Salvage surgery after definitive chemo-radiotherapy for patients with Non-Small Cell Lung Cancer

Laura Romero-Vielva[a,*], Santiago Viteri[b], Irene Moya-Horno[c], José Ignacio Toscas[d], José Antonio Maestre-Alcácer[a], Santiago Ramón y Cajal[e], Rafael Rosell[b]

[a] Thoracic Surgery Department, University Hospital General de Catalunya, C/ Pedro i Pons, 1., 08195, Sant Cugat del Vallès, Spain
[b] Medical Oncology Department, Rosell Oncology Institute (IOR), Dexeus University Hospital, Quironsalud Group, C/ Sabino Arana 5-19, 08028, Barcelona, Spain
[c] Medical Oncology Department Instituto Oncológico Dr Rosell (IOR), University Hospital General de Catalunya, C/ Pedro i Pons, 1., 08195, Sant Cugat del Vallès, Spain
[d] Radio-oncology Department, Institut Oncològic Teknon (IOT), Carrer de Vilana, 12, 08022, Barcelona, Spain
[e] Pathology Department, Vall d'Hebron Institute of Research, Vall d'Hebron University Hospital, Passeig Vall d'Hebron 119-129, 08035, Barcelona, Spain

ARTICLE INFO

ABSTRACT

Introduction: Despite all treatment advances, lung cancer is still the main cause of death worldwide. Treatment for resectable stage IIIA remains controversial including definitive chemoradiotherapy and induction treatment followed by surgery. After definitive chemoradiation up to 35% of patients will relapse locally. Experience with salvage resection after definitive chemoradiotherapy in lung cancer is limited. We present our experience in 27 patients who underwent surgical resection after definitive treatment.
Patients and methods: Between January 2007 and December 2016, 27 patients were evaluated in our department for surgical resection after receiving definitive chemoradiation treatment in different institutions. We conducted a retrospective study gathering the following data: age, gender, clinical and pathologic stage, histology, chemotherapy treatment regimen, radiotherapy dosage, surgical procedure and complications. Time between surgical resection and last follow-up was used to calculate Overall Survival (OS). Disease-Free Survival (DFS) was calculated from surgical resection to diagnosis of relapse.
Results: Most of the patients were men with a median age of 56.09 years. Median follow-up time was 46.94 months. All patients received platinum-based chemotherapy regimen and high-dose radiotherapy, except for one patient who received 45 Gy. Lobectomy and bilobectomy was performed in 7 patients each, and pneumonectomy in 13. Complications appeared in 5 patients. Bronchopleural fistula appeared in two patients, and only one death in the early postoperative period. The analysis showed an OS of 75.56 months, with 1-year, 3-year and 5-year survival of 74.1%, 57.8% and 53.3% respectively.
Conclusion: Salvage surgery in selected patients is technically feasible, with low morbidity and mortality rates and good long-term outcomes.

1. Introduction

Despite all treatment advances, lung cancer is still the main cause of death worldwide [1]. Approximately 30% of Non-Small Cell Lung Cancer (NSCLC) patients are diagnosed with locally advanced disease. Treatment for resectable stage IIIA remains controversial [2,3]. Guidelines recommendations include definitive chemoradiotherapy, induction chemotherapy followed by surgery, and induction chemoradiotherapy followed by surgical resection [4,5].

After definitive chemoradiation, with high-dose Radiotherapy (RT), up to 35% of patients will relapse locally [6–11]. Despite new chemotherapy drugs, long term survival is poor due to the resistance the

patients develop to the treatment [12]. This discouraging result compels clinicians to find other treatment options.

Salvage surgery is defined as the lung resection performed after definitive chemoradiation treatment. The initial treatment is planned as a curative intent; therefore, the patient receives high doses of radiotherapy, usually higher than 50 Gy and the surgical resection is performed more than 12 weeks after the last treatment session. This lapse between lung resection and high doses of radiotherapy increases the risk of complications. Fowler and cols reported a high postoperative morbidity and mortality in patients treated with 60 Gy of radiation therapy [13]. The higher rate of complications is thought to be related to postradiation fibrosis and the decrease in the microvascularity that

---

may impair the bronchial stump healing [8,14].

Several studies have shown that lung resections can be safely performed after high-dose radiotherapy [8,15–17].

We analyzed the results of a series of patients who underwent lung resection after definitive chemoradiation.

2. Patients and methods

Between January 2007 and December 2016, a total of 35 patients were evaluated in our department for surgical resection after receiving definitive chemoradiation treatment in different institutions. Reasons for submitting these patients to surgical evaluation included relapse on CT-Scan during follow-up after treatment or persistent disease in PET-Scan after treatment. Initial treatment and staging were performed in different institutions from Spain and other countries and were submitted to our institution, which is highly specialized in multimodality treatment of lung cancer patients, for a second opinion. All of them had received platinum-based chemotherapy and high dose-radiotherapy.

All the patients were evaluated individually and 27 were considered for salvage surgery. Eight patients were excluded of surgery because of medical comorbidities or unfitness for surgery.

We conducted a retrospective study gathering the following data: age, gender, clinical and pathologic stage, histology, chemotherapy treatment regimen, radiotherapy dosage, surgical procedure, complications, time between the end of treatment and surgical resection, type of relapse and last follow-up.

Patients evaluated before 2009 were staged according to the sixth edition of the TNM, and the seventh edition was used after 2010.

