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EUROPEAN LUNG CANCER CONFERENCE

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How to improve stage III NSCLC multimodality treatment

Surgical techniques relevant for stage III disease

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I have no conflicts of interest to declare

The heterogenity in the subgroups of stage III disease demands an implications of patients selection. It is for the treatment choice and the prognosis of important significance

(Recommendation grade B)

Subgroups Stage IIIA/IIIB disease

(IASLC, UICC-TNM Classification 2010)

IIIA	T1-2	N2	M0
	T3	N1-2	M0
	T3 same lobe	N1-2	M0
	T4 extension	N0-1	M0
	T4 other lobe ipsilateral	N0-1	M0

IIIB	**T4 extension**	N2	M0
	T4 other lobe ipsilateral	N2	M0
	T any	N3	M0

StageT4 N0-1 disease

Primary surgery or integration of surgery in a multimodality treatment is recommended for patients with functional and medical operability and involvement of

- carina / trachea
- heart (left atrium)
- great vessels (vena cava, pulmonary artery, aorta)
- vertebral body
- metastasis other lobe ipsilateral

(recommendation grade B)

StageT4 N2 disease

For patients with acceptable performance status, combination of Chemotherapy and Radiation is the choice of treatment
(recommendation grade A)

For selected cases after induction CTx/RTx and good response the integration of surgery could be followed (if possible inside of studies)
(recommendation grade D)

T4 - Surgical management

Carina/ Trachea
Left Atrium
Superior Vena cava
Pulmonary artery
Aorta
Vertebral body
Metastasis other lobe ipsilateral

Carina/Trachea

In the last decades the number of patients needed a carinal resection significantly decreased because of the induction treatment and the down staging effect
Publications with large experience
Not exactly define between T3 and T4 Tumoren
Induction treatment is not acceptable by all surgeons because of healing complications
Good long term results by R0-Resection und N0/N1 pathology are observed

Carina/Trachea

Author	n	Induction	R0	N2	Letality	5y Surv all	5y surv N2
Spaggiari (2013)	33	23p CT	79%	42%	18%	22%	22% (N+)
Jiang (2009)	41	NR	NR	NR	2,4	26,8%	7.1%
Liu (2009)	32	NR	NR	NR	9,4%	40,6%	NR
Yildizeli (2008)	92	21p. CT or CT/RT	98.5%	21%	6.7%	42.5%	17%
Rea (2008)	49	19p. CT	NR	NR	6,1%	27,5%	0%
Chen (2006)	73	NR	NR	NR	5.5%	23.3%	NR
Macchiarini (2006)	50	18p. CT/RT	98%	36%	4%	51%	12%
De Perrot (2006)	100	29p CT or CT/RT	94%	27%	7,6%	44%	15%
Regnardt (2005)	65	11p. CT	94%	35%	7,7%	26,5%	5.3%
Porhanov (2002)	151	NR	86%	20%	16%	24.7%	7.5%
Roviaro (2001)	48	22p.RT. CT or CT/RT	NR	25%	8.2%	24.5%	NR

Carina/Trachea – Technical details

Type of resection right sleeve pneumonectomy
left sleeve Pneumonectomy
RUL/carina sleeve
Various carinal resections and reconstructions

Technique of anastomosis end to end
end to side
end to end and end to side

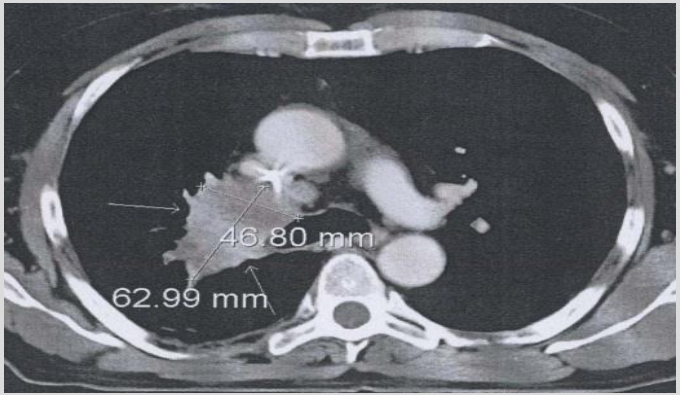
Mediastinoscopy to dissect the pretracheal plan to reduce tension at the anastomotic site

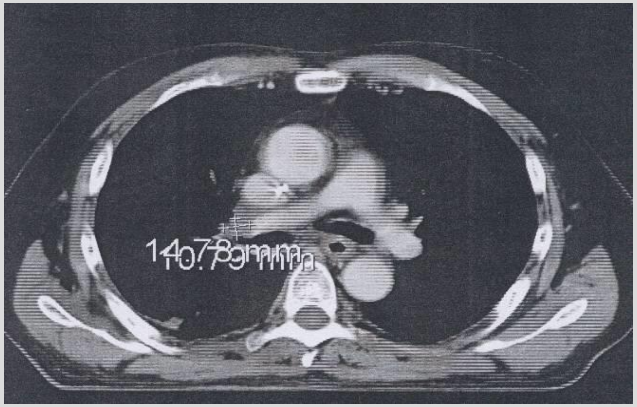
Reinforcement with omental flaps, muscle flap, or mediastinal fat

Release maneuvers

Induction treatment seems to improve survival if the mediastinal nodes can be sterilized before the lung resection. Some authors reported **anastomotic healing problems** after radiotherapy

