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ORIGINAL ARTICLE

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Pathological complete response after neoadjuvant/induction treatment: where is its place in the lung cancer staging system?†

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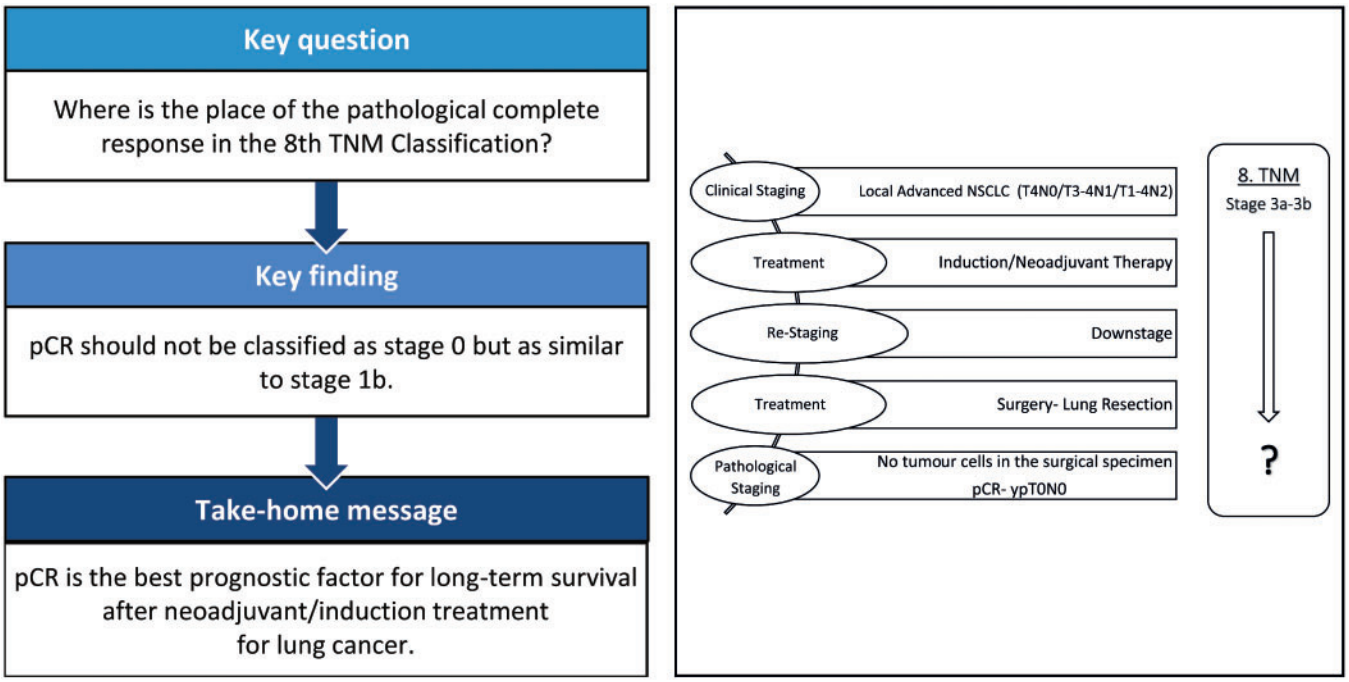

Abstract

OBJECTIVES: Prognosis for patients with non-small-cell lung cancer (NSCLC) who, after neoadjuvant/induction and surgery, have a pathological complete response (pCR) is expected to be improved. However, the place of the pCR patients in the context of the tumour, lymph node and metastasis (TNM) staging system is still not defined. The aim of this study is to investigate the long-term survival of NSCLC patients with pCR and to find their appropriate staging category within the TNM staging system.

METHODS: We retrospectively reviewed the prospectively recorded data of 1076 patients undergoing surgery (segmentectomy or more) for NSCLC between 1996 and 2016. Patients were divided into 2 groups. Group 1: clinical early-stage patients who underwent direct surgical resection ($n = 660$); group 2: patients who received neoadjuvant/induction treatment before surgical resection for locally advanced NSCLC ($n = 416$). Morbidity, mortality, survival rates and prognostic factors were analysed and compared.

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RESULTS: Postoperative histopathological evaluation revealed pCR in 72 (17%) patients in group 2. Overall 5-year survival was 58.7% (group 1 = 62.3%, group 2 = 52.8%, $P = 0.001$). Of note, 5-year survival was 72.2% for pCRs. In addition, 5-year survival for stage 1a disease was 82.6% in group 1 and 63.2% in group 2 ($P = 0.008$); 70.3% in group 1 and 60.5% in group 2 for stage 1b ($P = 0.08$). Patients with stage II had a 5-year survival of 53.9% in group 1 and 51.1% in group 2 ($P = 0.36$).