Patients underwent periodical follow-up by the thoracic surgeon and the medical oncologist every three months which included clinical examination, blood tests and CT-scan. Additional tests were ordered in case relapse signs or symptoms appeared.

Overall Survival (OS) and Disease-Free Survival (DFS) were analyzed with Kaplan-Meier and included any cause of death during the follow-up period. DFS was calculated from surgical resection to diagnosis of relapse. Time between surgical resection and last follow-up was used to calculate OS.

3. Results

Twenty-seven patients underwent salvage surgery after definitive chemoradiotherapy between January 2007 and December 2016. Most them were men (16 men and 9 women) with a median age of 56.09 years (34–73 years). Patient characteristics are detailed in Table 1. Median follow-up time was 46.94 months (0.80–119.83 months). Fourteen patients died during the follow-up period.

All patients received a platinum-based chemotherapy regimen and high-dose radiotherapy, except for one patient who received 45 Gy.

Regarding surgical procedures, 7 patients underwent a lobectomy, 7 patients a bilobectomy and pneumonectomy was performed in 13 patients (8 right pneumonectomies and 5 left ones). All the procedures were performed by open thoracotomy. A complete mediastinal lymphadenectomy was performed in all cases. An epidural catheter was placed for analgesia and all patients were submitted to an Intensive Care Unit during the immediate postoperative period. The median length of stay was 8 days (7–36 days).

Complications appeared in 4 patients, two presented postoperative bleeding, one of them requiring a thoracotomy. The two other complications were an atrial fibrillation in one patient and a bronchospasm in another. Bronchopleural fistula appeared in two patients, and only one of them died in the early postoperative period due to this complication.

All the resections were complete according to the definition of complete resection according to the definition of the International Association for the Study of Lung Cancer (IASLC) [18].

Eleven patients relapsed after surgical resection. Distant metastasis

Table 1
Patient characteristics.

Variables	No. of patients (%)
Overall	27
Sex	
Male	18 (66,7)
Female	9 (33.3)
Age (years, range)	56.09 y (34 – 73 y)
Histology	
Adenocarcinoma	18 (66.7)
Squamous cell carcinoma	7 (25.9)
Large cell carcinoma	2 (7.4)
Radiotherapy (GY)	
45	1 (3.7)
60	7 (25.9)
65	11 (40.7)
66	6 (22.2)
70	2 (7.4)
Type of resection	
Right upper Lobectomy	5 (18.5)
Middle Lobectomy	1 (3.7)
Right Lower Lobectomy	1 83.7)
Bilobectomy	7 (25.9)
Right Pneumonectomy	8 (29.6)
Left Pneumonectomy	5 (18.5)
cStage[a]	
IIIA	15 (55.6)
IIIB	9 (33.3)
IV	3(11.1)
pStage	
IA	4 (14.8)
IB	1 (3.7)
IIA	3 (11.1)
IIB	2 (7.4)
IIIA	12 (44.4)
IIIB	1 (3.7)
Complete response	4 (14.8)
Relapse	
No	15 (55.6)
Local relapse	4 (14.8)
Distant relapse	8 (29.6)
Complications	4 (14.8)
Bleeding	2 (7.4)
Atrial fibrillation	1 (3.7)
Bronchospasm	1 (3.7)
Postoperative mortality	1 (3.7)
Bronchopleural fistula	2 (7.4)

[a] cStage was considered the stage prior to definitive chemo-radiation.

appeared in 8 patients (29.6%), and another 4 of them relapsed locally (14.8%). Median DFS time in these patients was 14.97 months (HR 3.286 CI 95% 1.455–7.424) (Fig. 1A). Median Overall Survival time in this group was 52.70 months compared to 89.18 months in the group of patients that didn't relapse (HR 2.157 CI 95% 0.740–8.286) (p = 0.145).

Downstaging of the T category after chemoradiation was seen in 19 patients (70.37%) and downstaging of the N category was seen in 17 patients (62.96%).

The analysis showed a median OS of 75.56 months, (CI 95% 51.11–100.00), with 1-year, 3-year and 5-year survival rates of 74.1%, 57.8% and 53.3% respectively. (Fig. 1B)

There were no differences in survival according to gender or histology. Patients who relapsed locally had worse median survival than those who didn't relapse or relapsed distantly, 17.08 months (HR 4.041 CI 95% 1.118–14.415) vs 94.66 (HR 0.464 CI 95% 0.159–1.351) and 66.58 (HR 1.322 CI 95% 0.441–3.963) respectively (p 0.041). (Fig. 2)

