison to 4 (6 *vs.* 4 adjusted OR 1.34 95% CI: 0.81–2.21). We performed a sub analysis of both 4 and 6 chemotherapy cycle groups and these data can be seen in [Table S4](#). On the whole the groups were evenly balanced with the exception of PS (6 cycles PS0 21% *vs.* 4 cycles PS0 11%).

Receipt of PCI was associated with improved 1-year survival (received PCI adjusted OR 2.04 95% CI: 1.42–2.93). However, PCI was mostly offered to individuals who were younger [median age for PCI 64 years (IQR 59–70) *vs.* 69 years (62–75) no PCI] and had better PS (received PCI PS0 23% *vs.* no PCI PS0 16%). These results can be found in [Table S5](#). The median radiotherapy dose prescribed in ED-SCLC was 30Gy. A total radiotherapy dose of ≥ 40 Gy threshold both consolidative and palliative radiotherapy favoured survival but lacked statistical significance (consolidative ≥ 40 Gy *vs.* nil adjusted OR 1.88 95% CI: 0.91–3.87 and palliative *vs.* no radiotherapy adjusted OR 1.37 95% CI: 0.99–1.90). Reducing the threshold to ≥ 30 Gy resulted in consolidative radiotherapy being associated with improved survival and reduced the odds of survival with palliative radiotherapy (consolidative ≥ 30 Gy *vs.* nil adjusted OR 1.78 95% CI: 1.22–2.59, [Table 4](#)). In general, patients who received palliative radiotherapy <30 Gy were older [median age 68 years (IQR 62–74)] in comparison to those who received consolidative radiotherapy ≥ 30 Gy [65 years ≥ 30 Gy (IQR 60–72)]. In addition, there was a greater proportion of severe comorbidity and males in the group who received palliative radiotherapy (<30 Gy) (Charlson score $\geq 4.42\%$ palliative *vs.* 28% consolidative). [Table S6](#) is a table showing the patient demographics.

The chemotherapy regimen was not independently associated with survival ($P=0.12$). However, individuals that received single platinum therapy were less likely to survive 1-year (*vs.* carboplatin + etoposide adjusted OR 0.36 95%

Table 2 Features of patients with limited stage who received chemotherapy and survived 1 year with odds ratios for 1 year survival

Factor	Number surviving 1 year (n=381 from 628)	% who survived 1 year from all who received chemotherapy	OR 1-year survival	95% CI	*Adjusted OR 1-year survival	95% CI	P value (LR test)
Sex							
Female	220	65.1	1		1		0.07
Male	161	55.5	0.67	0.49–0.92	0.71	0.49–1.03	
Age group							
<60	78	73.6	1.92	1.20–3.08	1.20	0.69–2.09	0.59 [†]
60–79	271	59.2	1		1		
≥80	32	50.0	0.69	0.41–1.17	0.86	0.47–1.57	
Townsend quintile							
Least deprived-1	56	65.9	1		1		0.04
2	53	52.5	0.57	0.32–1.04	0.46	0.23–0.92	
3	74	61.7	0.83	0.47–1.49	1.03	0.53–2.00	
4	98	58.3	0.73	0.42–1.25	0.73	0.39–1.36	
Most deprived-5	100	64.9	0.96	0.55–1.67	1.10	0.57–2.10	
Performance status							
0	110	69.2	1		1		0.02
1	171	65.8	0.86	0.56–1.31	1.04	0.64–1.69	
2	63	48.8	0.43	0.26–0.69	0.63	0.36–1.11	
3–4	11	28.2	0.18	0.08–0.38	0.32	0.13–0.77	
Missing	26	63.4	0.77	0.38–1.58	1.00	0.44–2.27	
Charlson comorbidity index							
0	128	67.7	1		1		0.32
1	115	66.5	0.94	0.61–1.47	1.19	0.71–2.00	
2–3	86	52.8	0.53	0.35–0.82	0.75	0.45–1.24	
≥4	52	50.5	0.49	0.30–0.79	0.83	0.47–1.47	
Chemotherapy							
Carboplatin+ etoposide	254	57.0	1		1		0.01
Cisplatin + etoposide	107	82.3	3.52	2.16–5.73	2.09	1.17–3.74	
Other	8	72.7	2.02	0.53–7.70	3.64	0.84–15.66	
Single platinum	9	29.0	0.31	0.14–0.67	0.55	0.23–1.34	
Missing	3	30.0	0.32	0.08–1.27	0.43	0.08–2.27	