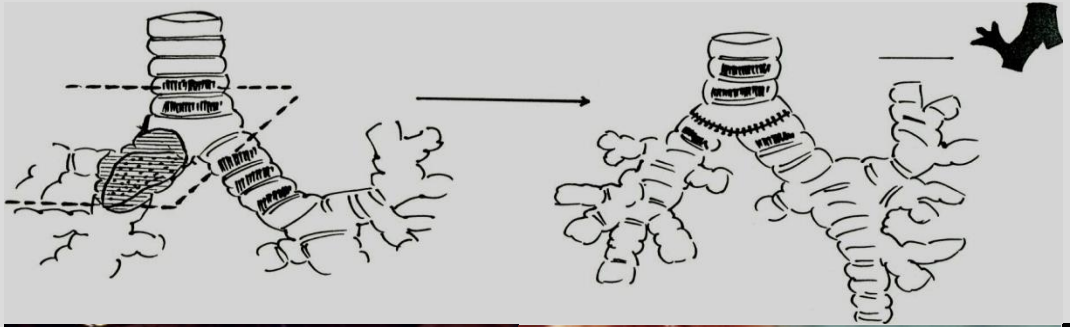
Carina/Trachea- Neoadjuvant treatment

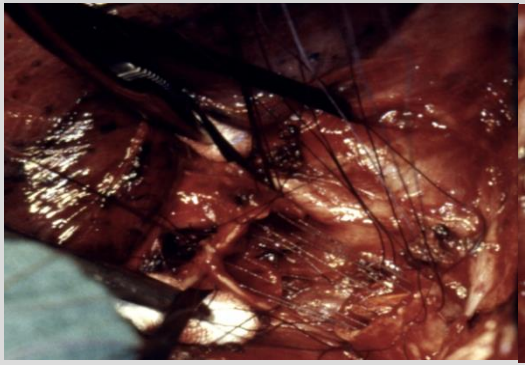


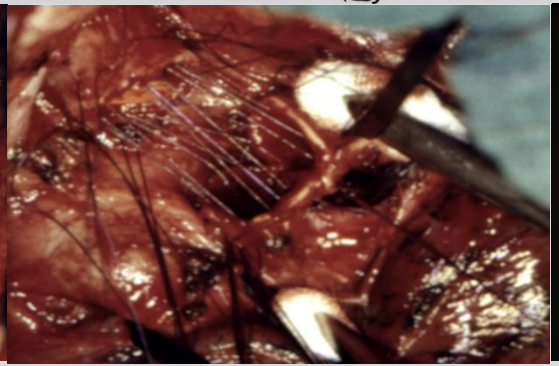


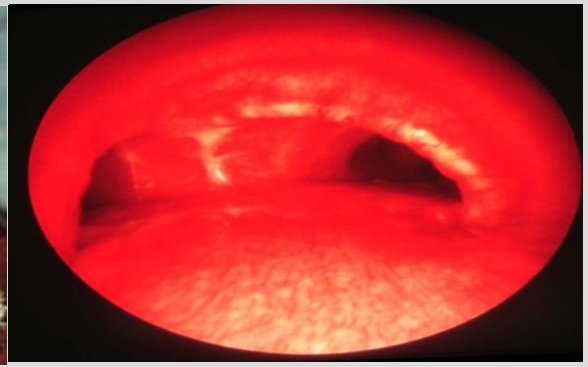
Before and after induction CT/RT

Carina/Trachea - Resection

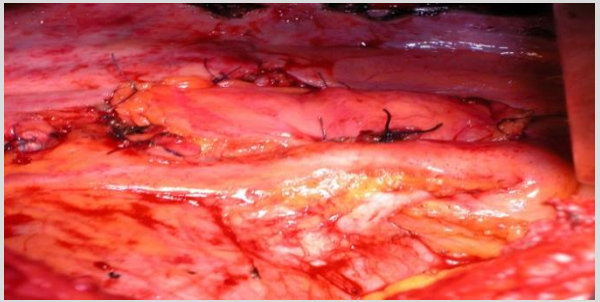




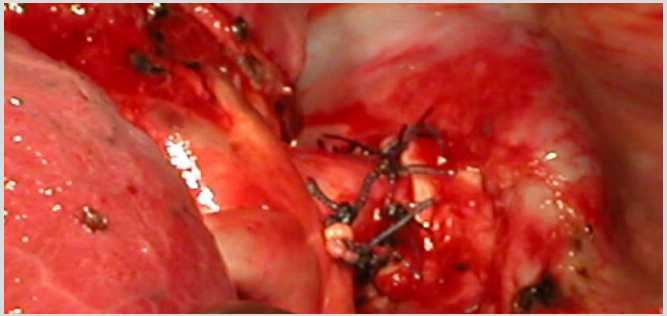


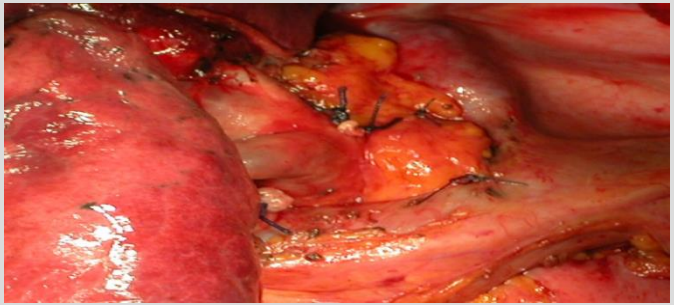


Stump protection with mediastinal fat



After right sleeve pneumonectomy



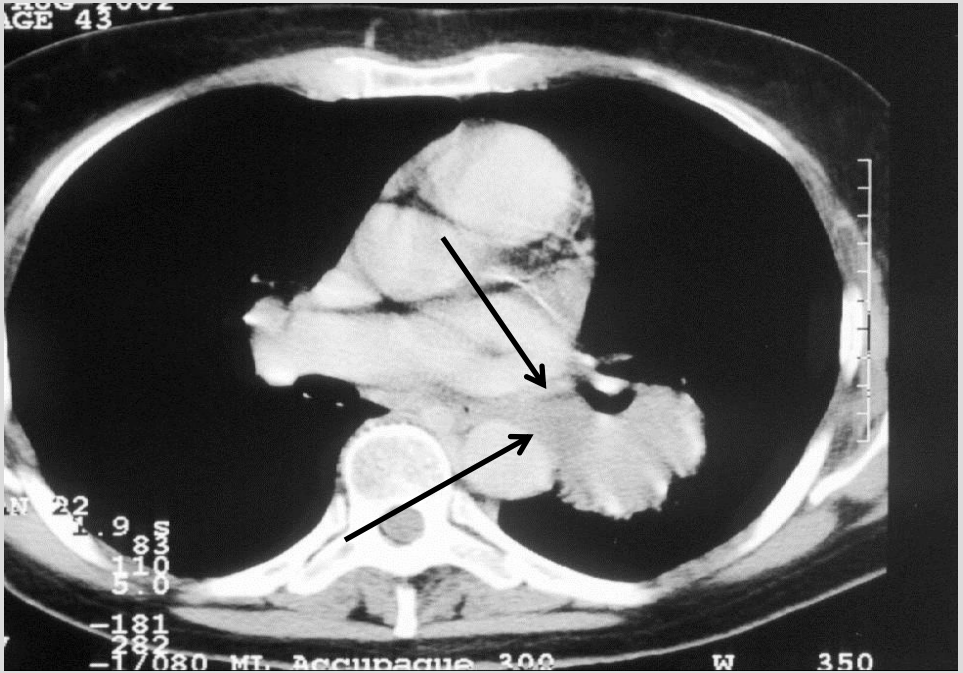


After RUL/sleeve lobectomy

Left atrium

Reports with small number and selected cases
Induction treatment is necessary in N2 disease and to reduce tumor size
NSCLC involves the left atrium either through direct tumor invasion or through tumor embolus in the pulmonary vein
Right sided tumors usually invade the left atrium widely, due to the shortness of the right upper pulmonary vein
Pneumonectomy rates between 66 and 95%
Cardiopulmonary bypass is seldom necessary
Mortality rate is low, morbidity acceptable
Residual tumor and lymph node status were factors significantly associated with survival

Left atrium



Left atrium

Author	n	Resection	N2%	Letality	5y survival
Galvaign (2014)	19	18PN/1	36%	10.5%	43.7%
Spaggiari (2013)	35	31PN/1Bilob/3Lob	45%	0%	25%
Wang (2010)	25	NR	32%	NR	36%
Wu (2009)	46	30PN/8Bilob/8Lob	NR	0%	22%(28%N0, 23%N1, 18%N2)
Mu (2008)	32	22PN/10Lob	NR	6,2%	43%(70%N0, 45%N1, 15%N2)
Akopov (2007)	28	26PN/12Lob	NR	4%	17.% MST 23 mo
Bobbio (2004)	23	22PN/1Lob	17%	9%	10%
Ratto (2004)	19	12PN/7Lob	57%	0%	14%
Fukuse (1997)	14	10PN/4Lob	22%	7.1%	14.3%, MST 10mo
Tsuchiya (1994)	44	29PN/15Lob	NS	8%	22%