T Downstaging significantly increased survival compared to the group of patients without downstaging. N downstaging showed a non-significant tendency to a better survival compared to the patients who were not N downstaged (Fig. 3A and B). Four patients presented a complete response with no viable tumor in the specimen. These four patients and the four patients staged as IA after surgery were alive at
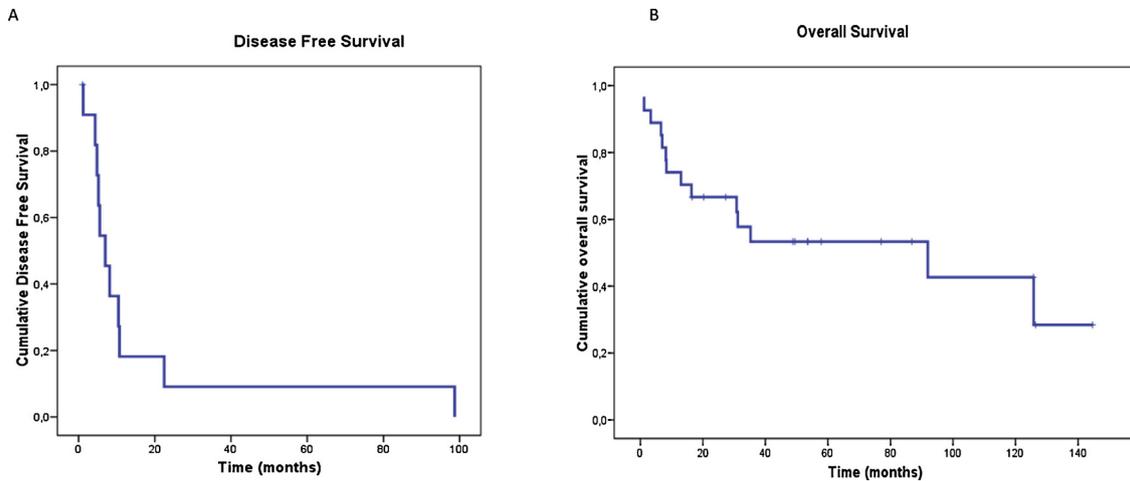
A

B

Fig. 1. (A) Disease Free Survival of patients undergoing salvage lung resection. (B) Overall Survival of patients undergoing salvage lung resection.
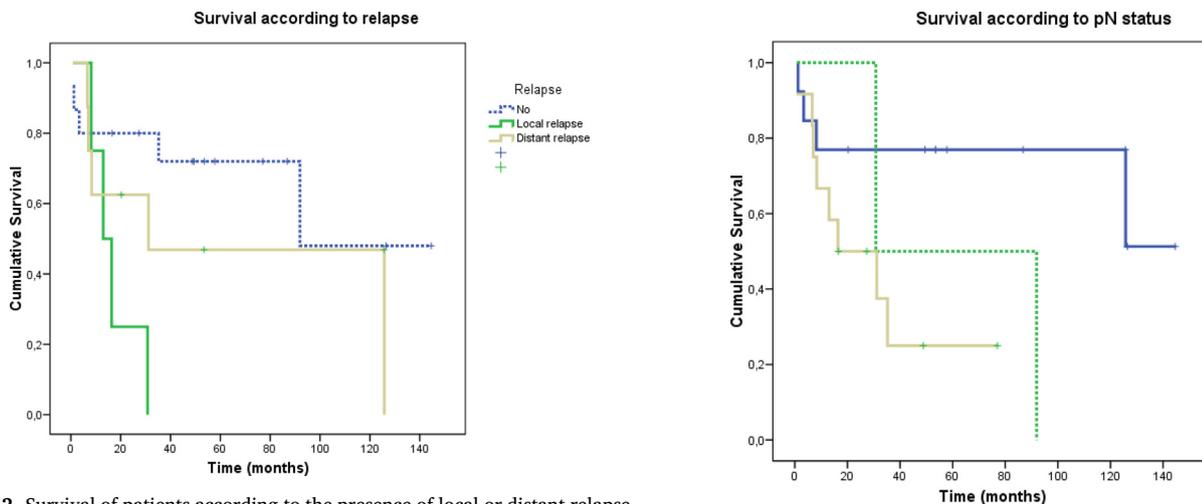

Fig. 2. Survival of patients according to the presence of local or distant relapse.

Fig. 4. Survival according to pN status.

last follow-up.

Survival according to pN status showed better results in pN0 patients at 107.40 months (HR 0.231 CI 95% $0.062 - 0.863$) compared to pN1 at 61.37 months (HR 1.686 CI95% 0.369–7.708) and pN2 at 31.89 months (HR 3.334 CI95% 0.988–11.254) (p0.061). 1-year survival rate of pN0 patients was 76.9% compared to 66.7% in pN2 patients. 3-year survival rate of pN0 was maintained at 76.9% and decreased to 25% in

pN2 patients. (Fig. 4)

4. Discussion

Guidelines include different options of treatment for patients with locally advanced NSCLC, such as, definitive chemoradiotherapy,
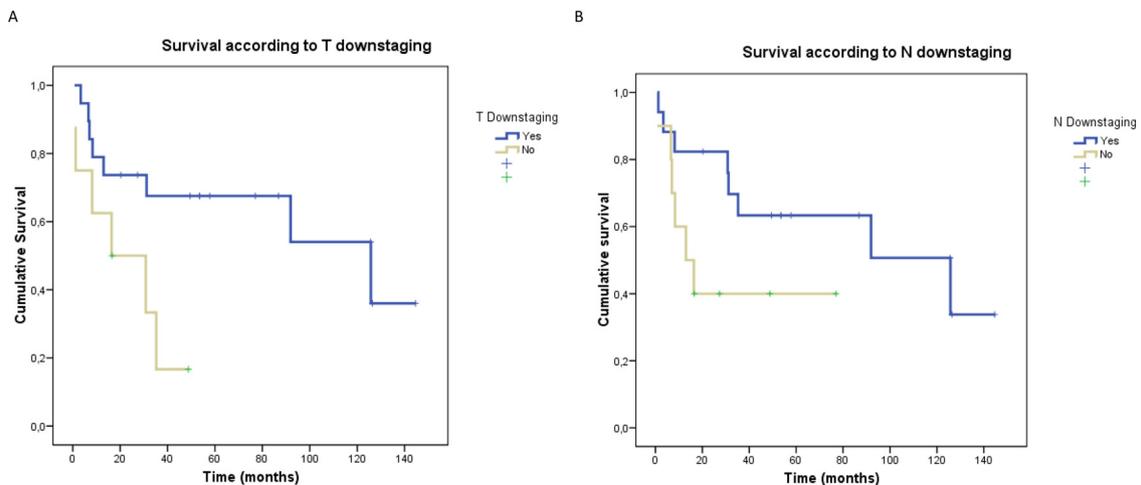
A

B

Fig. 3. (A) Survival according to T downstaging. (B) Survival according to N downstaging.

