

37th ESMO Congress
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Hot topics in early stage NSCLC

Who should be considered for surgery for stage III disease and why ?

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Stage III disease (IASLC 2010)

IIIA	T1-2a,b	N2	M0
	T3	N1-2	M0
	T4	N0-1	M0
IIIB	T4	N2	M0
	T1-4	N3	M0

Definition of N2,N3,T4 (IASLC 2010)

N2 Metastasis in ipsilateral and/or subcarinal LN

N3 Metastasis in contralateral mediastinal, hilar, ipsilateral or contralateral M. scalenus LN or supraclavicular LN

T4 Tumor any size with infiltration of mediastinum, heart, trachea, recurrent n., esophagus, main carina, vertebral body or metastasis in other lobe ipsilateral

The heterogeneity 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)

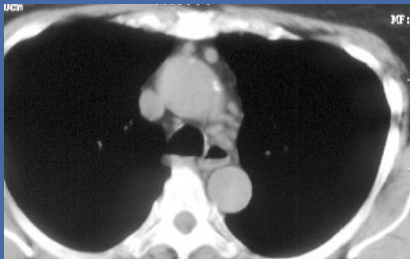
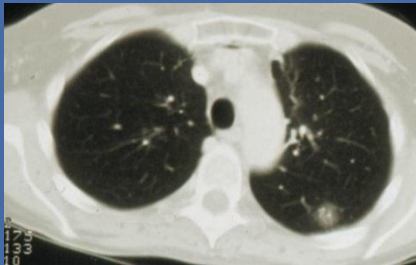
Relation between Evidence and Recommendation grade

Evidence	Recommendation	Grade
1a-c	strong	A
2a-c, 3a-b	moderate	B
4	poor	C
5	absent/incosistent studies	D

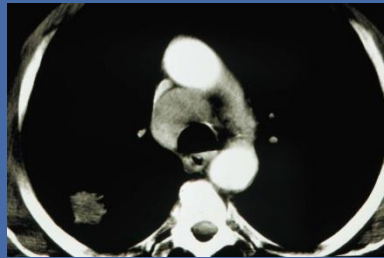
Oxford Center of Evidence-based Medicine 2001

Wich are the candidates for surgery in N2 disease?