Table 2 (continued)

Table 2 (continued)

Factor	Number surviving 1 year (n=381 from 628)	% who survived 1 year from all who received chemotherapy	OR 1-year survival	95% CI	*Adjusted OR 1-year survival	95% CI	P value (LR test)
Chemotherapy cycles received							
More than planned (mean 4 cycles)	10	71.4	0.75	0.21–2.64	0.80	0.19–3.34	0.53
Less than planned (mean 3 cycles)	169	56.0	0.38	0.22–0.65	0.67	0.37–1.24	
4 planned and received	70	76.9	1		1		
6 planned and received	80	67.8	0.63	0.34–1.18	0.97	0.48–1.97	
Received planned amount that was fewer than 4 cycles (mean 2 cycles)	18	52.9	0.34	0.15–0.78	0.70	0.24–2.04	
Missing planned cycles	34	49.3	0.29	0.15–0.57	0.57	0.26–1.23	
Received radiotherapy							
Did not receive radiotherapy	119	44.2	1		1		<0.01
Radical (≥ 40 Gy)	197	81.4	5.52	3.69–8.26	3.32	2.07–5.31	
Palliative (<40 Gy)	65	55.6	1.58	1.02–2.44	1.53	0.94–2.49	
Received PCI							
No	261	53.4	1		1		<0.01
Yes	120	86.3	5.52	3.29–9.24	2.42	1.33–4.39	

^y, LR test for trend. *Adjusted OR for all other factors in table.

Table 3 Features of patients with extensive stage who received chemotherapy and survived 1 year with odds ratios for 1 year survival

Factor	Number surviving 1 year (n=286 from 1,091)	% who survived 1 year from all who received chemotherapy	OR 1-year survival	95% CI	*Adjusted OR 1-year survival	95% CI	P value (LR test)
Sex							
Female	166	31.4	1		1		<0.01
Male	120	21.4	0.59	0.45–0.78	0.53	0.39–0.73	
Age group							
<60	64	29.6	0.88	0.63–1.23	1.10	0.75–1.62	0.30 ^y
60–79	210	27.1	1		1		
≥ 80	12	12.1	0.33	0.17–0.64	0.59	0.28–1.26	
Townsend quintile							

Table 3 (continued)

Table 3 (continued)

Factor	Number surviving 1 year (n=286 from 1,091)	% who survived 1 year from all who received chemotherapy	OR 1-year survival	95% CI	*Adjusted OR 1-year survival	95% CI	P value (LR test)
Least deprived- 1	34	28.1	1		1		0.16
2	48	26.4	0.92	0.55–1.53	1.01	0.57–1.80	
3	65	27.2	0.96	0.59–1.56	0.98	0.57–1.70	
4	81	30.3	1.11	0.69–1.79	1.29	0.76–2.21	
Most deprived- 5	58	20.6	0.66	0.41–1.08	0.73	0.42–1.27	
Performance status							
0	82	42.7	1		1		<0.01
1	125	29.7	0.57	0.40–0.81	0.53	0.36–0.79	
2	51	18.4	0.30	0.20–0.46	0.32	0.20–0.51	
3–4	12	10.5	0.16	0.08–0.31	0.22	0.10–0.45	
Missing	16	18.4	0.30	0.16–0.56	0.29	0.14–0.57	
Charlson comorbidity index							
0	102	31.4	1		1		<0.01
1	72	38.9	1.39	0.96–2.03	1.76	1.14–2.70	
2–3	37	21.0	0.58	0.38–0.90	0.80	0.49–1.30	
≥4	75	18.5	0.50	0.35–0.70	0.64	0.43–0.94	
Chemotherapy							
Carboplatin+ etoposide	254	28.2	1		1		0.12
Cisplatin + etoposide	20	33.9	1.30	0.75–2.28	1.02	0.53–1.95	
Other	4	16.0	0.48	0.16–1.43	1.05	0.32–3.52	
Single platinum	5	5.3	0.14	0.06–0.35	0.36	0.14–0.92	
Missing	3	25.0	0.85	0.23–3.16	2.63	0.50–13.74	
Chemotherapy cycles received							
More than planned (mean 5 cycles)	6	37.5	1.06	0.36–3.14	1.19	0.36–3.88	<0.01
Less than planned (mean 3 cycles)	91	17.0	0.36	0.23–0.57	0.37	0.23–0.61	
4 planned and received	39	36.1	1		1		
6 planned and received	117	44.8	1.44	0.91–2.28	1.34	0.81–2.21	
Received planned amount that was fewer than 4 cycles (mean 2 cycles)	8	13.8	0.28	0.12–0.66	0.27	0.09–0.76	
Missing planned cycles	25	22.5	0.51	0.28–0.93	0.46	0.24–0.88	
Received radiotherapy							
Did not receive radiotherapy	142	20.8	1		1		0.07
Consolidative (≥40 Gy)	21	51.2	4.00	2.11–7.57	1.88	0.91–3.87	
Palliative (<40 Gy)	123	33.4	1.91	1.44–2.54	1.37	0.99–1.90	
Received PCI							
No	191	21.8	1		1		<0.01
Yes	95	44.6	2.90	2.12–3.96	2.04	1.42–2.93	