Left atrium

Spaggiari L, D´Aiuto M, Veronesi, et al. Extended Pneumonectomy with Partial Resection of the Left Atrium, Without CardiopulmonryBbypass for Lung Cancer Ann Thorac Surg 2005;79:234-40
Spaggiari L, Tessitore A, Casiraghi M, et al. Survival after Extended Resection for Mediastinal Advanced Lung Cancer: Lessons Learned on 167 Consecutive cases. Ann Thorac Surg 2013;95:1717-25

15 patients (2005), 35 patients (2013)
CT–scan, PET, transthoracic echocardiography, lung perfusion scan
For suspected N2 disease , EBUS-TBNA or mediastinoscopy was performed
Neoadjuvant treatment – N2 disease in nodal stations R4 and 7)
- Reduce tumor size (risk of incomplete resection)

Resection - Satinski clamp to evaluate surgical feasibility and cardiocirculatory reduction of atrial volume
- Sondergaard technique is used to lengthen the atrial cuff to about 2 cm
- Atrial resection is performed after completion of lung resection
- Suturing the defect with 2 running stitches of monofilament nonabsorbable sutures

Superior Vena Cava

Only one report with large number of cases
Technical feasibility also without extracorporal circulation
Induction treatment is recommended
Complementary operations, mostly carina resection or PA sleeve
Factors affecting significantly survival were advanced age (>60), N2-disease and R1/R2 resection

SVC

Author	n	N2	R0	Letality	5J Survival
Spaggiari (2013)	43	15(35%)	36(84%)	4.6%	26% (46%N0, 22%N+)
Lanuti (2009)	9	NR	NR	11,1%	30%
Yildizeli (2008)	39	13(33.3%)	33(85%)	7.7%	29.4%
Politi (2007)	16	NR	NR	6,25%	20 months
Misthos (2006)	9	5(56%)	NR	0%	11%
Suzuki (2004)	40	NR	28(75%)	10%	
Rendina (1999/2007)	9/140			11,1%	30,5%
Thomas (1994)	15	6(40%)	12 (80%)	7%	24%

SVC – Technical aspects

Type of lung resection

right PN or sleeve PN
Bilobectomy or RUL
Segmentectomy
Wedge resection

Type of cava resection and reconstruction

Small involvement **less than 50%** of the vessels circumference

- resection and direct repair using mechanical suture or side clamp and manual-suture with nonabsorbable filament

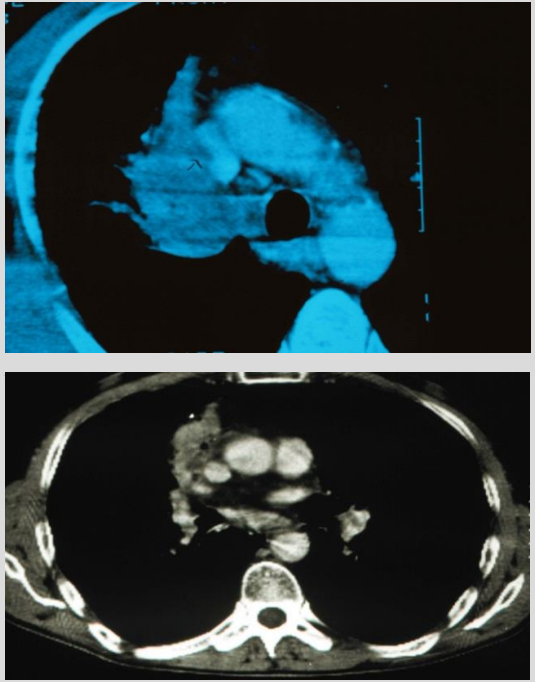
Larger involvement **less than 50%** of the vessels circumference

- resection and autologous (pericardium) or synthetic patch
- Azygos flap

Involvement **more than 50%** of the vessels circumference

- Cross-clamping, cava segmentresection and vascular prothesis (PTFE –graft or custom-made bovine pericardial tube)

SVC



Remissson after CT/RT

SVC and pericardial replacement after right sided pneumonectomy

Pulmonary artery

Resection and reconstruction of the pulmonary artery is technically feasible. Early reports were associated with significant mortality and poor overall survival

Tsuchiya 1994, Martini 1994, Fukuse 1997, Bernard 2001, Rice 2004

Pulmonary artery

Author	n	Resection	Letality	5y survival
Akopov (2007)	28	16PN/12Lob	3,5%	17% /23 Months
Wu (2009)	46	30PN/16Lob	0%	22%(23%N1, 18%N2)
Mu (2008)	32	22PN/10Lob	6,2%	53%(70%N0, 45%N1, 15%N2)
Venuta (2009)	105	3PN/101Lob/1Bil	1%	25%IIIA, 12% IIIB
Berthet (2013)	10	10 Lob	0%	66.7%
Galetta (2015)	150	56 Sleeve Lob, 94Lob	3.3%	50% all p., (61% N0/N1, 28%N2)

Pulmonary artery-Technical details

Infiltration - partial infiltration
- more extensive infiltration
- circumferential infiltration

CPB (in some left sided tumors)

Reconstruction technique
– suture small defects
- patches with autologous or bovine pericardium
- sleeve and end-to-end anastomosis
- interposition of pericardial conduit
- cryopreserved arterial allografts

Protection with - omental flaps
- muscle flap
- mediastinal fat

Pulmonary artery

Venuta F, Ciccone AM, Anile M, et al. Reconstruction of the pulmonary artery for lung cancer: long term results. J Thorac Cardiovasc Surg 2009;138:1185-91

31 IIIA and 22 IIIB disease among 105 patients
CT–scan all patients, MRI and PET in selected cases
Neoadjuvant treatment – CT in all patients with N2 disease
Surgery – 47p. PA sleeve resection
55p. reconstruction by pericardial patch
3p. pericardial conduit
- 3PN, 65 bronchial sleeve lobectomies, 35 lobectomies, 1 bilobectomy
Mortality 1p. (0, 95%)
Morbidity 30p. (28.5%)
Pathology - R0 resection 101p (96%)., R1 resection 4p. (4%)
- 61p SCC, 38p. AdenoCa, 5 LargeCellCa, 1p. mixed
Adjuvant treatment 42p. (40%) receive CT,
Results - 5 years survival for stage IIIA 25%, for IIIB 12%

Pulmonary artery

Berthet JB, Boada M, Paradela M, et al. Pulmonary sleeve resection in locally advanced lung cancer using cryopreserved allograft for pulmonary artery replacement. J Thorac Cardiovasc Surg 1013: 146:1191-7