Table 2
Salvage surgery studies.

Authors	Year	N	Indication	Time from RT to surgery (weeks) (range)	Follow up (months)	Morbidity (%)	Mortality (%)	Overall survival (months)	Relapse free survival (months)
Sonnet [26]	2004	40	Mixed	52.5 (20-258) (days)	2.82 (years)	17.5	0	53	Not reached
Bauman [27]	2008	24	Mixed	20.6 (5.4-93.7)	29	58	4	30	12
Kuzmik [28]	2013	14	Recurrent tumor after RT ipsilateral or contralateral	n.s.	n.s.	43	0	9	n.s.
Uramoto [21]	2014	8	Mixed	n.s.	14	25	0	n.s.	5.9
Yang [36]	2015	31	Recurrent or persistent tumor after Radiotherapy	18 (8-111)	n.s.	48	0	32	10
Dickhoff [30]	2016	15	Local recurrence and persistent tumor after chemo, radiotherapy	21 (3-95)	12.1	40	6.7	46	43.6
Schreiner [35]	2016	9	Local recurrence after chemo, radiotherapy	30 (12-165)	30	22	11	23	21
Shimada [31]	2016	18	Local recurrence and persistent tumor after chemo, radiotherapy	38 (3-282)	47	28	0	n.s.	n.s.
Sawada [37]	2017	8	Local recurrence and persistent tumor after chemo, radiotherapy	n.s.	48	38	0	n.s.	n.s.
Casiraghi [8]	2017	35	Local recurrence and persistent tumor after chemo, radiotherapy	7 (1-39) (months)	13	25.7	0	13	12
Kaba [23]	2017	30	Mixed	n.s.	15	70	3	15	11
This study	2018	27	Local recurrence and persistent tumor after chemo, radiotherapy	35.8 (3.7-152)	46.9	14.8	3.7	75.6	14.9

n.s. non specified.

induction chemotherapy followed by surgery, and induction chemoradiotherapy followed by surgical resection [4,5,19]. However, up to 35% of patients treated with definitive chemoradiation will relapse locally [6–11]. Second line chemotherapy provides moderate response rates and long term survival remains under 9 months [20]. Long term survival after reirradiation ranges from 5 to 14 months and lung, esophagus and cord toxicity limits the dose that can be delivered due to the risk of high toxicity after reirradiation [9,21].

Salvage surgery can be an option for these patients who present relapse after definitive chemoradiation. There are different reasons to submit patients for salvage surgery, for example, relapse during follow-up after treatment, persistent disease on PET-scan, changes in the initial treatment plan and patients seeking a second opinion [7,22,27].

Other series of salvage resection included patients who underwent surgery due to an emergency situation (such as hemoptysis) and patients who should have undergone neoadjuvant or definitive chemo and/or radiotherapy, but were contraindicated because of severe comorbidities, making comparisons difficult [23,24].

In published salvage surgery series, the number of patients is insufficient to determine the early and long-term effects, and indications remain unclear. Complexity of the procedures, the high morbidity and mortality associated in the postoperative period, and the need of a highly experienced team are some of the issues that may explain these small numbers.

In 1993, Fowler presented a series with unacceptable mortality rates of 50% after pneumonectomy and a mortality of 23% in the whole series. Acute Respiratory Distress and bronchopleural fistula were the most frequent complications reported in these series [13].

There are two issues that make salvage surgery a complex procedure. One is the high doses of radiotherapy administered. The second one is the time between finishing RT treatment and resection, which is usually more than 8 weeks.

Changes in chemo and radiotherapy in recent years, such as, improvements in surgical equipment, preoperative evaluation and postoperative management of NSCLC patients, have decreased morbidity and mortality rates, making salvage surgery a less risky procedure [25,26].

Sonnet, in 2004, published a series of 40 NSCLC patients who underwent surgical resection after definitive chemoradiotherapy. Median time between radiotherapy and surgery was 2 months [27]. The procedures included 11 pneumonectomies and no postoperative mortality was reported. The differences between this series and the previously published could be explained by a better selection of patients, a different radiation technique, the coverage of the bronchial stump and improvements in the postoperative management [26].

Bauman, in 2008, reviewed a series of 24 patients who underwent salvage surgery after definitive chemoradiation treatment. Complications appeared in 14 patients, with one death from acute respiratory distress syndrome. Median overall survival was 30 months and 3-year survival was 47% [28].

In a series of 14 patients from The Yale School of Medicine, published in 2013, the complication rate was 43% with no postoperative deaths and a 2-year survival of 49% [29].