‡, LR test for trend; *Adjusted OR for all other factors in table.

Table 4 Sensitivity analysis of 1-year survival with different radiotherapy thresholds for extensive stage SCLC

Type of radiotherapy received	Number surviving 1 year	Proportion surviving 1 year from all who received chemotherapy	OR 1-year survival	95% CI	Adjusted OR 1-year survival	95% CI	P value likelihood ratio test
Received radiotherapy dose threshold ≥ 40 Gy							
Did not receive radiotherapy	142	20.8	1	–	1	–	0.07
Consolidative (≥ 40 Gy)	21	51.2	4.00	2.11–7.57	1.88	0.91–3.87	
Palliative (< 40 Gy)	123	33.4	1.91	1.44–2.54	1.37	0.99–1.90	
Received radiotherapy dose threshold ≥ 30 Gy							
Did not receive radiotherapy	142	20.8	1	–	1	–	< 0.01
Consolidative (≥ 30 Gy)	113	45.2	3.14	2.30–4.28	1.78	1.22–2.59	
Palliative (< 30 Gy)	31	19.5	0.92	0.60–1.42	0.96	0.59–1.55	

Odds ratios are adjusted for sex, age, social deprivation, PS, comorbidity, receipt of PCI, chemotherapy regimen and cycles.

CI: 0.14–0.92).

Discussion

Main findings

We have shown that in all persons diagnosed with SCLC sex, age, PS, co-morbidity, stage and receipt of chemotherapy are independently associated with 1-year survival. For those individuals who go on to receive chemotherapy the majority of these factors, with the addition of radiotherapy and PCI, but not age, were also associated with 1-year survival. Continuing chemotherapy to 6 cycles did not increase the odds of 1-year survival in comparison to 4.

Strengths

These results provide an up-to date “real world” benchmark of survival for SCLC. 1-year survival is an important landmark that is sensitive to treatment effects in this aggressive cancer. Observational studies on this topic are important to confirm the impact of treatment recommendations derived from clinical trials. The complex linkage of national data used in our study provides a comprehensive picture of the treatments given for SCLC and importantly their survival impact to better inform treatment decisions for clinicians and patients. These data have enabled us to study a large population, which in turn, increases the reliability of our results as smaller studies

are more susceptible to bias, especially due to selection of healthier patients. Our data are likely to be reliable because there are quality assurance standards applied to the collection. Outlier hospitals that fall below 2–3 standard deviations from the national audit standard are investigated and their data submissions are reviewed.

Limitations

Our findings may be subject to bias, but these are likely to be lower in magnitude than for clinical trials. Some variables are prone to immortal time bias, however, many of the therapies for SCLC are given within days of diagnosis. Hence, the few days survival advantage treated groups have is too small a proportion of the 1-year survival to significantly bias our results. Similarly, individuals who receive treatment may inherently be healthier and fitter in comparison to those that do not receive treatment and therefore are more likely to survive. However, by adjusting for PS and comorbidity this selection bias is lessened and in the case of chemotherapy cycles these biases would tend to favour survival with 6 cycles over 4, which was not demonstrated in this research. The planned chemotherapy cycles is an estimated amount and in some patients this value may not actually reflect the intended duration as those that are less fit are sometimes given chemotherapy on a cycle-by-cycle basis. Lastly, our data did not contain the time to disease progression. Progression free survival is considered an important metric in the evaluation of

treatment efficacy but is not the gold standard. Similarly, from a patient perspective overall survival may be a more important metric. Our method of calculating Charlson comorbidity index may overestimate the number of people with no comorbidity. These comorbidity data are only captured when a patient is admitted to hospital and therefore those who are managed as an outpatient may have no comorbidity data recorded. However, over 2 thirds of people in our dataset had a Charlson score of >0.