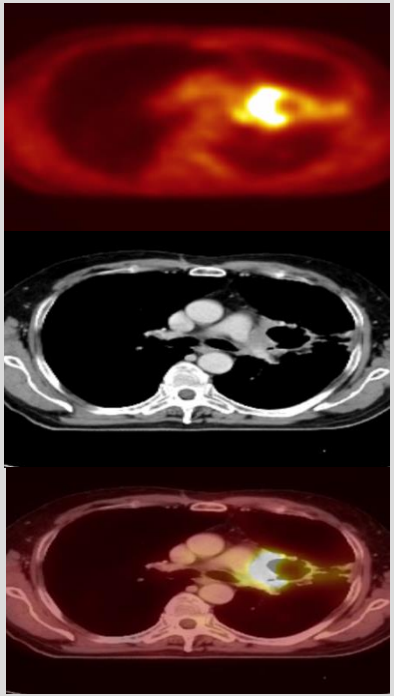
32 pulmonary artery reconstructions in 178 centrally located NSCLC
X-ray, CT-scan, bronchoscopy, PET-scan
Type of PA reconstruction – 20 end-to-end anastomosis
- 2 pericardial patch reconstructions
- 10 PA replacements (harvesting cryopreserved vessels from multiorgan donors)

Cryopreserved allograft – descending aorta 3
- pulmonary arteries 7

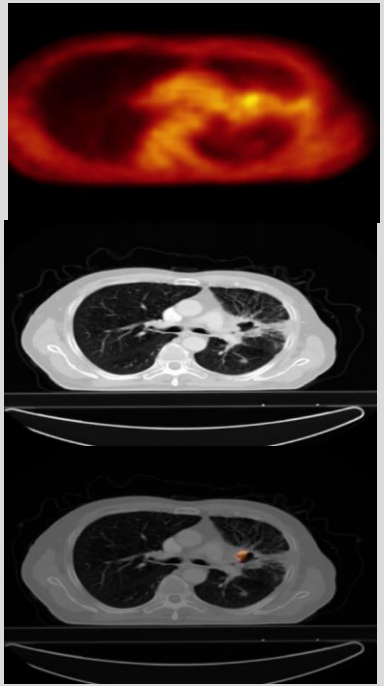
Neoadjuvant treatment by N2 disease 4/10p. (40%)
Resection – Lobectomy in 7 and bronchial sleeve in 3p.
Mortality 0%
Morbidity 4 p. (40%%), 1p. Thrombosis Pneumonectomy
Pathology – 7p. SCC, 2p. AdenoCa, 1p. Atypical Carcinoid
- 4p. pN0, 5p. pN1, 1p. pN2
- R0-resection 100%

Results - 5 year survival 66.7%, MST 42 months

Crypreserved arterial allografts can replace the PA, so that PN can be avoided



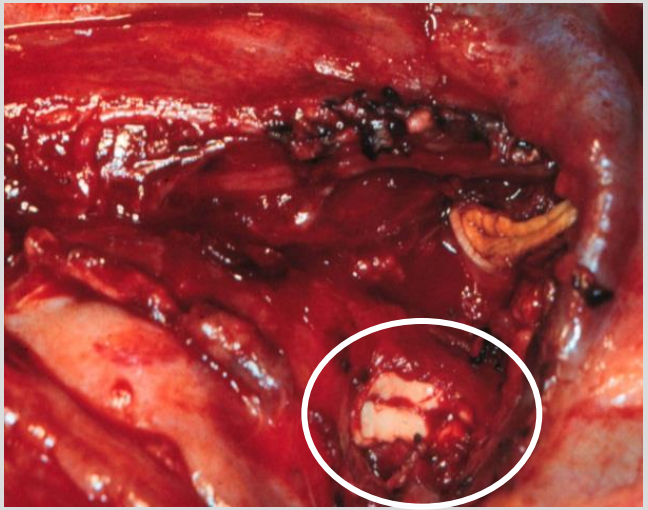
Before CTx/RTx



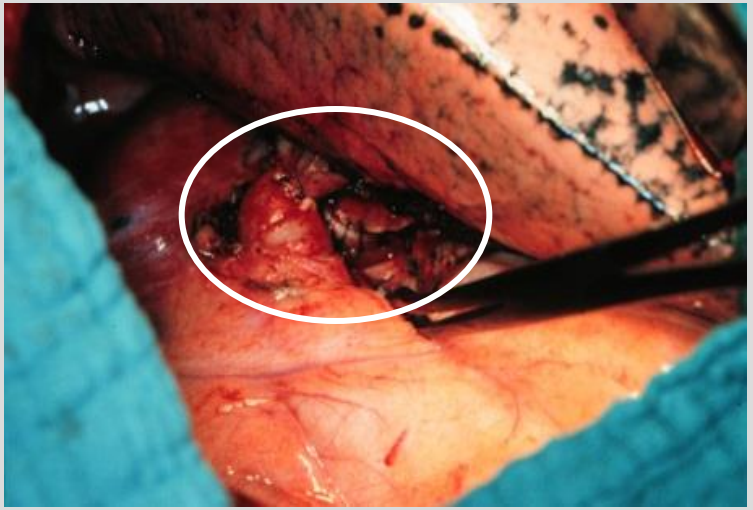
after CTx//RTx

Downstaging left PA
after induction treatment

Pulmonary artery



Right pneumonectomy



Left bronchial and PA sleeve resection

T4-Aorta

Series with small number of cases
Radiologic findings on aortic infiltration may be unreliable in differentiating invasion limited to the adventia or extending to the medial or intima layers
Induction treatment is recommended
Thoracic aortic endografting allowed safe en bloc resection
For the prognosis important the R0 Resektion und N0/N1disease

T4-Aorta

Author	n	Induction	Site of invasion	Resection	Letality
Klepetko (1999)	7	1p. CT	6 descending/ 1 arch	6PN/1LUL	0%
Ohta (2005)	16	10p. CT	7descending/ 9 arch	6PN/9LUL	12.5%
Misthos (2006)	13	No induction	13 descending	5PN/8LUL	0%
Collaud (2014)	5	4p. CT/RT	3 descending/ 2 arch	3PN/2LUL	0%
Yoshida (2015)	8	NR	5 descending/3 arch	5PN/3LUL	0%
Marulli (2015)	9	4p. CT	8 descending/1 arch	3PN/6LLL	0%

T4-Aorta

Author	N	pTNM	Adjuvant	replacement	5J Survival
Klepetko (1999)	7	2p. T4N0, 3p. T4N2	3p. CT, 1p. RT	5 tubular grafts, 2 patch	20% (4years)
Ohta (2005)	16	10p.T4N0, 6p.T4N2/3	4p.CT	10 prosthetic grafts, 5 patch, 1 suture	70% N0, 16,7% N2/3
Misthos (2006)	13	1p. T4N0, 8p.T4N1 4p. T4N2	13p. CT	10 patch graft	30.7% 100% N0, 37.5% N1, 0% N2
Collaud (2014)	5	NR	1p. CT/RT	**5 Endograft/** 2 Reinforcement	All patients alive
Yoshida (2015)	8	NR	NR	5 total grafts/3 patch	50%
Marulli (2015)	9	5 T4N0, 4 T4N1	5p. CT/1p.RT 1p. CT/RT	**9 Endograft/** 5 Reinforcement	62% (3year)