Casiraghi et al published a series of 35 patients who underwent salvage resection after definitive chemoradiotherapy. The series included a group of patients who received less than 59 Gy, but with an extended period between RT and surgery, and a group who received more than 59 Gy, but surgery was performed less than 8 weeks after finishing RT. They reported 51% morbidity and 5.7% mortality rates. The authors found that morbidity was associated with more than 3 chemotherapy cycles, but not related with a higher dose of RT or longer interval between end RT and surgery [8].

Uramoto compared 16 patients treated with salvage surgery with 54 patients treated with induction chemotherapy followed by surgery. Five-year OS rates in induction patients was 63.1% and 40.4% in salvage surgery patients (p = 0.147), showing that long-term outcome of

salvage surgery is favorable [30].

Twenty-one patients underwent salvage surgery in the series reported by Dickhoff, with a median follow-up of 12.1 months, an OS of 46 months and an event-free survival of 43.6 months. The postoperative mortality was 6.7% (1 patient) and the morbidity rate was 40% (6 patients) [31].

Reasons to consider salvage surgery vary among the different series published. (Table 2) In our series, all the patients were submitted to our department after definitive treatment with chemo and radiotherapy presenting recurrent or persistent tumor after treatment, as previously mentioned. Median time between last RT dose and surgical resection was 8.35 months, with one patient being operated 35.47 months after finishing RT.

Among the whole series of 27 patients, 13 underwent a pneumonectomy (8 right pneumonectomies and 5 left ones). Despite the fact that some patients showed high risk characteristics, there was only one postoperative death, a patient who developed pneumonia after a right pneumonectomy, accounting for a 3.7% postoperative mortality.

The morbidity rate in our series was 14.8%. The main complications included one atrial fibrillation, one bronchospasm, and two major bleedings during the immediate postoperative period; but only one patient required a thoracotomy to control the bleeding. The patients who presented complications had undergone two pneumonectomies, one bilobectomy and one lobectomy. This morbidity rate is lower than the one reported in Shimada's series [32], and can also be explained by a careful patient selection.

Two patients presented a bronchopleural fistula during follow-up (7.4%), one after a right pneumonectomy and one after a left pneumonectomy. Both patients were managed successfully with conservative treatment.

The low complication rate is noteworthy, and it may be attributable to a meticulous surgical technique and a careful management during the postoperative period. The resected bronchus was managed carefully in all patients, leaving a short stump surrounded by mediastinal tissue to facilitate healing. The stump was covered in some patients, if needed, with pleura, intercostal muscle or, in recent years, by a free pericardial fat pad, as published by Matsuoka [33].

The survival rate in our series is a 74.1% 1-year survival and a 53.3% 5-year survival, comparable to some of the series published of IIIA and IIIB NSCLC patients [26,27,29,34,35]. This fact may be related to patient selection and the early diagnosis of relapses due to close patient follow-up.

DFS in our series is 14.97 months. The significant disparity between DFS and OS could be explained by the different second or third line systemic therapies that the patients underwent after the surgical resection, according to pStage or to the development of a relapse. None of the patients received immunotherapy.

OS is related to lymph node involvement. The group of pN0 patients showed an OS of 107.40 months higher than the group of pN2 patients, with an OS of 31.89 months.

The group of patients who didn't relapse showed a better OS (89.18 months) compared to 52.70 months of the group who relapsed, similar to the data published. Four patients suffered local relapse and 8 showed distant metastases, with a DFS of 16.24 months in the relapse group.

Surgical resection is recommended to be performed within the next two months after finishing radiotherapy treatment. In our series, this time was longer, with a median of 8 months between the end of RT treatment and surgery. The main reason for this was because the patients received their initial treatment in a different center and were later submitted to our department for evaluation.

The long period of time between radiotherapy and surgery increases the fibrotic reaction and increases the difficulty in the dissection of major vessels [27]. In addition, the decrease in tissue vascularization may impair wound healing, increasing the risk of bronchopleural fistula. However, in our experience, as it has been published by other authors, the number of complications is low and there was only one

death in the postoperative period, showing that a thoughtful selection of patients and a careful surgical technique makes the procedure safe [8,27,28,36,31,36].

Four of the patients showed a complete pathologic response, with no viable tumor on the surgical specimen. All the patients had a PET-CT scan that showed a hypermetabolic area. Histologic confirmation of the hypermetabolic area was not performed due to the poor sensitivity of this procedure after definitive chemoradiotherapy [8,27,37,38]. As has been reported in previous series, transthoracic fine-needle aspiration provides limited pathologic information and is difficult to distinguish between radiation-induced fibrosis and tumor-induced fibrosis, and may lead to false-negative findings. [39] Besides, inflammation processes or superinfection of the tumor area can make difficult to achieve a histologic diagnosis. [8]. Therefore, we decided not to obtain histological confirmation before surgery.

Considering only downstaged patients for surgery requires a reliable method to identify them before resection. Many studies have evaluated different methods of restaging after induction and the results vary depending on the option [40,41]. Restaging by imaging alone is unreliable because both False Negative (FN) and False Positive (FP) rates are high. Mediastinal node involvement has FN and FP rates of 33% and 33% by CT scan, and 25% and 33% by PET-CT scan. Remediastinoscopy carries a high FN rate (22%). Needle-based mediastinal staging (Endobronchial ultrasound BUS and Esophageal Ultrasound EUS) has been associated with a FN rate of approximately 20–25% [40,41].