CONCLUSIONS: This study shows that patients with locally advanced NSCLC developing a pCR after neoadjuvant/induction treatment have the best long-term survival and survival similar that of to stage Ib patients.

Keywords: Pathological complete response • Induction treatment • Neoadjuvant treatment

INTRODUCTION

Lung cancer is a major public health problem and the leading cause of cancer-related mortality in the USA and Europe [1]. The first step in the treatment of lung cancer is to identify the stage of the disease. The purpose of the staging system is to obtain groups of homogeneous patients, define groups with similar survival rates, select the appropriate treatment algorithms based on the stage and identify groups that have diseases with similar biological behaviour [2]. The 8th version of the classification of tumour, lymph node and metastasis (TNM) has been in use since 2017 for lung cancer staging [3]. In the TNM staging system, clinical staging (cTNM), done before starting treatment, is vital in determining and evaluating treatment selection. Pathological staging (pTNM) is done based on histopathological findings after surgery and provides the most accurate data to reach final results and predict prognosis, and ypTNM is used after neoadjuvant treatment [2].

The standard treatment options for each stage of lung cancer include surgery, radiation therapy and systemic treatments (chemotherapy, immunotherapy and targeted agents). Surgery affords the best chance of long-term survival in the early stage of the disease, with an expected 5-year survival rate of approximately 73–90% for stage I disease and 65–56% for stage II disease [3]. The optimal management of patients with locally advanced non-small-cell lung cancer (NSCLC) remains controversial, and the choice of local treatment modality can vary across countries and centres [4, 5]. Generally, surgical resection results in improved overall survival when downstaging is achieved after neoadjuvant/induction therapy (N/I) [6, 7]. Five-year survival rate is only 24–41% for stage III disease, despite aggressive treatment [3]. Neoadjuvant therapy for locally advanced stage aims to increase complete resection rates, reduce rates of pneumonectomy, increase survival and disease-free survival, avoid any delay of surgery, minimize surgical mortality and morbidity and obtain the most desirable outcome which is complete treatment of tumour [6, 8]. The most favourable results were achieved in patients with pCR; however, there are only few studies analysing the subgroup of patients due to small number of pCR patients in the series. Although it was proposed as stage '0' by some authors, pCR patients are not clearly defined in the 8th TNM classification [3, 9].

The aim of this study is to investigate the long-term survival of patients with pCR and define the appropriate TNM staging of their tumours.

MATERIALS AND METHODS

We retrospectively reviewed the prospectively recorded data of 1076 patients who underwent surgery (segmentectomy, lobectomy or pneumonectomy) for NSCLC between 1996 and 2016.

In the clinical evaluation of the patients, positron emission tomography/computed tomography (PET/CT, whole body scintigraphy was used prior to 2007) and cranial CT or magnetic resonance imaging were performed in all patients to exclude the presence of a distant metastasis. Clinical stage 1–2 patients were considered as early stage and these patients were evaluated primarily for surgical treatment. For mediastinal staging, thorax CT, PET/CT, mediastinoscopy (videomediastinoscopy after 2006), mediastinotomy and endobronchial ultrasound-guided fine-needle aspiration were used. The European Society of Thoracic Surgeons (ESTS) guidelines of 2007 and 2010 were used for mediastinal lymph node staging in NSCLC in selected patients for invasive staging. For clinical N2–N3 cases, mediastinal involvement was always pathologically proven before or after neoadjuvant/induction (N/I) therapy by endoscopy, transbronchial fine-needle aspiration, endobronchial ultrasound, mediastinoscopy or mediastinotomy. Mediastinotomy was performed in patients with left central-upper lobe and station 5 & 6 lymph node metastasis in clinic evaluation for those who were candidates for pneumonectomy. Extended mediastinoscopy, endo-oesophageal ultrasound-guided fine-needle aspiration or videothoracoscopy were not performed. For patients with clinically early-stage disease, surgical treatment was performed if the patient accepted surgery and if their cardiopulmonary function was appropriate for surgery. Patients with non-early-stage NSCLC were evaluated by a multidisciplinary team. The decision to initiate N/I treatment, chemotherapy or chemoradiation was based on the presence of mediastinal lymph node metastases (N2) and the T stage. Chemotherapy consisted of at least 2 cycles of platinum-based therapy, and radiotherapy involved administering a dose of 45–66 Gy. Restaging after oncological treatment was done using CT or PET/CT. Patients without disease progression after treatment were evaluated as candidates for surgical treatment. Patients who were suspected to have N2 disease were assessed with invasive staging methods (endobronchial ultrasound, remediastinoscopy and mediastinotomy) and lung resection was performed on patients without N2. Surgery was performed at least 3 weeks after chemotherapy and maximally 4–6 weeks after chemoradiotherapy.