T4-Aorta – Technical aspects

No bypass used
Passive shunt between ascending and descending aorta
Cardiopulmonary bypass

Resection of adventitia
media
intima
Reconstruction direct closure by suturing
Prosthetic patch
Prosthetic grafts
Aortic endografting (one or two stage procedures)
Reinforcement with synthetic patches
omental flaps
muscle flap

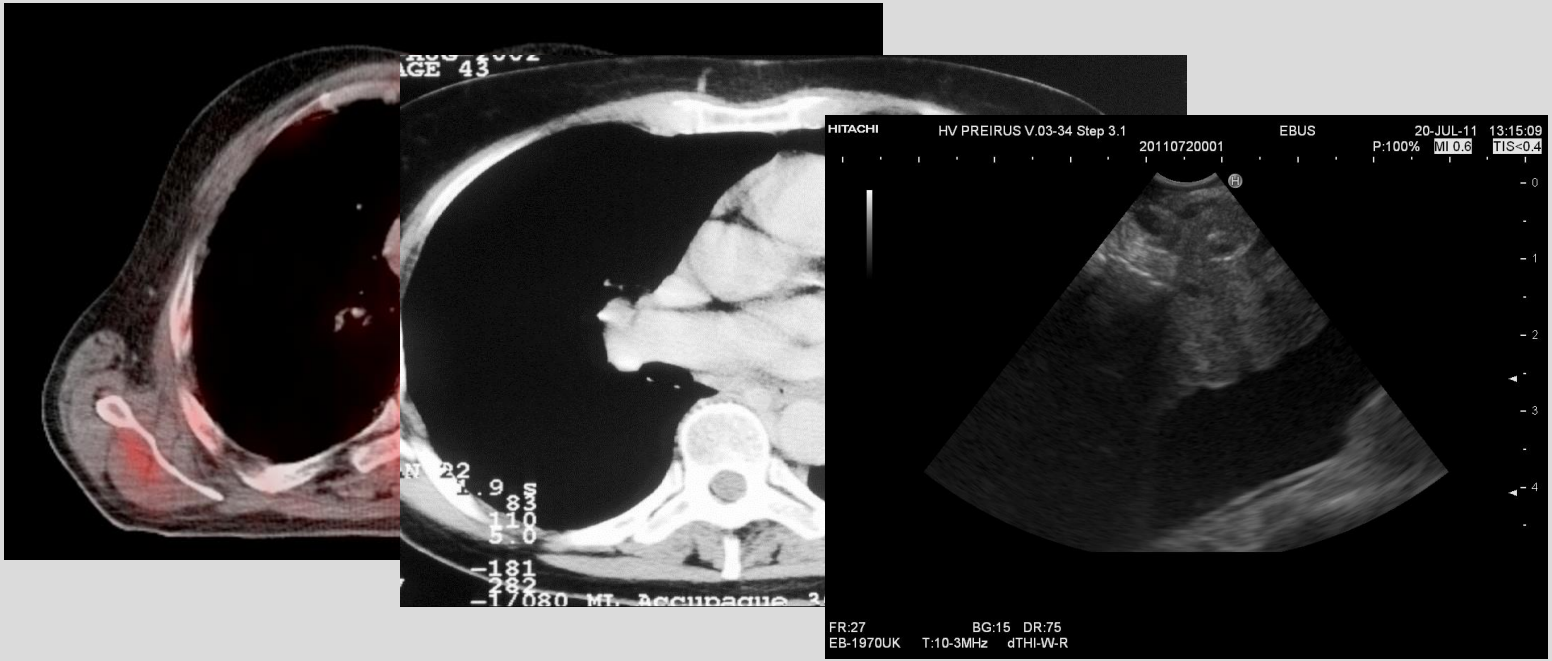
T4-Aorta

Marulli G, Rea F, Zampieri D, et al. Safe Resection of the Aortic Wall Infiltrated by Lung Cancer after Placement of an Endoluminal Prothesis. Ann Thorac Surg 2015;99:1768-74

9 patients
CT or MRI of the chest, PET/CT-scanning
EBUS_TBNA or mediastinoscopy only for PET-positive nodes
CT angiography (assess vessel size and anatomy
Radiologic findings suggesting aortic invasion
- Contact between aortic wall and tumor for more than 3cm
- Obliteration of the fat plane between aorta and tumor
- Contact by the tumor of more than 90° of aortic circumference

Neoadjuvant treatment – 4 patients (45%)
Resection –Pneumonectomy 4p. (45%)
- Lobectomy 5p. (55%)

T4-Aorta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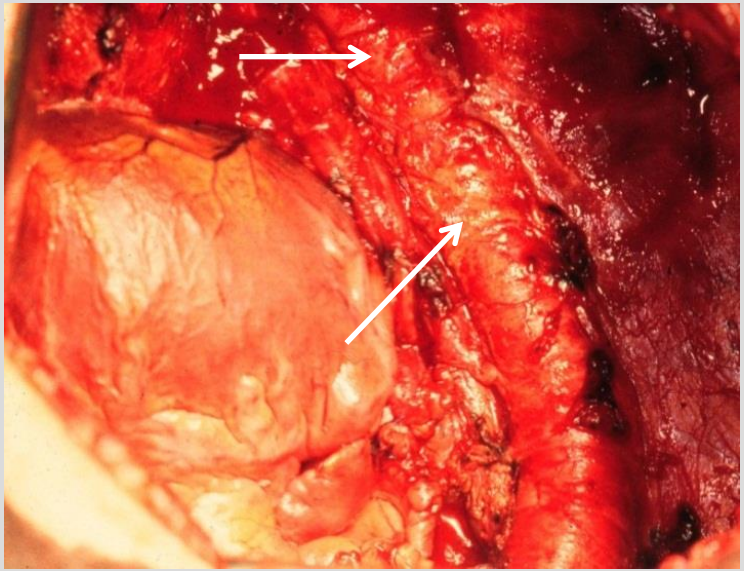
T4-Aorta