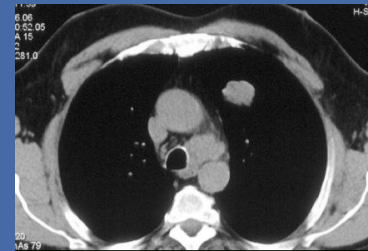
NSCLC N2-disease



T1aN2M0

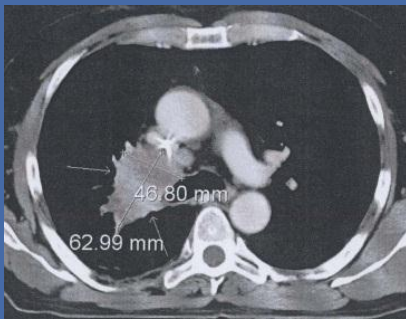


T1bN2M0



T2aN2M0

NSCLC N2-disease



T3N2M0



T4N2M0

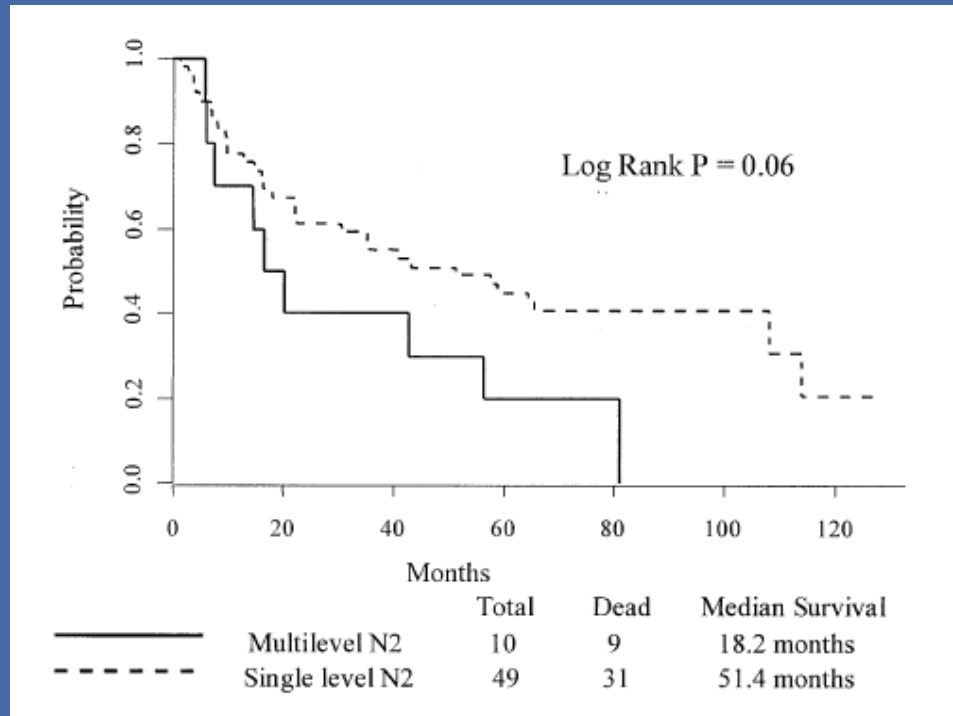


T4N2M0

Heterogeneity of N2 disease

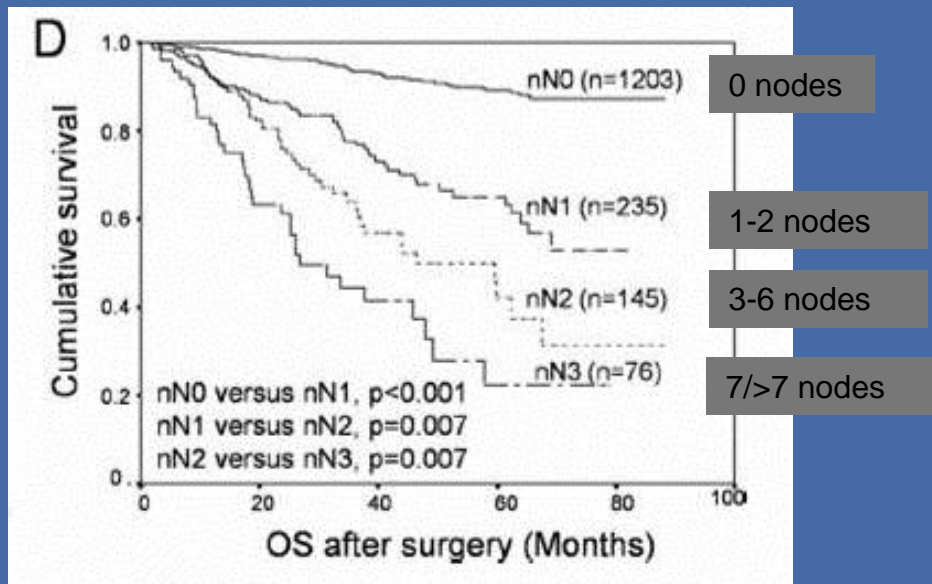
- Single vs. multilevel disease?
- Absolute number of involved lymph nodes?
- Patients with „bulky disease“?
- Downstaging after Induction?