Systematic mediastinal lymph node dissection was performed in all cases. When intraoperative persistent N2 was detected and the tumour required pneumonectomy, the operation was ended as exploratory. The pathological stage of the tumour was assigned according to the 8th edition of TNM classification system. The TNM staging system used in previous years were revised according to the 8th edition. The patients were re-evaluated at the multidisciplinary team meeting for chemotherapy or chemoradiation.

Patients with contralateral nodal metastases and supraclavicular, extranodal invasion at mediastinoscopy, unresectable T4 tumour or severe cardiopulmonary impairment precluding surgical

resection and additional cancer, and incomplete (R1–R2) resection were excluded.

The patients in the study were divided into 2 groups. Group 1: clinical early-stage patients who underwent direct surgical resection ($n = 660$); group 2: patients who received N/I treatment for locally advanced NSCLC ($n = 416$). Pathological complete response was defined as the absence of tumour cells in the surgical specimen. Perioperative mortality was accepted in 90 days of surgery. Survival was calculated as the time between the date of surgery and the date of death or last available follow-up. The disease-free survival was calculated from the day of surgery until the first diagnosis of recurrence. Written informed consent was obtained from all patients; patients attested that they understood their treatment options, potential toxicities, expected risks and potential benefits of chemotherapy drugs, radiotherapy and surgery.

Statistical analysis

The Shapiro–Wilk test was used to test variable normality. Normally distributed variables are presented as the mean ± standard deviation and were compared using Student's *t*-test. Variables that were not normally distributed are presented as median (minimum–maximum) and were compared using the Mann–Whitney *U*-test. The Pearson χ^2 test (frequency >5%) and the Fisher's exact χ^2 test (frequency <5%) were used to compare categorical variables, which are presented as *n* (%). Overall survival was calculated from the time of diagnosis to death or last follow-up. Survival analysis was performed using the Kaplan–Meier method. Survival times between the groups were compared with the log-rank test. Significance level was taken as $\alpha = 0.05$ [10]. All the statistical analyses were performed using IBM SPSS Statistics software. For multivariate analysis, a Cox regression model was used with a forwards stepwise selection of variables. The parameters evaluated included age, gender, smoking habits, comorbidity, pulmonary functional tests [forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC value], tumour's SUVmax value, clinical stage, type of lung resection, extended resection, complications, tumour cell type, pathological staging and adjuvant therapy.

RESULTS

Demographic and clinical data of 1076 patients are described in Table 1. On the last Cox regression model ($P < 0.001$), gender [$P = 0.039$, hazard ratio (HR) 8.72, confidence interval (CI) 1.11–68.14], pulmonary functional tests ($P = 0.001$; HR 5.73, 95% CI 2.02–16.24), clinical stage ($P = 0.013$; HR 2.18, 95% CI 1.18–4.04) and pathological stage ($P < 0.001$; HR 5.73, 95% CI 2.02–16.24) were significant, while no statistically significant differences between smoking habits, tumour cell type, lung resection type and tumour's SUVmax value were identified.

There were 949 (88.2%) male and 127 (11.8%) female patients with a mean age of 60 ± 9.94 years. Lung resection involved lobectomy in 846 cases (78.6%) and pneumonectomy in 154 cases (14.3%). Squamous cell carcinoma (SCC) was the most common subtype ($n = 540$, 50.2%), followed by adenocarcinoma (AC) ($n = 350$, 32.5%) and other cell type ($n = 186$, 17.3%). Postoperative histopathological investigation revealed pCR in 72 (17%) patients, stage 1 in 426 patients (group 1 $n = 308$, group 2 $n = 118$), stage 2 in 305 patients (group 1 $n = 198$, group 2 $n = 107$), stage 3 in 229 patients (group 1 $n = 134$, group 2 $n = 95$) and stage 4 in 44 patients (group 1 $n = 20$, group 2 $n = 24$) (Table 2).

Table 1: Cox proportional hazard regression analysis of the demographics, clinical and diagnostic characteristics of all patients

Variables	*P*-value	HR	95% CI
Gender			
Woman			
Man	0.039	8.72	1.11–68.13
Pulmonary functional tests			
FEV_1 <1.5	0.001	5.73	2.02–16.24
FEV_1 ≥1.5			
FEV_1/FVC	0.025	1.02	1.00–1.04
Clinical stage			
Early stage			
Local advanced stage	0.013	2.18	1.18–4.04
Pathological stage			
pStage 1 (R.C)	<0.001		
pStage 2	0.809		
pStage 3	0.000	4.78	2.29–9.96
pStage 4	0.002	3.82	1.61–9.09
ypT0N0	0.877		

CI: confidence interval; HR: hazard ratio; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; R.C: reference category.