Comparisons with other research

One-year survival

After chemotherapy 1 year survival in our study was approximately 26% for ED-SCLC and 60% LD-SCLC. In comparison a systematic review that examined one-year survival from mostly clinical trial research estimated 1 year survival to be approximately 73% in LD-SCLC and 38% in ED-SCLC (14). Better survival in clinical trials can be explained by selection bias. Indeed most clinical trials included patients with PS 0-1 and excluded patients with brain metastases whereas our study cohort is unselected in this regard.

Patient factors

The associated survival factors identified in our study have been identified previously for all people diagnosed with SCLC. Females were more likely to survive 1 year than males. This finding may relate to greater cardiovascular comorbidity in men or delayed presentation. Other factors which might be part of this finding are differences in drug metabolism between the sexes, whereby females have higher circulating concentrations of cytotoxic drug metabolites. This has been hypothesised in non-small cell lung cancer (15). Similarly, it has been shown that females have decreased DNA repair capacity and have higher DNA adducts which is relevant to platinum agents as these work by inhibiting DNA repair causing further DNA adducts triggering cellular apoptosis(16-19) In addition, hormonal factors, such as estrogen, may also influence SCLC survival. Indeed, when estrogen beta receptors have been identified on SCLC cells from males this has been associated with better survival (20).

Age (<70 years) has been shown to confer better long term survival in clinical trials as well as real world settings (21,22). Indeed, for all patients diagnosed with SCLC those who were >79 years old were less likely to

survive. This is likely a reflection of selection bias due to increased comorbidity and treatment nihilism in this group of patients i.e., patients are less likely to want treatment (23). This hypothesis is supported by our sub analysis of patients who received chemotherapy where we found that age was not a prognostic factor as comorbidity and PS are the main factors that determine whether chemotherapy can be administered (24) Survival was not considerably different for people with LD-SCLC who were PS 0 and 2. This finding is inconsistent with other research and is likely a result of small patient numbers not giving rise to statistical significance. Indeed overall, we found that PS was an independently associated factor with 1-year survival. This finding, in addition to stage, is consistent with other research and both are used in the Manchester prognostic score to estimate 2-year survival (25). Rich *et al.* demonstrated that a worse Charlson Index was associated with poorer survival in all stages of SCLC (9).

Chemotherapy

Contrary to our observation of better survival with cisplatin + etoposide in LD-SCLC, a meta-analysis of individual patient data has shown no difference between carboplatin *vs.* cisplatin regimens (26). The difference in our results may relate to residual selection bias in our cohort. Indeed, PS was a strong confounder to receiving chemotherapy, suggesting cisplatin was reserved for fitter individuals and people receiving concurrent chemo-radiotherapy. Similarly, single agent platinum was mostly given to people who had worse PS or died before receiving etoposide. In clinical practice clinicians may select carboplatin over cisplatin when prognosis is short due to a favourable side effect profile and convenience of administration.

PCI

There is strong clinical trial evidence to support PCI use in LD-SCLC. A systematic review which included mostly LD-SCLC patients from 7 clinical trials found that PCI improved survival for people who were in complete remission following chemo-radiotherapy for SCLC (27). The evidence for the benefit of PCI in ED-SCLC is less clear. The European Organisation for Research and Treatment of Cancer (EORTC) showed, in 2007, that PCI augmented survival for individuals with ED-SCLC who had responded to chemotherapy (28). However, this study did not report response to chemotherapy or screen for asymptomatic brain metastases in all participants. More

recently, with the pitfalls of the EORTC study addressed, a phase III randomized controlled trial found that PCI did not augment survival in a cohort consisting mostly of partial chemotherapy responders with ED-SCLC (7). Importantly, in our study, patients who received PCI were younger and had better PS than those who did not. This suggests that in order to achieve this survival benefit careful treatment selection is needed. We were unable to ascertain the response to chemotherapy before PCI administration. However, one can assume that PCI was given to individuals who had responded to chemotherapy, in accordance with treatment recommendations (1,2).