Single vs. multilevel disease



Keller SM et al., J Thorac Cardiovasc. Surg., 2004

Number of involved LN



Wei S et al., J Thorac Oncol., 2011; 6, 310

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Downstaging N2 disease after induction CTx

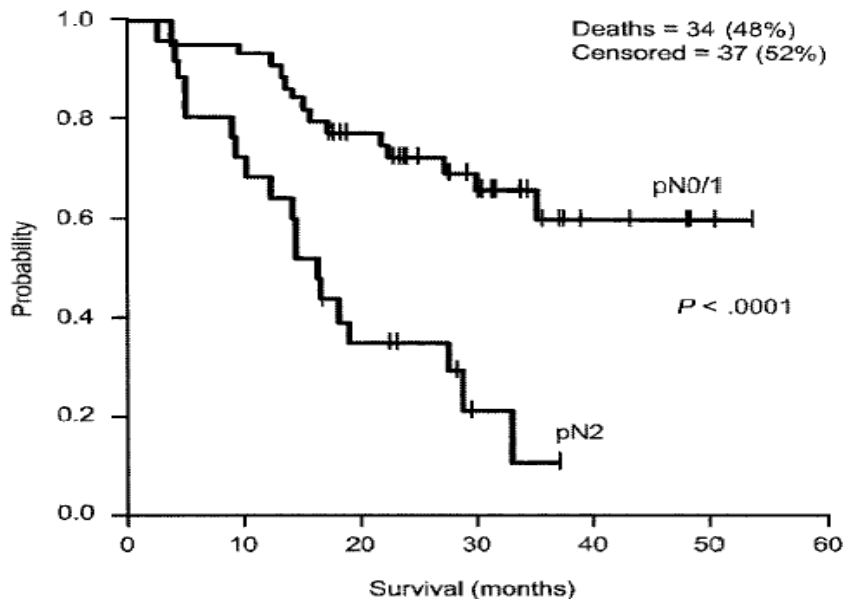


Fig 2. Overall survival dependent on pN2 clearance in the univariate analysis (patients with tumor resection, $n = 71$; $P =$ log-rank test P value). Data were unavailable for four patients.

downstaged N2
ypN0/N1

persistend N2
ypN2

Betticher D et al. J.Clin. Oncol. 2003; 21, 1752

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Subclassification of N2 disease

Stage IIIA N2 NSCLC represents a heterogeneous group of patients. To categorise further subsets a subdivision has been proposed

- Stage IIIA1
Pathologic assessment of removed nodes postoperatively
- Stage IIIA2
Pathologic assessment of removed nodes intraoperatively
- Stage IIIA3
Single- or multistation nodal metastasis recognised by prethoracotomy staging (Mediastinoscopy, EUS, EBUS, FDG-PETscan)
- Stage IIIA4
„Bulky“ or multistation N2 disease is detected at initial staging

Robinson L, et al Chest (2003)

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N2 disease

Results after surgery alone

Author	Year	n	Subgroup	5-J Survival
Patterson	1985	62	single 5L	24%
Watanabe	1991	43	single N2	35%
Naruke	2001	414	only T1-2	22%
Andre	2002	-	single N2	34%
Keller	2004	49	single N2	42%

N2 disease - Phase III studies

Author	Jahr	N Patienten	5-J Überleben	p
Pass	1992	27	CTx+S 42% S 22%	ns
Rosell	1992	60	CTx+S 17% S 0%	0,005
Roth	1994	60	CTx+S 36% S 15%	0,04
Depierre	2002	167	CTx+S 28% S 21%	ns

Intergroup 0139 - Outcomes

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

Albain K. et al, Lancet 2009

Stage T1-3 N2 **A3** disease

For technically resectable patients induction treatment (CTx or CTx/RTx) followed by resection is recommended (grade B)

For patients with surgery and R0 resection after induction CTx alone, postoperative RTx is recommended (grade B)