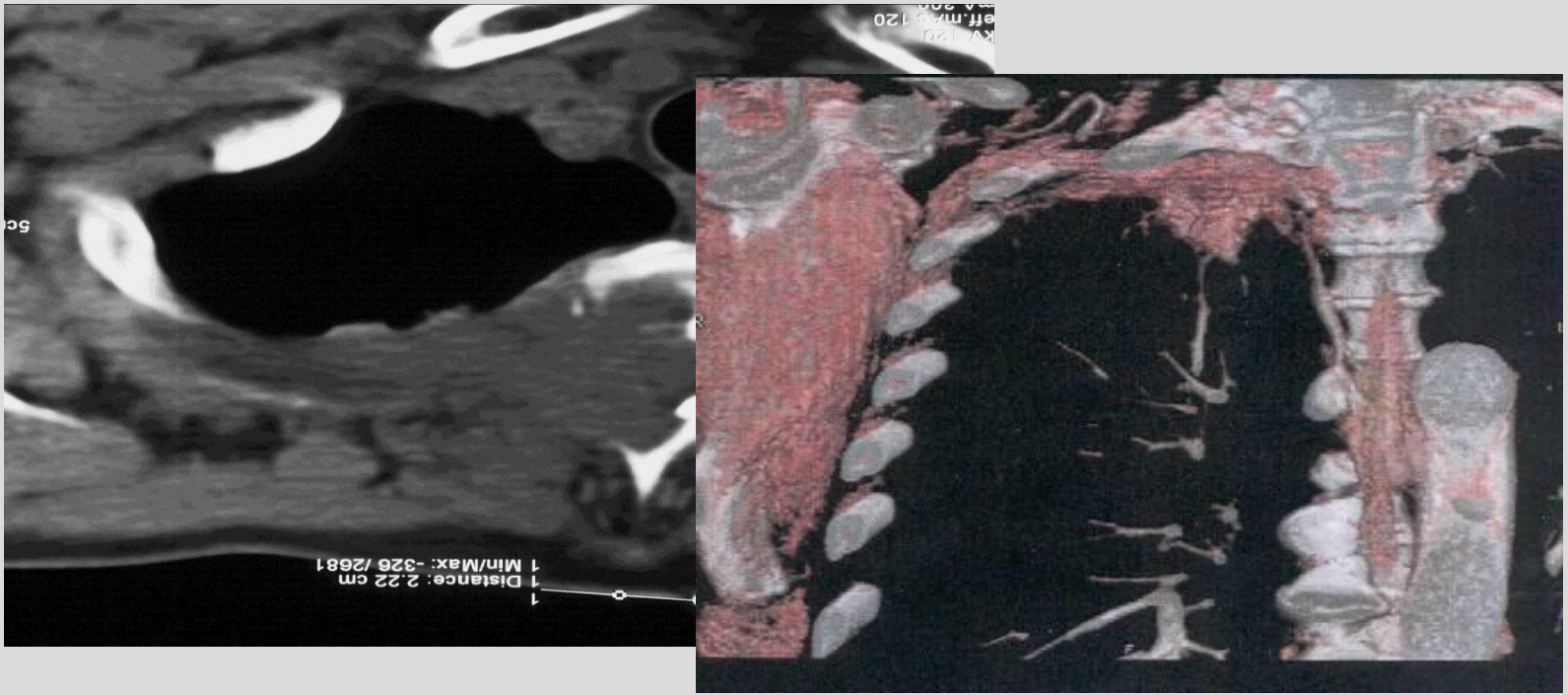


Left pneumonectomy with resection of aorta adventitia

T4 – Vertebral body

Experience with small number off patients
Most resections with Pancoast tumors
Resection after CTx/RTx
Cooperation with neurosurgeon/orthopedics necessary
Good long term results only by R0-Resection and N0/N1 pathology

T4 – Vertebral body



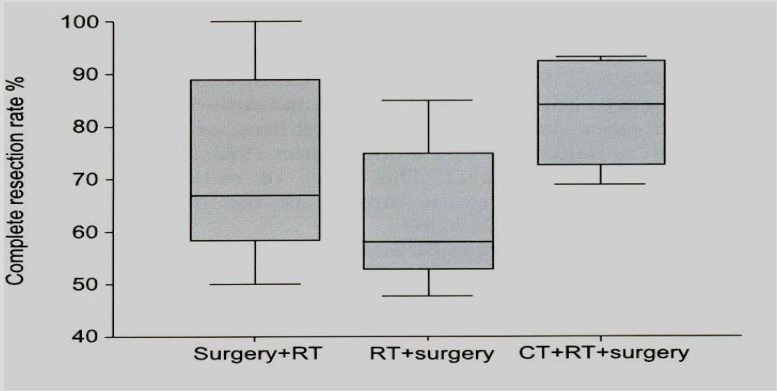
T4 – Vertebral body

Author	n	Induction	Letality	5J survival
Bolton (2009)	39	CTx/RTx	5%	27%
Yokomise (2007)	7	CTx/RTx	0%	67,7%
Koizumi (2007)	8	CTx/RTx	0%	22,9%
Mazel (2003)	36	CTx-RTx*	2,7%	28%
Fadel (2002)	17	CTx-Rtx*	0%	20%

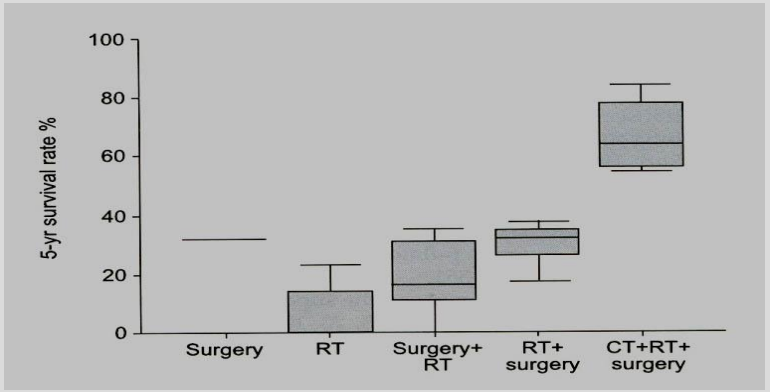
* Not all patients

T4 – Vertebral body

Mara et al, ERS 2007



R0-resection and treatment concept



Survival and treatment concept

T4 other lobe ipsilateral

Rami-Porta R, Ball D, Crowley DJ, et al. The IASLC Lung Cancer Staging project: proposals for the revisoon of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 2007;2:593-602
180p./100.869p. 5y survival 22%

Voltolini L, Rapicetta C, Luzzi L et al. Surgical traetment of synchronous multiple lung cancer located in a different lobe or lung: high survival in node negative subgroup Eur J Cardiothorac Surg 2010; 37:1198-204
15p/1551p. unilateral, 28p/1551p. bilateral (1990-2007)
5y surv 43% bilateral, 23% unilateral without N disease, 0% with lymph node metastasis

Watanabe S, Asamura H, Miyaoka E et al. Results of T4 surgical cases in the Japanese Lung Cancer registry Study: Should mediastinal fat tissue invasion realle be included in the T4 category? J Thorac Oncol 2013;8:759-65
87p./11663 p. 5y surv 50.3% vs 19,9%, nodal status and age >70 years significant prognostic factors

Carefully selected patients may benefit from an aggressive surgical approach

Stage N2A3- disease

Chemotherapy plus radiotherapy with or without resection (preferably lobectomy) are options for patients with IIIA (N2) NSCLC

Albain KS et al., Lancet 2009;374:379-86

Intergroup 0139 - Outcomes

	CTx/RTx/Surgery	CTx/RTx
Overall survival	27%	20%
PFS	22%	11%
Local recurrence	10%	22%
- primary tumor	2%	14%

Albain KS. et al, Lancet 2009;374:379-86

Stage N2A4 disease

For patients with acceptable performance status, combination of Chemotherapy and Radiation is the choice of treatment
(recommendation grade A)