Radiotherapy

Radiotherapy doses ≥ 40 Gy augmented the odds of 1-year survival but lacked statistical significance in ED-SCLC. When reduced to ≥ 30 Gy these odds decreased for LD-SCLC and became statistically significant for ED-SCLC. This is the resultant effect of 30 Gy doses being used for palliative as well as consolidative (life prolonging) treatment, in addition it is the median dose prescribed for ED-SCLC. The lowest recommended dose by the Royal College of Radiologists to treat LD-SCLC is 40 Gy whereas, for ED-SCLC, 30 Gy can be used as consolidation therapy in chemotherapy responders (where the goal is to prolong survival) or as palliation of persistent thoracic symptoms following chemotherapy (10).

In LD-SCLC the survival benefits of early thoracic radiotherapy within the first 2 cycles of chemotherapy were established using a schedule of 40 Gy in 15 fractions (29). Other studies have also given ≥ 40 Gy but have investigated the delivery of radiotherapy i.e., once *vs.* twice daily. Turrisi *et al.* found that a total dose of 45 Gy given twice daily was superior to once daily (30). This finding was validated by the CONVERT trial which demonstrated that a total dose of 66 Gy given as 2 Gy in once daily fractions was no better, in terms of survival and toxicity, than a total dose of 45 Gy given in twice daily fractions (31). Nevertheless, both these regimens would have been captured in our radical radiotherapy group.

For ED-SCLC the addition of thoracic radiotherapy in chemotherapy responders has been associated with improved survival before (32). A meta-analysis of two randomized controlled trials that gave 30 Gy in 10 fractions and 54 Gy in 36 fractions found that thoracic radiotherapy augmented survival in chemotherapy responders when compared no radiotherapy (HR 0.81 95% CI: 0.69–0.96).

The typical radiotherapy dose given in the palliative dosing group was 8 Gy in 1 fraction. We found this had no benefit to survival in comparison to not receiving radiotherapy. This finding is congruous with the main aim of palliative radiotherapy being to reduce symptoms and not prolong survival.

Cycles of chemotherapy

There was no difference between 1-year survival of 4 and 6 cycles of chemotherapy in our study and the supporting evidence in this area is limited. Powell *et al.* found a reduction in the risk of death when more chemotherapy cycles were given but was unable to directly compare 4 with 6 (33). To our knowledge only one study has compared both and found no difference in survival for LD-SCLC patients and a trend to improved survival with 6 cycles for ED-SCLC, but this lacked statistical significance ($P=0.09$) (4). In our study, the poorer survival associated with receiving less than the planned amount of chemotherapy in ED-SCLC is a reflection of underlying treatment selection bias that we were unable to adjust for. This would include factors such as: disease progression (treatment failure), complications and side effects. These factors were not recorded in the data we analysed.

Relevance

Our findings relate to clinical practice and add to the evidence base for treatment recommendations. We have shown that thoracic radiotherapy (above 40 Gy in LD-SCLC and 30 Gy in ED-SCLC) and PCI are associated with improved 1-year survival and that 6 cycles of chemotherapy is no better than 4. This may serve to ensure that the treatment emphasis is placed on delivering more effective radiotherapy as opposed to extending chemotherapy beyond 4 cycles.

Conclusions

This research adds further evidence to factors associated with long-term survival in SCLC. Receiving chemotherapy is one of the strongest predictors of survival. Balancing the survival benefits of chemotherapy with the toxicities is important if quality as well as quantity of life is to be preserved. We have shown that this may be supported by giving 4 cycles of chemotherapy rather than 6, as there is no survival advantage from the latter. Appropriate administration of radiotherapy and PCI should be

encouraged as they provide a survival benefit. In the future, advances in SCLC survival may come from adding novel therapies to four cycles of optimally delivered chemo and radiotherapy and prospective collection of national lung cancer data, like that used in this analysis, will be a key resource in measuring the success (34).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The data are routinely collected National health service hospital data and consent is assumed unless the patient specifically withdraws this. Ethical approval was obtained from the NHS Health Research Authority, London- Camden and King's cross research ethics committee (Reference 16/LO/0503).