Only 77% of the patients who were thought to have an early stage as a result of clinical staging (group 1) were diagnosed as early stage after the pathological examination. In the staging of lung cancer, during the time period where PET/CT was not used (before 2007), 281 of 370 patients, and 379 of 706 patients after 2007 (PET/CT was used) were evaluated as clinical early stage and treated with surgery without N/I therapy. Of the 281 patients, 209 (74.4%) and 297 (78.4%) of the 379 patients were detected as early stage. However, the increase in the accuracy of this clinical staging was not statistically significant ($P = 0.23$).

In group 2, chemotherapy alone was administered in 288 (69%) and chemoradiotherapy was used in 128 (31%). Pathological complete response was achieved in 27 (9.4%) patients after chemotherapy and in 45 (35%) patients after chemoradiation ($P < 0.001$). The dominant histology type was SCC (54.2%). Characteristics of patients with pCR are included in Table 3.

The 90-day postoperative mortality rate was 2.7% for all patients. The mortality rate was 2.3% in group 1, 3.4% in group 2 ($P = 0.18$) and 3.16% in patients with pCR.

The 5-year survival rate in all patients was 58.7% (95% CI 108.3–123.9) [in group 1 = 62.3% (95% CI 112.5–131.4), in group 2 = 52.8% (95% CI 94.7–119.8)]. However, 5-year survival rate was 72% (95% CI 113.0–168.5) for pCR and for patients with stage Ia disease, survival rates were 82.6% (95% CI 139.0–173.6) for group 1 and 63.2% (95% CI 93.0–137.9) for group 2 ($P = 0.008$). Patients with stage Ib had 5-year survival rates of 70.3% (95% CI 115.2–157.9) for group 1 and 60.5% (95% CI 56.2–101.9) for group 2 ($P = 0.08$). Patients with stage II had 5-year survival rates of 53.9% (95% CI 95.3–130.6) for group 1 and 51.1% (95% CI 80.9–126.0) for group 2 ($P = 0.35$) (Table 4). When we evaluated group 2 according to the ypTNM stage, the 5-year survival rate was 72.2%, 63.2%, 60.5% and 51.1% in pCR, stages 1a, 1b and 2,

Table 2: Patient characteristics

	Total ($n = 1076$)	Group 1 ($n = 660$)	Group 2 ($n = 416$)	*P*-value	Group 2 with pCR ($n = 72$)	Group 2 without pCR ($n = 344$)	*P*-value
Age (years)	59.95 ± 9.94	60.7 ± 10.78	58.7 ± 8.31		57.7 ± 6.82	58.9 ± 8.58	
Gender (male/female)	949/127	558/102	391/25	<0.01	71/1	320/24	0.07
Pathology							
Squamous cell	540 (50.0)	302 (45.8)	238 (57.2)		39 (54.2)	199 (57.8)	
Adenocarcinoma	350 (32.5)	239 (36.2)	111 (26.7)		9 (12.5)	102 (29.7)	
Other	186 (17.3)	119 (18.0)	67 (16.1)		24 (33.3)	43 (12.5)	
Type of lung resection				0.007			0.6
Segmentectomy	76 (7.1)	56 (8.5)	20 (4.8)		3 (4.2)	17 (4.9)	
Lobectomy	846 (78.6)	523 (79.2)	323 (77.6)		55 (76.4)	268 (77.9)	
Pneumonectomy	154 (14.3)	81 (12.3)	73 (17.5)		14 (19.3)	59 (17.2)	
Number of lymph node stations harvested	4.2 (3–7)	4.3 (3–7)	4.1 (3–7)	0.9			
Hospital stay (days)	7.25 ± 6.4	6.8 ± 5.6	7.8 ± 7.6	0.1	8 ± 6	7.8 ± 7.8	
Complication	364 (33.8)	214 (32.4)	150 (36)	0.1	22 (37.5)	123 (35.7)	0.44
Mortality	29 (2.7)	15 (2.3)	14 (3.4)	0.18	3 (4.2)	11 (3.2)	0.67
Pathological stage							
pCR-T0N0	72 (6.7)		72 (17.3)		72 (17.3)		
1a1	51 (4.7)	24 (3.6)	27 (6.5)			27 (6.5)	
1a2	95 (8.8)	76 (11.5)	19 (4.6)			19 (4.6)	
1a3	128 (11.9)	89 (13.5)	39 (9.4)			39 (9.4)	
1b	152 (14)	119 (18)	33 (7.9)			33 (7.9)	
2a	50 (4.6)	31 (4.7)	19 (4.6)			19 (4.6)	
2b	255 (23.7)	167 (25.3)	88 (21.2)			88 (21.2)	
3a	197 (18.3)	116 (17.6)	81 (19.5)			81 (19.5)	
3b	32 (3)	18 (2.7)	14 (3.4)			14 (3.4)	
4	44 (4.1)	20 (3.1)	24 (5.8)			24 (5.8)	

Data are expressed as *n* evaluations (%) and mean ± standard deviations.
pCR: pathological complete response.

respectively ($P = 0.03$) (Fig. 1). When pCR was compared with group 1, survival rates were similar versus stage 1b and better versus stages 2, 3 and 4 ($P = 0.1$, $P = 0.048$) (Fig. 2).