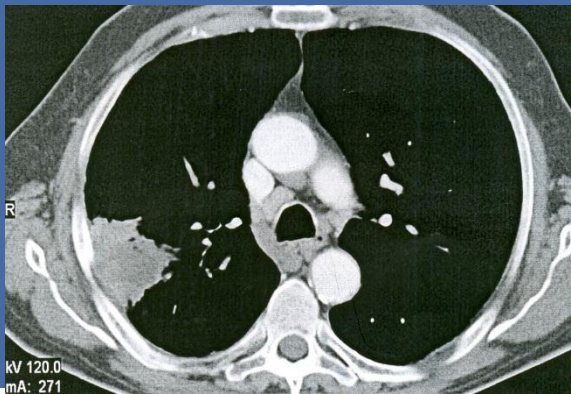
For patients with single LN station involved, primary Surgery followed by CTx/RTx is possible (grade C)

N2 bulky - Stage IIIA4

Bulky mediastinal nodal disease is defined as those

- involving lymph nodes >2 cm in the short-axis diameter measured by CT-scan,
- with extra nodal infiltration,
- multistation nodal disease and/or
- groupings of multiple, positive smaller lymph nodes

Robinson L, et al Chest (2003)



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N2 bulky Stage IIIA4

Autor	n P.	Induction	Resection	Letality	5J-Survival
Grossi (2002)	16	CTx	6/16	0%	n R
Johnstone (2002) RTOG 89-01	26	CTx	20/26	7,6%	70% at 1 year
	19	CTx/RTx	-	5,2%	66% at 1 year
Giannitto (2005)	52	CTx	22/52	0%	15% at 2 years
Yokomise (2007)	41	CTx/RTx	41/41	0%	85;7% N0/N1 52,4% N2
Stamatis (2007)	144	CTx/RTx	111/144	3,6%	36% N0/N1 20% N2

EORTC 08941 - Outcomes

	Radiotherapy(n=165)	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 - Survival

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

Stage T1-3 N2 **A4 bulky** disease

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

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

Is there any role for surgery in N3 disease?

Downstaging for N3 disease

SWOG 8805 (phase II)

Induction ChemoRT followed by resection for patients with cStage IIIA and cStage IIIB

Path CR in 22%

3 years survival 25% in 27 patients with N3 disease

(-) residual mediastinal LN	Median 30 mo
(+) residual mediastinal LN	Median 10 mo
	(p=0.0005)

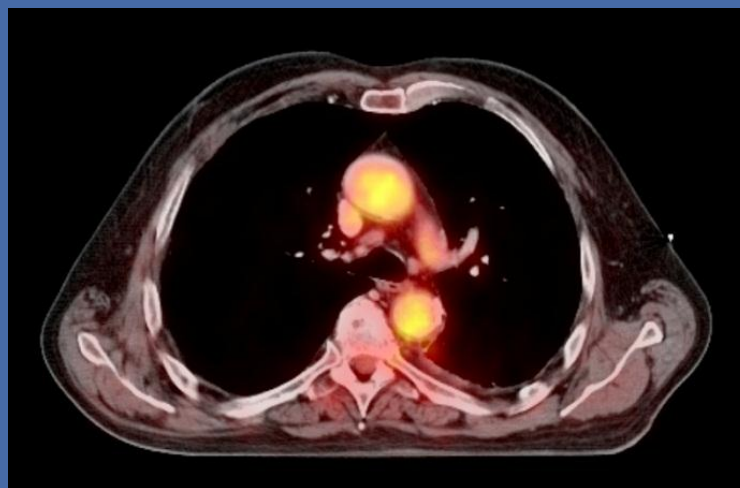
Albain K. et al 1994

N3 disease

before CTx/RTx



before surgery



N3 disease

* 2-years
** 3-years

Authors/trial	n	nodes removed	nodes pCR	5 y-survival
SWOG 8805	27	ipsilateral	53%	25%*
Stamatis et al, 1999	32	27 ipsilateral/ 5 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%
SAKK 2009	9	-	38%	47%**

