SICT
Mantova, 4-6 October 2018

SALVAGE SURGERY FOR LUNG CANCER

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DEFINITION 1

Salvage surgery may be defined as surgical resection after definitive medical treatment to improve patient survival in absence of other treatment options

Kuzmik et al European Journal of Cardio-Thoracic Surgery 2013

DEFINITION 2

Salvage surgery may be considered an extension of surgery to achieve cure when nothing seems possible

That is called
EXTENDED RESECTION

WHEN

- Lung cancer recurrence/persistance following definitive chemo-radiation therapy
- Resection for chronic persistent disease after biological treatment
- Progression after induction therapy?
- Emergency?

SALVAGE SURGERY AFTER DEFINITIVE CHEMORADIOTHERAPY

- Following definitive chemoradiation therapy, 24–35% of patients with locally advanced NSCLC have recurrence
- Surgical resection for lung cancer recurrence following definitive chemoradiation may be considered to improve patient survival → **salvage surgery**
- The role of salvage resection remains poorly defined and associated with high morbidity and mortality

WHAT IS DEFINITIVE CHEMORADIOTHERAPY?

- Radiotherapy > 59 Gy
- Surgery after definitive CT/RT > 12 weeks
- No planned surgery
- No trimodality treatment

Literature

Authors	N°	RT (Gy)	Timing (weeks)	Morbidity (%)	Mortality (%)	OS
Sonett 2004	40	59-66	2.8-36.8	17.5	-	46% 5 yrs
Bauman 2008	24	59-70	5.4-93.7	58	4	47% 3 yrs
Kuzmik 2013	14	30-74	-	43	-	49% 2 yrs
Dickhoff 2016	15	60-70	3-95	40	6.7	46 months
Casiraghi 2017	43	45-74	4-156	45	3.7	42% 3 yrs
Kaba 2018	30*	-	-	70	3	15 months
Daly 2006	30	59	-	16	13	38% 5 yrs
Cerfolio 2009	216	60-72	4.8-12.7	17	2.3	34% 5yrs
Krasna 2010	29	37.5-69.6	3.2-22.1	52	3.4	48% 3 yrs

* Only 10 after definitive CT/RT
Yellow: induction CT/RT

Salvage thoracic surgery in patients with lung cancer: potential indications and benefits

Kaba, J CardioThor Surg 2018

	Total (n = 30)	Group 1 (n = 22)	Group 2 (n = 3)	Group 3 (n = 5)
Age (years, ± SD)	63 ± 7	63 ± 8	64 ± 3	62 ± 8
Male/Female	26/4	21/1	3/0	2/3
Presence of comorbidity (n, %)	18 (60%)	11 (50%)	2 (67%)	5 (100%)
Operation type (n)				
Lobectomy	14	11	0	3
Greater resection	11[a]	8[b]	2[c]	1[d]
Segmentectomy	5	3	1	1
Extended resection (n, %)**	16 (53%)	13 (59%)	1 (33%)	2 (40%)
Length of hospital stay (mean days ± SD)	11 ± 4	10 ± 4	14 ± 2	13 ± 9
Mortality (n, %)	1 (3%)	0	0	1 (20%)
Morbidity (n, %)	21 (70%)	14 (64%)	3 (100%)	4 (80%)
Overall survival (mean months ± SD)	19 ± 13	22 ± 13	13 ± 5	6 ± 2
Relapse-free survival (mean months ± SD)	14 ± 12	16 ± 13	9 ± 4	6 ± 2

Group 1: definitive CT/RT
Group 2: emergency
Group 3:IIIA, IIIB, or IV disease but no CT/RT for comorbidities

HOW

- Selection of the candidate for this type of surgery is paramount
- Extended surgery
- Radicality -> R0
- Multidisciplinary team and expert thoracic surgeon

Salvage Surgery After Definitive Chemoradiotherapy for Non–small Cell Lung Cancer