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Table S1 Features of patients who received chemotherapy and survived 1 year with odds ratios for 1 year survival in all stages							
Factor	Number surviving 1 year (n=695)	% surviving 1 year from those receiving chemotherapy	OR 1-year survival	95% CI	Adjusted OR 1-year survival	95% CI	P value (LR test)
Sex							
Female	404	45.3	1		1		
Male	291	33.5	0.61	0.50–0.73	0.61	0.48–0.76	<0.01
Age group							
<60	150	45.2	0.79	0.62–1.01	1	0.74–1.35	
60–79	498	39.4	1		1		
≥80	47	28.3	0.48	0.32–0.72	0.74	0.45–1.21	0.53 [¥]
Townsend quintile							
Least deprived- 1	97	44.7	1		1		
2	108	37.2	0.73	0.51–1.05	0.8	0.52–1.22	
3	142	39.1	0.79	0.57–1.12	1.02	0.68–1.53	
4	185	41.3	0.87	0.63–1.21	1.01	0.68–1.50	
Most deprived- 5	163	36.8	0.72	0.52–1.00	0.88	0.59–1.31	0.61
Performance status							
0	196	54.9	1		1	1	
1	307	44.2	0.65	0.50–0.84	0.71	0.53–0.97	
2	119	28.9	0.33	0.25–0.45	0.44	0.31–0.63	
3	24	16.7	0.16	0.10–0.27	0.29	0.17–0.51	
4	1	7.7	0.07	0.01–0.53	0.05	0.00–0.63	
Missing	48	34.3	0.43	0.29–0.64	0.46	0.29–0.75	<0.01
Charlson comorbidity index							
0	240	45.4	1		1		
1	193	52.6	1.34	1.02–1.74	1.42	1.03–1.96	
2–3	128	37	0.71	0.54–0.93	0.84	0.60–1.17	
≥4	134	25.8	0.42	0.32–0.54	0.75	0.55–1.01	<0.01
Stage							
Limited	381	60.7	1		1		
Extensive	286	26.2	0.23	0.19–0.29	0.3	0.23–0.39	
Missing	28	66.7	1.3	0.67–2.51	1.54	0.72–3.28	<0.01
Chemotherapy							
Carboplatin+ etoposide	530	38.4	1		1		
Cisplatin + etoposide	133	67.9	3.39	2.46–4.66	1.48	0.99–2.21	
CAV	1	20	0.4	0.04–3.60	0.64	0.05–8.59	
Other	11	34.4	0.84	0.40–1.76	1.4	0.61–3.24	
Single platinum	14	11.1	0.2	0.11–0.35	0.42	0.23–0.79	
Missing	6	27.3	0.6	0.23–1.55	1.06	0.33–3.41	0.02
Chemotherapy cycles received							
More than planned (mean 5 cycles)	16	53.3	0.89	0.41–1.93	0.9	0.36–2.27	
Less than planned (mean 3 cycles)	275	32	0.37	0.27–0.50	0.47	0.32–0.68	
4 planned and received	115	56.1	1		1		
6 planned and received	203	52.5	0.86	0.61–1.21	1.22	0.82–1.83	
Received planned amount excluding 4 & 6 cycles (mean 2 cycles)	27	28.4	0.31	0.18–0.52	0.36	0.18–0.72	
Missing planned cycles	59	32.1	0.37	0.24–0.56	0.45	0.28–0.74	<0.01
Received radiotherapy							
Did not receive radiotherapy	269	27.8	1		1		
Radical (≥40 Gy)	233	77.4	8.91	6.58–12.09	2.94	2.04–4.25	
Palliative (<40 Gy)	193	39.3	1.69	1.34–2.12	1.43	1.10–1.87	<0.01
Received PCI							
No	469	33.6	1		1		
Yes	226	61.9	3.21	2.53–4.08	2.08	1.54–2.79	<0.01

¥: LR test for trend. Adjusted OR for all other factors in table.

Table S2 Sensitivity analysis of 1-year survival with different radiotherapy thresholds for limited stage SCLC

Radiotherapy received	Number surviving 1 year	Proportion surviving 1 year from all who received chemotherapy	OR 1-year survival	95% CI	Adjusted OR 1-year survival	95%CI	P value likelihood ratio test
Received radiotherapy							
Did not receive radiotherapy	119	44.2	1	–	1	–	<0.01
Radical (≥40 Gy)	197	81.4	5.52	3.69–8.26	3.32	2.07–5.31	
Palliative (<40 Gy)	65	55.6	1.58	1.02–2.44	1.53	0.94–2.49	
Received radiotherapy							
Did not receive radiotherapy	381	44.2	1	–	1	–	<0.01
Radical (≥30 Gy)	236	77.6	4.37	3.15–6.28	2.83	1.84–4.34	
Palliative (<30 Gy)	26	47.3	1.13	0.63–2.02	1.31	0.69–2.47	

Odds ratios are adjusted for sex, age, social deprivation, PS, comorbidity, receipt of PCI, chemotherapy regimen and cycles.