In group 1, incidental N2 was found in 72 of the 660 patients (11%). This rate was 14.2% (40/281) in pre-PET/CT era and 8.4% (32/379) after using PET/CT. Nodal staging was N2a1 in 28, N2a2 in 40 and N2b in 4. Five-year survival was 47.9 for incidental N2. In group 2, a total of 56 patients (13.5%) had persistent N2. Persistent N2 after chemotherapy was 12.1% (35/238) and 16.1% (21/128) after chemoradiation. Pathological examination revealed N2a1 in 20, N2a2 in 22 and N2b in 14 patients. Five-year survival was 34.3%. The subcarinal lymph node was the most common positive lymph node in the incidental and persistent N2 groups. These results clearly revealed that acceptable good survival can be achieved in patients with complete response and incidental or skip N2 (Table 5 and Fig. 3).

Patients with pCR have a potential for recurrence rate up to 23.6% in which the majority was distant metastasis (70.6%) rather than local recurrence. Five-year disease-free survival was 72% (95% CI 155.12–204.22).

DISCUSSION

Surgery or oncological treatment alone is not sufficient for controlling locally advanced NSCLC, making neoadjuvant treatment combined with surgery preferable, especially as it results in better treatment outcomes such as downstaging or pCR [8]. Although downstaging of the tumour has been reported to be 40–60% after neoadjuvant treatment, the pCR rate varies between 4% and 34% [8,11–16]. One of the most important reasons for the differences in the pCR rates detected after neoadjuvant therapy is the definition of what constitutes a complete response. Betticher *et al.* [16] included 75 patients in their study and found pCR in 14 patients (19%) when they defined pCR as tumours consisting of 95% or more necrosis and fibrosis. Cerfolio *et al.* [11] found pCR in 19 of 56 patients (33.9%), but they defined the pCR as 1% or less of live tumour cells in the whole pathological specimen. As in our study, when the pCR was defined as no residual living tumour cells, Chen *et al.* [13] found pCR in 51/211 (24.1%) patients, Coroller *et al.* [14] in 27/127 (21.3%) patients, Depierre *et al.* [15] in 19/173 (11%) patients, and Mouillet *et al.* [12] in 41/492 (8%) patients. In our study, 17.3% (72/416) of 416 patients had a pCR which parallels the rates seen in the literature. Another reason for the reported different rates of pCR may be the choice of chemotherapy or chemoradiotherapy as N/I. Overall, in 15 studies involving neoadjuvant chemotherapy, the median frequency of pCR was 4% (0–16%) [17]. pCR rate was reported as 10–22% in stage III NSCLC after induction chemoradiotherapy followed by lung resection [9, 17–19]. Quite clearly, pCR is more frequently seen in neoadjuvant chemoradiotherapy [9, 17]. In our study, 45 of 128 (35%) patients had a pCR after chemoradiation, a significantly higher proportion than that among patients undergoing chemotherapy (9.4%).

When tumour histological types were evaluated, there were studies that found that the pCR rate was higher in SCC patients [12, 20]. Mouillet *et al.* [12] noted SCC as the sole predictor of pCR. In our study, 16.4% (39/238) of patients with SCC undergoing surgery after N/I therapy and 8.1% (9/111) of patients with AC were found to have pCR ($P = 0.024$). However, 28% (62/238) of patients with SCC and 38.7% (43/111) of patients with AC received chemoradiation ($P = 0.018$).

Table 3: Characteristics of patient with pCR

Clinical stage, *n* (%)	
2b	7 (9.7)
3a	47 (65.3)
3b	14 (19.5)
4	4 (5.5)
Neoadjuvant/induction treatment, *n* (%)	72
Chemotherapy	27 (37.5)
Chemoradiation	45 (62.5)
Radiation dose (Gy)	
≤60	15
>60	30
Chemotherapy cycles	
2	2
3	7
4	13
5	3
6	2
PET/CT SUVmax, median (range)	
Pretreatment	14 (3–26)
Post-treatment	4 (0–7)
Side	
Left, *n* (%)	27 (37.5)
Pneumonectomy	6 (8.3)
Upper lobectomy	12 (16.6)
Lower lobectomy	7 (9.7)
Segmentectomy	2 (2.7)
Right, *n* (%)	45 (62.5)
Pneumonectomy	8 (11.1)
Upper lobectomy	24 (33.3)
Lower lobectomy	5 (6.9)
Bilobectomy	7 (9.7)
Segmentectomy	1 (1.4)
Patients receiving adjuvant chemotherapy, *n* (%)	7 (9.7)
Tumour recurrence	17 (23.6)
Distant	12 (70.6)
Local	3 (17.6)
Distant and local	2 (11.8)
Recurrence time (months), *n* (%)	
Within 24	9 (52.9)
(More) 24	8 (47.1)

CT: computed tomography; pCR: pathological complete response; PET: positron emission tomography.