For selected cases after induction CTx/RTx and good response the integration of surgery could be followed (if possible inside of studies)
(recommendation grade D)

EORTC 08941 – Outcomes

		CTx/RTx(n=165)	CTx/RTx/Surgery (n=167)
Median follow-up (mo)		73	67
Overall survival	Median (mo)	17.5	16.4
	2 years (%)	41	35
	5 years (%)	14	15.7
Site of relapse	Locoregional	71 (54%)	37 (32%)
	Distant	50 (39%)	70 (61%)
	Both	9 (7%)	8 (7%)
PFS	Median (mo)	11.3	9
	2 years (%)	24	27

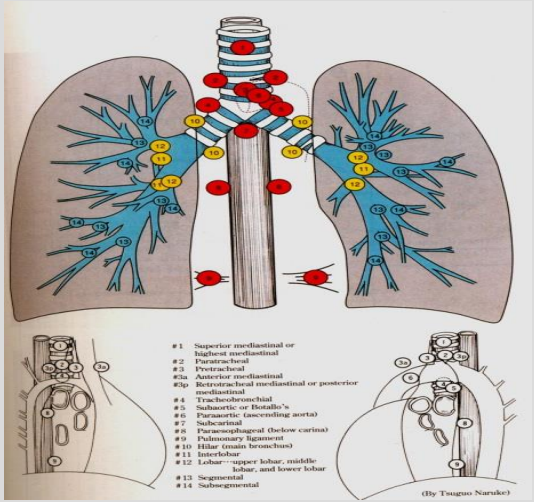
Van Meerbeeck JP et al,2007

EORTC 08941 – Outcomes

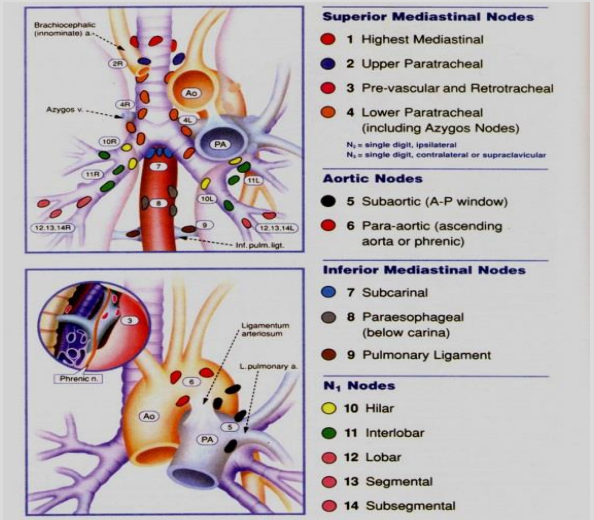
Subgroup	Median	5 year(%)
Extend of resection		
(Bi-)Lobectomy	25.4	27
Pneumonectomy	13.4	12
Mediastinal nodes		
ypN0-1	22.7	27
ypN2	14.9	12
Type of resection		
Complete	24.1	27
Incomplete	12.1	7

Van Meerbeeck JP et al,2007

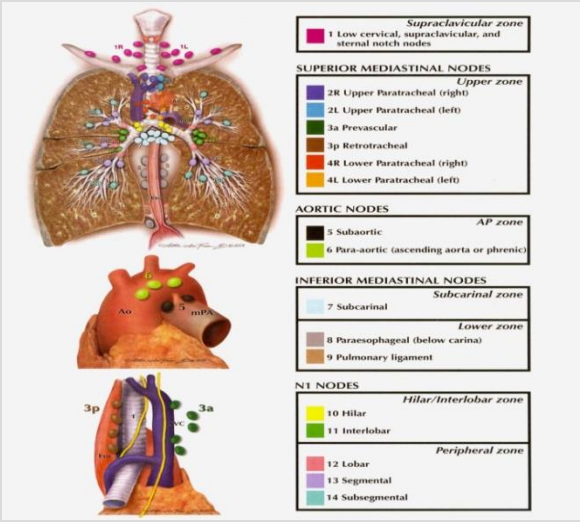
Different lymph nodes mapping



Naruke (1960)



Mountain-Dresler (1997)



IASLC (2009)

Definition according the extension of LA

„Sampling“
Only suspected LN are removed after an individual interpretation of the surgeon

„Systematic LN dissection“ (Martini)
En bloc dissection of all ipsilateral compartiments
Right side: 2R, 4R, 3, 7, 8, 9, 10, 11
Left side: 2L, 4L, 5, 6, 7, 8, 9, 10, 11

„Supraradical LN dissection“ (Naruke)
Additionally to systematic dissection , the anterior mediastinum (incl. thymus fat), contralareral 2 and 4 stations and the supraclavicular stations are removed

Sampling vs. Systematic LN dissection

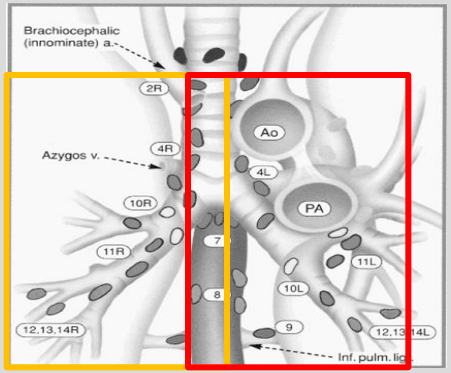
1023 patients randomised
498p. sampling 525p. systematic LN dissection
Right side 2,4,7,10R
Left side 5,6,7, 10L
Died: 217(44%) sampling 218(42%) systematic LN d.
Median survival: 8,1y sampling 8,5y systematic LN d.
5y Survival: 64% sampling 68% systematic LN d.
Occult N2 21 patients in systematic LK dissection

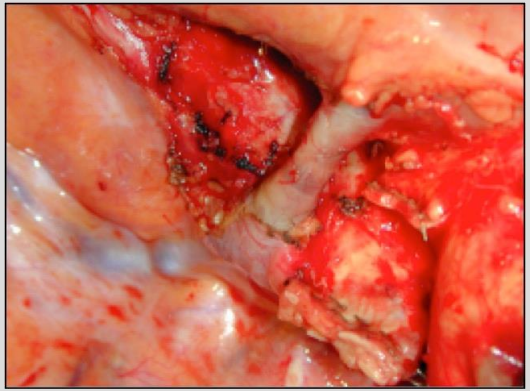
Darling G et al. 2010

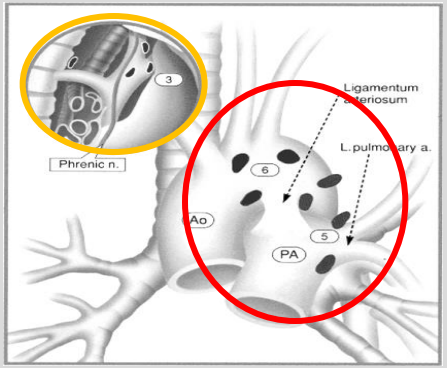
For lung cancer(UICC and AJCC)
CMountain CF, Dresler CM, Chest 1997)

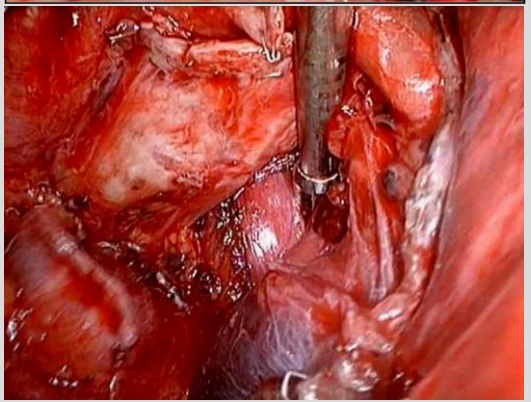
Systematic lymphadenectomy (Martini)

Right side: 2R, 4R, 3, 7, 8, 9, 10, 11
Left side: 2L, 4L, 5, 6, 7, 8, 9, 10, 11









Surgical techniques relevant for stage III disease

Why systematic lymph node dissection ?