Table S3 Characteristics of individuals receiving chemotherapy who had limited stage

Factor	Received 4 cycles		Received 6 cycles		P value for differences between treatment groups (chi ²)
	Number	Percentage	Number	Percentage	
Sex					
Male	40	44	57	48	0.53
Female	51	56	61	52	
Age (median & IQR)	69 (60-75)		67 (60-73)		0.60 (t test)
Performance status					
0	29	32	30	25	0.57
1	42	46	52	44	
2	13	14	20	17	
3	1	1	4	3	
Missing	6	7	12	10	
Charlson comorbidity score					
0	35	38	30	25	0.12
1	26	29	50	42	
2-3	21	23	24	20	
4	9	10	14	12	
Socioeconomic status					
1-Least deprived	14	15	18	15	0.89
2	15	16	20	17	
3	16	18	21	18	
4	25	27	26	22	
5-Most deprived	21	23	33	28	

Table S4 Characteristics of individuals receiving chemotherapy who had extensive stage

Factor	Received 4 cycles		Received 6 cycles		P value for differences between treatment groups (chi ²)
	Number	Percentage	Number	Percentage	
Sex					
Male	49	45	137	52	0.21
Female	59	55	124	48	
Age (median + IQR)	68 (62-74)		68 (61-73)		0.24 (t test)
Performance status					
0	12	11	55	21	0.03
1	41	38	105	40	
2	38	35	61	23	
3	10	9	14	5	
Missing	7	6	26	10	
Charlson comorbidity index					
0	38	35	87	33	0.94
1	20	19	46	18	
2-3	16	15	37	14	
≥4	34	31	91	35	
Socioeconomic status					
1-Least deprived	17	16	30	11	0.624
2	21	19	47	18	
3	24	22	59	23	
4	21	19	68	26	
5-Most deprived	25	23	57	22	

Table S5 Characteristics of individuals receiving PCI who had extensive stage

Factors	Did not receive PCI		Received PCI		P values for differences between treatment groups (chi²)
	Number	Percentage	Number	Percentage	
Sex					
Male	455	52	107	50	0.68
Female	423	48	106	50	
Age (median & IQR)	69 (62-75)		64 (59-70)		<0.01 (t test)
Performance status					
0	143	16	49	23	<0.01
1	320	36	101	47	
2	238	27	39	18	
3	101	12	13	6	
Missing	76	9	11	5	
Charlson score					
0	250	28	75	35	0.08
1	147	17	38	18	
2-3	152	17	24	11	
≥4	329	37	76	36	
Socioeconomic status					
Least deprived-1	95	11	26	12	0.95
2	147	17	35	16	
3	190	22	49	23	
4	218	25	49	23	
Most deprived-5	228	26	54	25	

Table S6 Characteristics of individuals receiving radiotherapy who had extensive stage

Factors	Received palliative dose (<40 Gy)		Received consolidative dose (≥40 Gy)		P value for difference between treatment groups (chi²)	Received palliative dose (<30 Gy)		Received consolidative dose (≥30 Gy)		P value for difference between treatment groups (chi²)
	Number	%	Number	%		Number	%	Number	%	
Sex										
Male	204	55	18	44	0.16	104	65	118	47	<0.01
Female	164	45	23	56		55	35	132	53	
Age (median and IQR)	67 (61-72)		65 (60-73)		0.84 (t test)	68 (62-74)		65 (60-72)		0.02 (t test)
Performance status										
0	78	21	10	24	0.15	24	15	64	26	0.07
1	154	42	19	46		71	45	102	41	
2	78	21	5	12		32	20	51	20	
3	33	9	1	2		18	11	16	6	
Missing	25	7	6	15		14	9	17	7	
Charlson comorbidity score										
0	129	35	13	32	<0.01	52	33	90	36	<0.03
1	61	17	15	37		25	16	51	20	
2-3	44	12	9	22		15	9	38	15	
≥4	134	36	4	10		67	42	71	28	
Socioeconomic status										
Least deprived-1	37	10	4	10	0.28	15	9	26	10	1.00
2	58	16	6	15		25	16	39	16	
3	72	20	13	32		35	22	50	20	
4	99	27	12	29		44	28	67	27	
Most deprived-5	102	28	6	15		40	25	68	27	