A number of studies have reported that survival rates of patients with pCR who underwent complete surgical resection after oncological treatment were comparable to early-stage NSCLC [9, 12, 16]. High survival rates of 64–80% were seen in these patients. A 5-year survival rate of around 55% was seen in those without pCR, and was found that statistically, pCR cases had prolonged survival [9, 12]. In our study, the 5-year survival rate of N/I patients was 72.2% in the pCR group and 63.2%, 60.5% and 51.1% in stages 1a, 1b and 2, respectively ($P = 0.03$). As a result, it was concluded that pCR can be seen as a response to neoadjuvant treatment and could be used as a survival indicator [17]. It has also been shown that the ypTNM staging system can be used effectively.

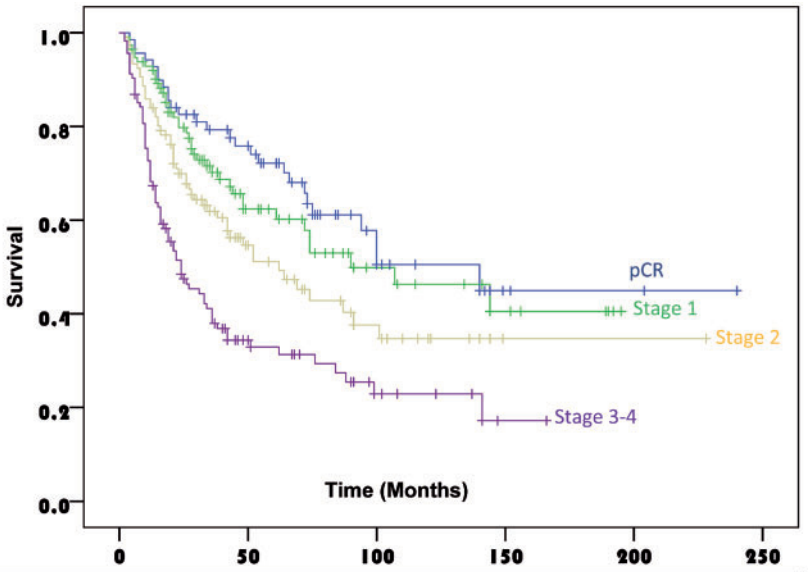
In light of the above data, the following conclusion can be reached. Long-term survival for patients with pCR may be extended by adding radiotherapy to chemotherapy, as an increased rate of pCR is achieved after chemoradiation. Interestingly enough, neoadjuvant chemoradiation did not result in a further increase in survival, as life expectancy is similar in patients receiving chemotherapy and chemoradiotherapy [8, 17, 21]. A possible explanation is that radiotherapy causes secondary complications within a year of treatment, which are not accounted for in the mortality figures. In addition, dissection during surgery may be difficult and unsafe because of the development of dense fibrosis and adhesions that vary over time after chemoradiation therapy. It is also important to consider that postoperative pneumonia, bronchopleural fistula and infection may result in mortality, particularly after right pneumonectomy [8]. We did not observe any adverse effects of chemotherapy or chemoradiotherapy on mortality. There was no difference in survival between patients receiving chemotherapy and chemoradiotherapy. Even though chemoradiotherapy is more frequently used in patients with AC, fewer pCRs suggest that a more detailed subgroup analysis on this subject is necessary.

Recurrences were more frequently seen (30–75%) which mainly depended on the stage of the disease [22]. In patients with T1N0 and T2N0 NSCLC, 5-year recurrence rates were 29% and 40%, respectively [23]. Wang *et al.* [24] found that 487 of 2633 stage I NSCLC patients who underwent surgery without

Table 4: Five-year survival according to pathological stage in patients with complete response