Some studies have shown that survival for patients who have not been downstaged after induction have acceptable survival rate, similar to the downstaged patient [42–44]. Our group uses restaging by image only to rule out progression after induction, and therefore we used the same approach for these patients.

We acknowledge that this series has important limitations. It is a single institution retrospective series, including highly selected patients during a long period of time. The patients were first treated at different institutions and sent for evaluation of salvage surgery for different reasons, reflecting the heterogeneity with treatment approaches. The series is small, which didn't allow to make any conclusions regarding the relationship between preoperative parameters, factors predicting failure or time between RT and surgery in overall results.

The study lacks a control group because it is difficult to make a randomized controlled trial. Therefore, the results of our study must be carefully interpreted due to the low number of patients included.

In our opinion, lung cancer patients, especially those with locally advanced stages, should always be evaluated by an experienced multidisciplinary team including a thoracic surgeon, as the treatment guidelines recommend [4].

As a conclusion, salvage surgery in selected patients is technically feasible, with low morbidity and mortality rates and good long-term outcomes.

Conflicts of interest

None.

Acknowledgements

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 68 (1) (2018) 7–30, https://doi.org/10.3322/caac.21442.

[2] M. Reck, D.F. Heigener, T. Mok, J.-C. Soria, K.F. Rabe, Management of non-small-cell lung cancer: recent developments, Lancet 382 (9893) (2013) 709–719, https://

doi.org/10.1016/S0140-6736(13)61502-0.

[3] N. Ramnath, T.J. Dilling, L.J. Harris, A.W. Kim, G.C. Michaud, A.A. Balekian, et al., Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest 143 (5 Suppl) (2013) e314S–e340S, https://doi.org/10.1378/chest.12-2360.

[4] NCCN guidelines https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

[5] D.S. Ettinger, D.E. Wood, W. Akerley, L.A. Bazhenova, H. Borghaei, D.R. Camidge, et al., Non-small cell lung cancer, version 1.2015, J. Natl. Compr. Can. Netw. 12 (12) (2014) 1738–1761.

[6] M. Perol, C. Chouaid, D. Perol, F. Barlesi, R. Gervais, V. Westeel, et al., Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer, J. Clin. Oncol. 30 (28) (2012) 3516–3524, https://doi.org/10.1200/JCO.2011.39.9782.

[7] A. Van Breussegem, J.M. Hendriks, P. Lauwers, P.E. Van Schil, Salvage surgery after high-dose radiotherapy, J. Thorac. Dis. 9 (Suppl. 3) (2017) S193–S200, https://doi.org/10.21037/jtd.2017.03.88.

[8] M. Casiraghi, P. Maisonneuve, G. Piperno, R. Bellini, D. Brambilla, F. Petrella, F. Marinis, L. Spaggiari, Salvage surgery after definitive chemoradiotherapy for non-small cell lung Cancer, Semin. Thorac. Cardiovasc. Surg. 29 (Summer (2)) (2017) 233–241, https://doi.org/10.1053/j.semtcvs.2017.02.001.

[9] K.L. Wu, G.L. Jiang, H. Qian, L.J. Wang, H.J. Yang, X.L. Fu, S. Zhao, Three-dimensional conformal radiotherapy for locoregionally recurrent lung carcinoma after external beam irradiation: a prospective phase I-II clinical trial, Int. J. Radiat. Oncol. Biol. Phys. 57 (5) (2003) 1345–1350, https://doi.org/10.1016/S0360-3016(03)00768-5.

[10] E.L. Gressen, M. Werner-Wasik, J. Cohn, A. Topham, W.J. Curran Jr., Thoracic reirradiation for symptomatic relief after prior radiotherapeutic management for lung cancer, Am. J. Clin. Oncol. 23 (2) (2000) 160–163, https://doi.org/10.1097/00000421-200004000-00011.

[11] J.D. Bradley, R. Paulus, R. Komaki, G. Masters, G. Blumenschein, S. Schild, J. Bogart, C. Hu, K. Forster, A. Magliocco, V. Kavadi, Y.I. Garces, S. Narayan, P. Iyengar, C. Robinson, R.B. Wynn, C. Koprowski, J. Meng, J. Beitler, R. Gaur, W. Curran Jr, H. Choy, Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study, Lancet Oncol. 16 (2) (2015) 187–199, https://doi.org/10.1016/S1470-2045(14)71207-0.

[12] H. Uramoto, S. Yano, F. Tanaka, T790M is associated with a favorable prognosis in Japanese patients treated with an EGFR-TKI, Lung Cancer 76 (1) (2012) 129–130, https://doi.org/10.1016/j.lungcan.2012.01.010.

[13] W.C. Fowler, C.J. Langer, W.J. Curran Jr., S.M. Keller, Postoperative complications after combined neoadjuvant treatment of lung cancer, Ann. Thorac. Surg. 55 (4) (1993) 986–989.

[14] F.M. Kong, R. Ten Haken, A. Eisbruch, T.S. Lawrence, Non-small cell lung cancer therapy-related pulmonary toxicity: an update on radiation pneumonitis and fibrosis, Semin. Oncol. 32 (2 Suppl. 3) (2005) S42–54.