Monica Casiraghi, MD,[*] Patrick Maisonneuve, Eng,[†] Gaia Piperno, MD,[‡] Roberto Bellini, MD,[*] Daniela Brambilla, Msc,[*] Francesco Petrella, MD,[*] Filippo De Marinis, MD,[§] and Lorenzo Spaggiari, MD, PhD[,‖]*

Semin Thoracic Surg 2017

53 NSCLC after definitive chemo-radiotherapy
Explorative thoracotomies: 10 (10.8%)
Resected patients: 43 (81.2%)

All pts received preoperative chemotherapy (1-3 cycles) and radiotherapy (Gy mean: 51)

Median time from chemo-radiation to resection was 12 weeks

→ Pet scan and cyto-histological confirmation of relapses were attempted in all pts

Results

2002 - 2012

Resected patients: 43

Pneumonectomy	20 (46%)
Lobectomy	21 (48%)
Bilobectomy	1 (2%)
Segmentectomy	1 (2%)

R0	41 (95%)
R1	2 (5%)

Kaba, 2018: 59%

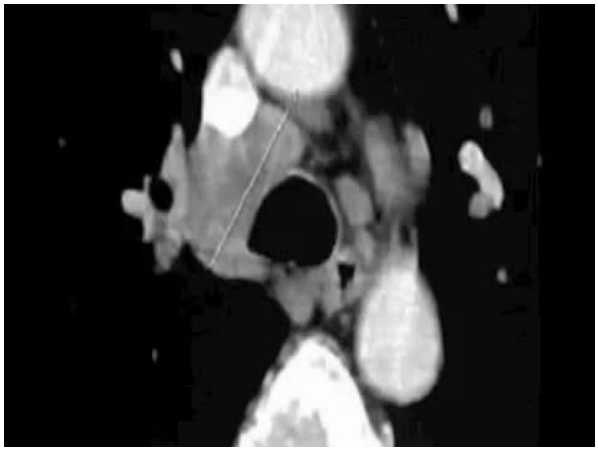
Extended resection:	**24 (55%)**
Pancoast/chest wall	7
SVC	2
Tracheal sleeve	3
Atrium/aorta	2/1
Sleeve bronchial/vascular	2/1
Vertebrae	1
Intrapericardial	5

30 days Mortality: 2 (3.7%)

Morbidity:

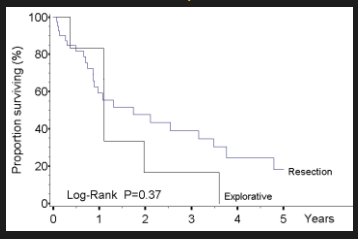
minor	13	(24.5%)
major	11	(20.8%)

Kaba, 2018: 64%



OVERALL SURVIVAL

Mean follow up 21 months



	Baseline	1year	2 years	3 years	4 years	5 years
Overall survival						
Explorative	100%	88% (65-100)	18% (0-49)	18% (0-49)	0%	0%
Resection	100%	**62%** (47-78)	**51%** (33-68)	**42%** (24-60)	**26%** (8-44)	**20%** (2-37)

THORACIC – Editorial Commentary

Salvage Resections for Stage III Non–small Cell Lung Cancer: A Curious Area of Investigation

Jessica S. Donington, MD, MSCr

Semin Thoracic Surg 2018

Table. Outcomes of Salvage Resections for Stage III Non Small Cell Lung Cancer

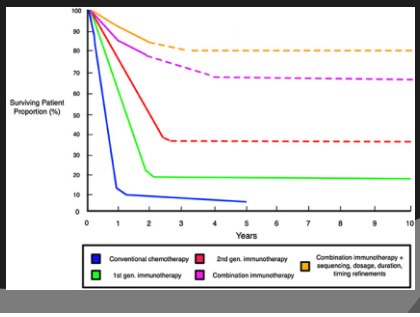
Author	Year	#	Average interval in weeks from therapy to surgery	Morbidity	Mortality	Median survival (mo)
Bauman et al[3]	2008	24	18	58%	4%	30
Kuzmik et al[9]	2013	14	33	43%	0%	9
Yang et al[4]	2015	31	21	48%	0%	32
Casiraghi et al[7]	2017	35	30	26%	6%	13