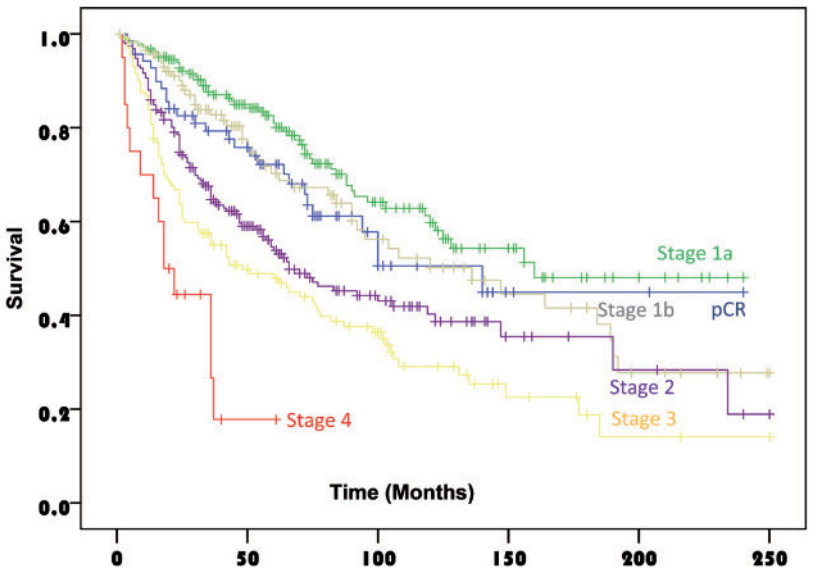
Stage	Total 5-Year survival HR (95% CI)	G1 5-Year Survival HR (95% CI)	G2 5-year Survival HR (95% CI)	*P*-value G1 versus G2	*P*-value pCR versus G1	*P*-value pCR versus without G2
All stage	58.7% 116.12 (108.35–123.89)	62.3% 121.94 (112.49–131.39)	52.8% 107.24 (94.72–119.76)	0.001		
pCR-T0N0	72.2% 140.76 (112.98–168.54)		72.2% 140.76 (112.98–168.54)			
Stage 1a	77.2% 149.31 (134.19–164.44)	82.6% 156.34 (139.04–173.65)	63.2% 115.43 (92.98–137.88)	0.008	0.113	0.46
Stage 1b	68.3% 130.93 (111.29–150.56)	70.3% 136.58 (115.21–157.95)	60.5% 79.03 (56.19–101.86)	0.08	0.860	0.19
Stage 2	52.8% 110.44 (95.58–125.30)	53.9% 112.96 (95.34–130.59)	51.1% 103.42 (80.87–125.97)	0.36	0.048	0.015
Stage 3a	43.7% 82.42 (67.33–97.50)	47.9% 91.89 (73.27–110.52)	32% 58.36 (42.85–73.87)	0.01	0.005	0.0001
Stage 3b/4	28.2% 45.96 (32.88–59.04)	21.6% 38.94 (23.77–54.10)	26.8% 51.24 (31.24–71.24)	0.43	0.0001	0.0001

CI: confidence interval; G1: group 1, G2: group 2l; HR: hazard ratio; pCR: pathological Complete Response.



pCR	69	42	13	3	2	0
Stage 1	114	23	8	1	0	0
Stage 2	113	34	14	6	0	0
Stage 3-4	106	31	13	1	1	0

Figure 1: Overall survival according to ypTNM stage of patients who underwent surgery after neoadjuvant/induction treatment. pCR: pathological complete response.



pCR	69	42	13	3	2	0
Stage 1a	185	113	51	20	7	0
Stage 1b	117	52	29	15	7	0
Stage 2	192	86	38	10	4	0
Stage 3	129	53	28	8	3	0
Stage 4	21	2	0	0	0	0

Figure 2: Overall survival in patients with clinical early stage and pCR. pCR: pathological complete response.

Table 5: Characteristics and results of patients with N2

	Group 1: incidental N2, *n* (%)	Group 2: persistent N2, *n* (%)	pCR, *n* (%)
Number	72	56	72
Gender (male/female)	60/12	46/10	
N/I treatment		56	72
Chemotherapy		35 (36.8)	27 (37.5)
Chemoradiation		21 (21)	45 (62.5)
Type of lung resection			
Segmentectomy	5 (6.9)	2 (3.6)	3 (4.2)
Lobectomy	52 (72.2)	41 (73.2)	55 (76.4)
Pneumonectomy	15 (20.8)	13 (23.2)	14 (14.4)
Pathological positive lymph node station			
4	20 (27.8)	13 (23.2)	
7	24 (33.3)	16 (28.5)	
5 or 6	15 (20.8)	12 (21.4)	
8 or 9	9 (12.5)	1 (2)	
Lymph node staging			
N2a1	28 (38.9)	20 (35.7)	
N2a2	40 (55.5)	22 (39.3)	
N2b	4 (5.5)	14 (25)	
5-Year survival	49.9	34.3	72
	96.75 (95% CI 71.7–121.76)	59.42 (95% CI 41.64–77.20)	140.75 (95% CI 113–168.5)
N2a1	58	46.9	
N2a2	44	32.2	
N2b		2-Year 18	

N/I: neoadjuvant/induction treatment; pCR: pathological complete response.