[15] R.J. Cerfolio, A.S. Bryant, V.L. Jones, R.M. Cerfolio, Pulmonary Resection after concurrent chemotherapy and High Dose (60Gy) Radiation for Non-Small Cell Lung Cancer is safe and may provide increased survival, Eur. J. Cardiothorac. Surg. 35 (4) (2009) 718–723, https://doi.org/10.1016/j.ejcts.2008.12.029.

[16] B.D. Daly, H.C. Fernando, A. Ketchedjian, T.A. Dipetrillo, L.A. Kachnic, D.M. Morelli, R.J. Shemin, Pneumonectomy after high-dose radiation and concurrent chemotherapy for non small cell lung cancer, Ann. Thorac. Surg. 82 (1) (2006) 227–231, https://doi.org/10.1016/j.athoracsur.2006.02.061.

[17] M.J. Krasna, Z. Gamliel, W.M. Burrows, J.R. Sonett, K.F. Kwong, M.J. Edelman, P.F. Hausner, L.A. Doyle, C. DeYoung, M. Suntharalingam, Pneumonectomy for lung cancer after preoperative concurrent chemotherapy and high-dose radiation, Ann. Thorac. Surg. 89 (1) (2010) 200–206, https://doi.org/10.1016/j.athoracsur.2009.08.069 discussion 206.

[18] R. Rami-Porta, C. Wittekind, P. Goldstraw, International Association for the Study of Lung Cancer (IASLC) Staging Committee. Complete resection in lung cancer surgery: proposed definition, Lung Cancer 49 (1) (2005) 25–33, https://doi.org/10.1016/j.lungcan.2005.01.001.

[19] P.E. Van Schil, L. Berzenji, S.K. Yogeswaran, J.M. Hendriks, P. Lauwers, Surgical management of stage IIIA non-small cell lung cancer, Front. Oncol. 7 (2017) 249, https://doi.org/10.3389/fonc.2017.00249.

[20] N. Hanna, Second-line treatment of non-small cell lung cancer: big targets, small progress; small targets, big progress? J. Thorac. Oncol. 1 (9) (2006) 927–928, https://doi.org/10.1016/S1556-0864(15)31622-1.

[21] J. Noble, P.M. Ellis, J.A. Mackay, W.K. Evans, Lung Cancer Disease Site Group of Cancer care Ontario's Program in Evidence-based Care. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a systematic review and practice guideline, J. Thorac. Oncol. 1 (9) (2006) 1042–1058, https://doi.org/10.1016/S1556-0864(15)31641-5.

[22] H. Uramoto, Current topics on salvage thoracic surgery in patients with primary lung Cancer, Ann. Thorac. Cardiovasc. Surg. 22 (2) (2016) 65–68, https://doi.org/10.5761/atcs.ra.16-00019.

[23] H. Uramoto, Tanaka F salvage thoracic surgery in patients with primary lung cancer, Lung Cancer 84 (2) (2014) 151–155, https://doi.org/10.1016/j.lungcan.2014.02.004.

[24] E. Kaba, M.O. Ozyurtkan, K. Ayalp, T. Cosgun, M.R. Alomari, A. Toker, Salvage thoracic surgery in patients with lung cancer: potential indications and benefits, J. Cardiothorac. Surg. 13 (1) (2018) 13, https://doi.org/10.1186/s13019-018-0693-x.

[25] P.C. Lee, A. Nasar, J.L. Port, S. Paul, B. Stiles, Y.L. Chiu, et al., Long-term survival after lobectomy for non-small cell lung cancer by video-assisted thoracic surgery versus thoracotomy, Ann. Thorac. Surg. 96 (3) (2013) 951–960, https://doi.org/10.1016/j.athoracsur.2013.04.104 discussion 60-1.

[26] J. Subramanian, S.N. Waqar, D. Morgensztern, R. Govindan, Recent advances in lung cancer: summary of presentations from the 47 th annual meeting of the American Society of Clinical Oncology (ASCO) 2011, J. Thorac. Oncol. 7 (1) (2012) 260–265, https://doi.org/10.1097/JTO.0b013e31823a40a6.

[27] J.R. Sonett, M. Suntharalingam, M.J. Edelman, A.B. Patel, Z. Gamliel, A. Doyle, et al., Pulmonary resection after curative intent radiotherapy (&59 Gy) and concurrent chemotherapy in non-small-cell lung cancer, Ann. Thorac. Surg. 78 (4) (2004) 1200–1205, https://doi.org/10.1016/j.athoracsur.2004.04.085 discussion 6.

[28] J.E. Bauman, M.S. Mulligan, R.G. Martins, B.F. Kurland, K.D. Eaton, D.E. Wood, Salvage lung resection after definitive radiation (&59 Gy) for non-small cell lung cancer: surgical and oncologic outcomes, Ann. Thorac. Surg. 86 (5) (2008) 1632–1638, https://doi.org/10.1016/j.athoracsur.2008.07.042 discussion 8-9.

[29] G.A. Kuzmik, F.C. Detterbeck, R.H. Decker, D.J. Boffa, Z. Wang, I.B. Oliva, A.W. Kim, Pulmonary resections following prior definitive chemoradiation therapy are associated with acceptable survival, Eur. J. Cardiothorac. Surg. 44 (July (1)) (2013) e66–70, https://doi.org/10.1093/ejcts/ezt184.

[30] H. Uramoto, Y. Nakajima, H. Kinoshita, H. Akiyama, Equivalent outcome of patients with locally advanced NSCLC treated with salvage surgery compared to induction chemotherapy followed by surgical resection, Anticancer Res. 36 (August (8)) (2016) 4243–4247.