Systemic lymph node dissection is the only method to obtain a precise pathological staging (prognosis, adjuvant treatment et c.)

(Ogata 1987, Naruke 1996, Ginsberg 1997)

Why systematic lymph node dissection ?

The incidence of the so-called „skip metastasis“ is to high (6-30%) to be ignored

(Riquet 1995, Graham 1999, Passlick 2001)

Why systematic lymph node dissection ?

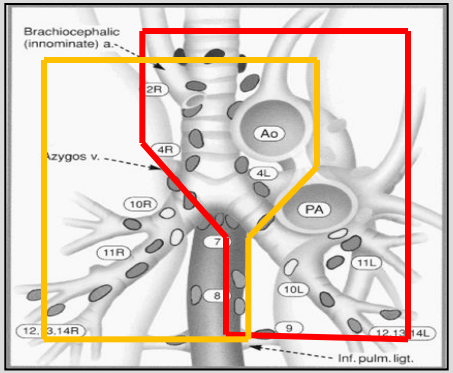
The evidence of the importance of nodal micrometastasis enhances the limits of sampling

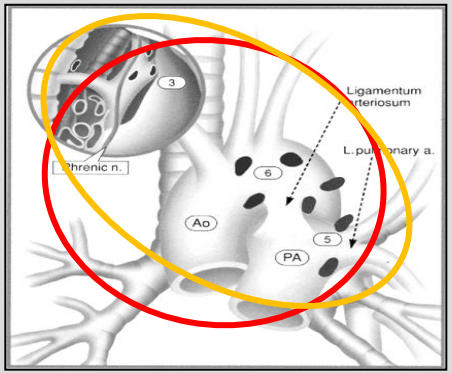
(Passlick 2002)

N3- disease

For N3 disease, treatment with neoadjuvant chemotherapy or chemoradiotherapy followed by surgery has been proved in limited phase II studies with a small number of cases
These trials showed that surgery is feasible and promising with long term survival only in selected downstaged patients
There are no phase III trial data available to document that surgery adds to survival (EORTC 08981 is failed)
Therefore, this approach should be considered only inside of studies

For lung cancer(UICC and AJCC)
CMountain CF, Dresler CM, Chest 1997)



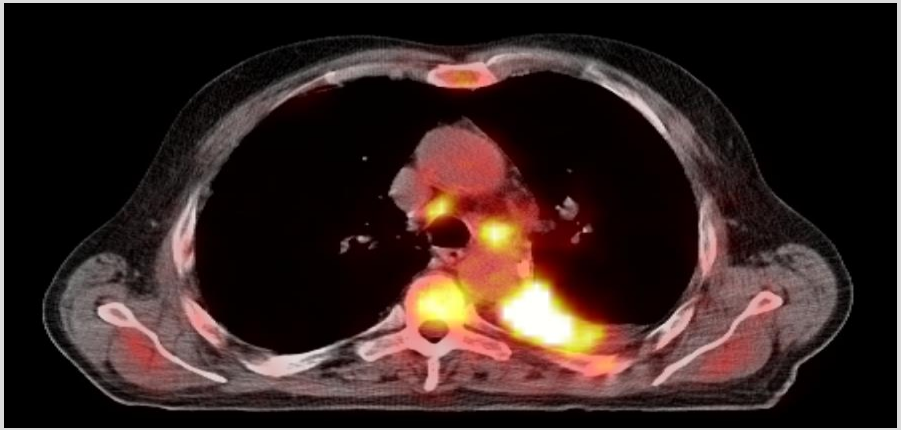


Supraradical lymphadenectomy (Naruke)

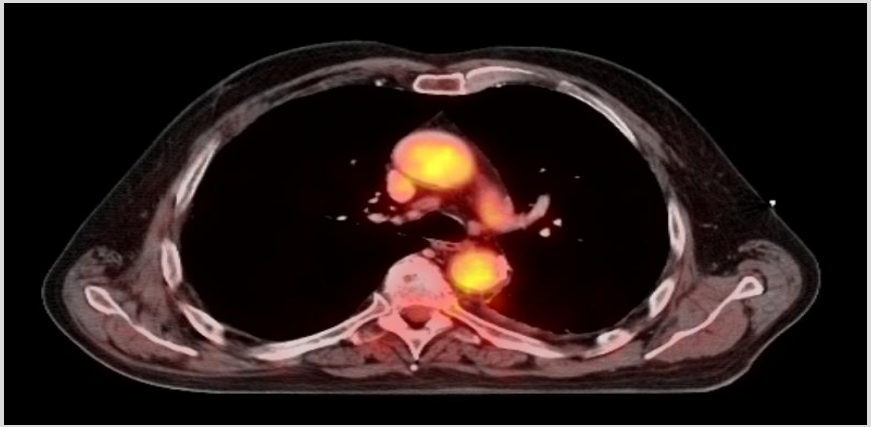
Right side: 2R, 4R, 3, 7, 8, 9, 2L, 4L
thymus fat, supraclvicular R/L
Left side: 2L, 4L, 5, 6, 7, 8, 9, 2R,
4R, thymus fat, supraclavicular R/L

N3- disease

before induction CTx/RTx



before surgery



N3- disease

nodal sterilisation survival)

SWOG 8805 (Rusch VW 1994, Albain KS 1995)	27	ipsilateral	53%	25% *
Stamatis et al, 1999	32	ipsi-/bilateral	25%	28%
Grunenwald et al, 2001	18	bilateral	30%	17%
DeCamp MM et al, 2003	21	ipsilateral	30%	15%*
Ichinose Y et al, 2003	7	bilateral	26%	67%
Galetta D et al, 2003	5	ipsilateral	-	23%
Yokomise H et al, 2007	4	ipsilateral	25%	50%
Stupp R (SAKK 2009)	15	ipsilateral	13% ‡	40% ‡
Steger V et al (2012)	13	ipsi-/bilateral	66%	31mo †
Riquet M et al (2013)	11	ipsi-/bilateral	27.3%	54.5%

*2-years, ‡ all IIIB, † median survival

Surgery for stage III disease

Inderdisciplinary approach of stage III disease is today the basis of succesfully treatment

(recommendation grade A)