- Patients initially excluded from surgery more for institutional bias rather than extend of disease → "…>30% local recurrence…surgery represents the only chance of cure"
- 17 pneumonectomy and 13 extended resection → "…complexity of resection safely performed"
- Vascularized flap used extensively → "…amazing ability to rescue patients from post operative complications"

Immuno-Oncology: Emerging Targets and Combination Therapies

Henry T. Marshall and Mustafa B. A. Djamgoz*

Front Oncol 2018



The NEW ENGLAND JOURNAL of MEDICINE 2018

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

METHODS

In this double-blind, phase 3 trial, we randomly assigned (in a 2:1 ratio) 616 patients with metastatic nonsquamous NSCLC without sensitizing *EGFR* or *ALK* mutations who had received no previous treatment for metastatic disease to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy. Crossover to pembrolizumab mono-

CONCLUSIONS

In patients with previously untreated metastatic nonsquamous NSCLC without *EGFR* or *ALK* mutations, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and progression-free survival than chemotherapy alone. (Funded by Merck; KEYNOTE-189 ClinicalTrials.gov number, NCT02578680.)

Immunotherapeutics in the form of checkpoint inhibitors have dramatically altered the treatment of stage IV disease and are now being moved in to trials in stage III. They may significantly impact the treatment landscape before, after, or in lieu of surgery.

Tecemotide in unresectable stage III non-small-cell lung cancer in the phase III START study: updated overall survival and biomarker analyses

P. Mitchell[1]*, N. Thatcher[2], M. A. Socinski[3], E. Wasilewska-Tesluk[4], K. Horwood[5], A. Szczesna[6], C. Martín[7], Y. Ragulin[8], M. Zukin[9], C. Helwig[10], M. Falk[10], C. Butts[11] & F. A. Shepherd[12]

Ann Oncol 2018

Background: Tecemotide is a MUC1-antigen-specific cancer immunotherapy. The phase III START study did not meet its primary end point but reported notable survival benefit with tecemotide versus placebo in an exploratory analysis of the predefined patient subgroup treated with concurrent chemoradiotherapy. Here, we attempted to gain further insight into the effects of tecemotide in START.

Patients and methods: START recruited patients who did not progress following frontline chemoradiotherapy for unresectable stage III non-small-cell lung cancer. We present updated overall survival (OS) data and exploratory analyses of OS for baseline biomarkers: soluble MUC1 (sMUC1), antinuclear antibodies (ANA), neutrophil/lymphocyte ratio (NLR), lymphocyte count, and HLA type.

Results: Updated OS data are consistent with the primary analysis: median 25.8 months (tecemotide) versus 22.4 months (placebo) (HR 0.89, 95% CI 0.77–1.03, $P = 0.111$), with ~20 months additional median follow-up time compared with the primary analysis. Exploratory analysis of the predefined subgroup treated with concurrent chemoradiotherapy revealed clinically relevant prolonged OS with tecemotide versus placebo (29.4 versus 20.8 months; HR 0.81, 95% CI 0.68–0.98, $P = 0.026$). No improvement was seen with sequential chemoradiotherapy. High sMUC1 and ANA correlated with a possible survival benefit with tecemotide (interaction $P = 0.0085$ and 0.0022) and might have future value as biomarkers. Interactions between lymphocyte count, NLR, or prespecified HLA alleles and treatment effect were not observed.

Conclusion: Updated OS data support potential treatment benefit with tecemotide in patients treated with concurrent chemoradiotherapy. Exploratory biomarker analyses suggest that elevated sMUC1 or ANA levels correlate with tecemotide benefit.

Conclusions

- Salvage pulmonary resection is a viable option to improve survival in the setting of recurrent lung cancer after chemoradiotherapy
- Extended resections after chemoradiotherapy are feasible but it is still challenging; the selection of the candidate is paramount considering the high morbidity and mortality
- No surgery if disease progressive after induction therapy

Conclusions

Multidisciplinary team and expert thoracic surgeon are essential for the correct treatment choice