[31] C. Dickhoff, M. Dahele, M.A. Paul, P.M. van de Ven, A.J. de Langen, S. Senan, E.F. Smit, K.J. Hartemink, Salvage surgery for locoregional recurrence or persistent tumor after high dose chemoradiotherapy for locally advanced non-small cell lung cancer, Lung Cancer 94 (2016) 108–113, https://doi.org/10.1016/j.lungcan.2016.02.005.

[32] Y. Shimada, K. Suzuki, M. Okada, H. Nakayama, H. Ito, T. Mitsudomi, H. Saji, K. Takamochi, Y. Kudo, A. Hattori, T. Mimae, K. Aokage, T. Nishii, M. Tsuboi, N. Ikeda, Feasibility and efficacy of salvage lung resection after definitive chemoradiation therapy for Stage III non-small-cell lung cancer, Interact. Cardiovasc. Thorac. Surg. 23 (6) (2016) 895–901, https://doi.org/10.1093/icvts/ivw245.

[33] K. Matsuoka, N. Imanishi, T. Yamada, T. Matsuoka, S. Nagai, M. Ueda, Y. Miyamoto, Clinical results of bronchial stump coverage using free pericardial fat pad, Interact. Cardiovasc. Thorac. Surg. 23 (4) (2016) 553–559, https://doi.org/10.1093/icvts/ivw193.

[34] K.S. Albain, V.W. Rusch, J.J. Crowley, T.W. Rice, A.T. Turrisi 3rd, J.K. Weick, et al., Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805, J. Clin. Oncol. 13 (8) (1995) 1880–1892, https://doi.org/10.1200/JCO.1995.13.8.1880.

[35] S.A. Vora, B.D. Daly, L. Blaszkowsky, J.J. McGrath, M. Bankoff, S. Supran, T.A. Dipetillo, High dose radiation therapy and chemotherapy as induction treatment for stage III nonsmall cell lung carcinoma, Cancer 89 (9) (2000) 1946–1952.

[36] W. Schreiner, W. Dudek, H. Sirbu, Is salvage surgery for recurrent non-small-cell lung cancer after definitive non-operative therapy associated with reasonable survival? Interact. Cardiovasc. Thorac. Surg. 21 (2015) 682–684, https://doi.org/10.1093/icvts/ivv243.

[37] C.F. Yang, R.R. Meyerhoff, S.J. Stephens, T. Singhapricha, C.B. Toomey, K.L. Anderson, C. Kelsey, D. Harpole, T.A. D'Amico, M.F. Berry, Long-term outcomes of lobectomy for non-small cell lung Cancer After definitive radiation treatment, Ann. Thorac. Surg. 99 (6) (2015) 1914–1920, https://doi.org/10.1016/j.athoracsur.2015.01.064.

[38] S. Sawada, H. Suehisa, T. Ueno, M. Yamashita, Eight cases of salvage pulmonary resection for residual disease of isolated local recurrence detected after definitive chemoradiotherapy for N2 Stage-IIIA lung cancer, Asian J. Surg. 40 (2) (2017) 95–99, https://doi.org/10.1016/j.asjsur.2015.05.006.

[39] W. Schreiner, W. Dudek, S. Lettmaier, R. Fietkau, H. Sirbu, Should salvage surgery be considered for local recurrence after definitive chemoradiation in locally advanced non-small cell lung cancer? J. Cardiothorac. Surg. 11 (2016) 9, https://doi.org/10.1186/s13019-016-0396-0.

[40] S. de Cabanyes Candela, F.C. Detterbeck, A systematic review of restaging after induction therapy for stage IIIA lung cancer: prediction of pathologic stage, J. Thorac. Oncol. 5 (3) (2010) 389–398, https://doi.org/10.1097/JTO.0b013e3181ce3e5e.

[41] F. Detterbeck, M. Jantz, M. Wallace, et al., Invasive mediastinal staging of lung cancer: an ACCP evidence based clinical practice guideline (2nd edition), Chest 132 (2007) 202S–220S, https://doi.org/10.1378/chest.07-1362.

[42] R.T. Ripley, K. Suzuki, K.S. Tan, et al., Postinduction positron emission tomography assessment of N2 nodes is not associated with ypN2 disease or overall survival in stage IIIA non-small cell lung cancer, J. Thorac. Cardiovasc. Surg. 151 (2016) 969–977, https://doi.org/10.1016/j.jtcvs.2015.09.127 979.e1-3.

[43] A. Stefani, M. Alifano, A. Bobbio, M. Grigoroiu, R. Jouni, P. Magdeleinat, J.F. Regnard, Which patients should be operated on after induction chemotherapy for N2 non-small cell lung cancer? Analysis of a 7-year experience in 175 patients, J. Thorac. Cardiovasc. Surg. 140 (August (2)) (2010) 356–363, https://doi.org/10.1016/j.jtcvs.2010.02.018.

[44] S. Renaud, P.E. Falcoz, A. Olland, J. Reeb, N. Santelmo, G. Massard, Mediastinal downstaging after induction treatment is not a significant prognostic factor to select patients who would benefit from surgery: the clinical value of the lymph node ratio, Interact. Cardiovasc. Thorac. Surg. 20 (2) (2015) 222–227, https://doi.org/10.1093/icvts/ivu378.