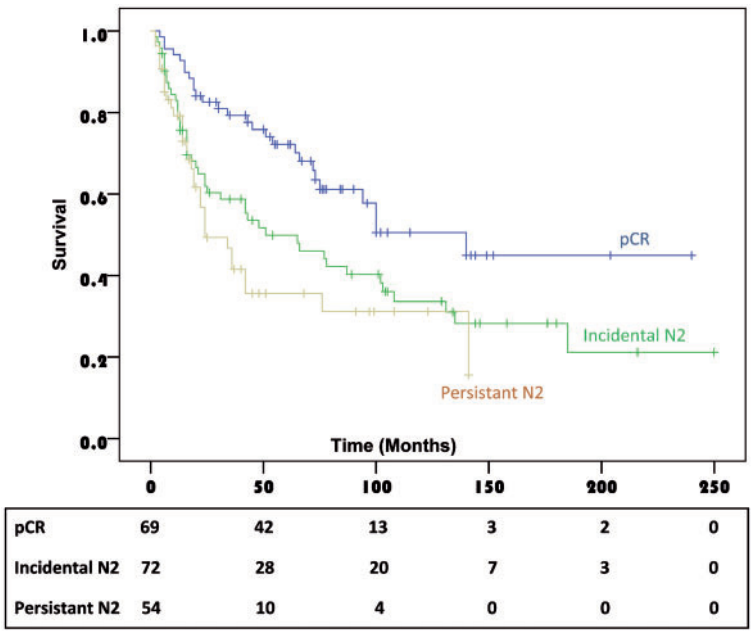


Figure 3: Overall survival in patients with N2 stages and pCR. pCR: pathological complete response.

neoadjuvant therapy had 18.5%. A new study showed that recurrence rates continued to be similar to those reported in previous years and were a permanent problem [25]. For patients with pCR, low recurrence rates were observed [15, 16]. Mouillet *et al.* [12] reported recurrence in 2 of 41 patients with pCR. However, Lococo *et al.* [9] found recurrences in 17 of 37 (46%) patients with pCR after chemoradiation and 32% of these were distant organ recurrences. In our study, 23.6% of the patients in the pCR group were found to have recurrences during postoperative follow-up. Seventy percent of these recurrences were seen in distant organs.

It is known that the TNM stage of the disease is the strongest determinant of survival in NSCLC patients. The new version has been shown to be more selective when compared with the older version [3]. However, patients with pCR have not yet been defined. Some authors have defined pCR as cT0N0-stage '0'. The presence of *in situ* carcinoma without distant organ and lymph node metastasis has been classified as stage 0 in the 8th edition.

As the difference between tumour size and survival is statistically significant, the 8th edition has classified stage I into 3 subgroups. In stage 1a1 group, 5-year survival (90%) after surgery was excellent in patients with a tumour diameter of less than 1 cm, whereas survival after surgery in stage 1b was less satisfactory (73%). In our study, 5-year survival rates of 82.6% were seen for stage 1a, 70.1% for stage Ib and 53.9% for stage 2 patients with early clinical stage disease following surgical resection. For pCR to be defined as stage 0, survival rates need to be superior to stage 1a1 and recurrence rates are expected to be lower. A 5-year survival rate of around 70% and a 20% recurrence rate in patients with pCR were found to be worse than stage 1a and similar to stage 1b. For this reason, the definition of stage 0 is wrong.

Limitations

Although all patients were prospectively recorded, our study had the same limitations as any retrospective analysis. The number of chemotherapy cycles varied between 2 and 6, and the radiotherapy dose was increased from 45 to 66 Gy over a period of 20 years. In addition, PET/CT was only available after 2007 in our centre, even though it represents a significant improvement over other methods.

CONCLUSION

- In all reported series, the number of pCR cases was fewer than 100. N/I therapy is rapidly becoming the preferred treatment modality. As a result of this treatment trend, the number of patients where pCR is seen is also expected to rise. Hence, further investigation regarding ypTNM and pCR is crucial.
- ypTNM staging remains the most important prognostic factor for patients undergoing direct surgical treatment as well as those who undergo surgery after N/I.
- Survival of patients after surgical excision was worse in ypTNM compared to pTNM even though stages were similar.
- Pathological complete response had the best long-term survival in group 2; so, pCR is a good prognostic factor.
- Compared to group 1, pCR had worse results compared stage 1a, similar compared to stage 1b and better compared to stages 2, 3 and 4.
- Based on these results, pCR should not be classified as stage 0.
- There is a need for larger series to determine the most fitting place of the pCR in TNM classification.

Conflict of interest: none declared.

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