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T1-3N3 disease

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

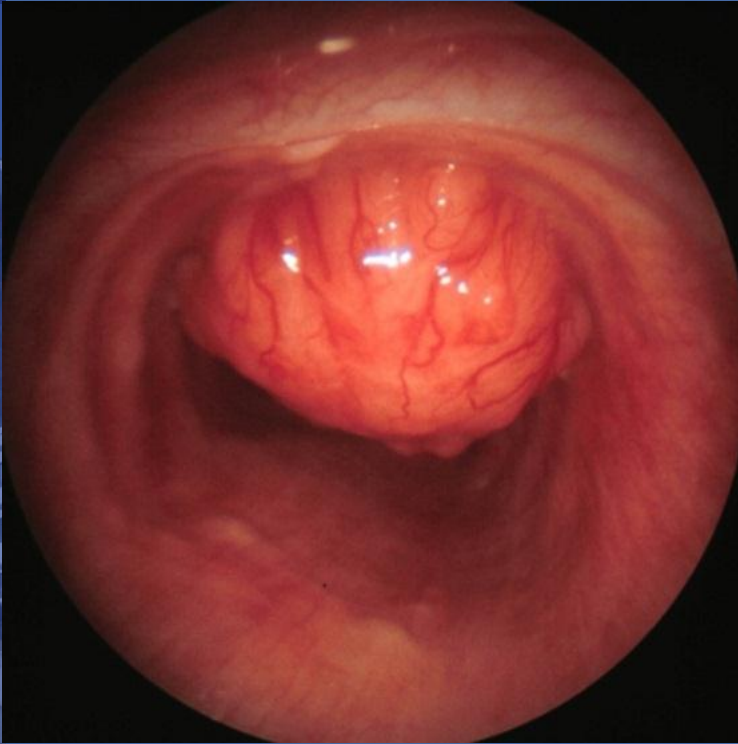
For selected cases after induction CTx/RTx and good response (N3 in ipsilateral sulcus superior tumor or limited N3 in station 2R/4R) the integration of surgery could be followed (if possible inside of studies) (grade D)

Stage T4 N0-1 disease

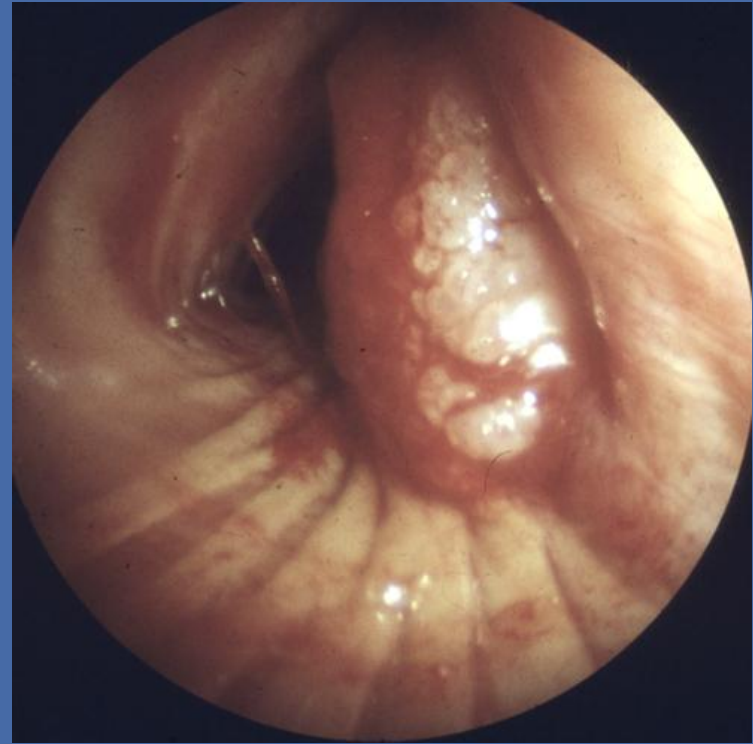
Primary surgery or integration of surgery in a multimodality treatment is recommended for patients with functional and medical operability and involvement of

- carina
- trachea
- atrium
- vena cava
- pulmonary artery
- vertebral body
- metastasis other lobe ipsilateral (grade B)

T4 Carina/Trachea

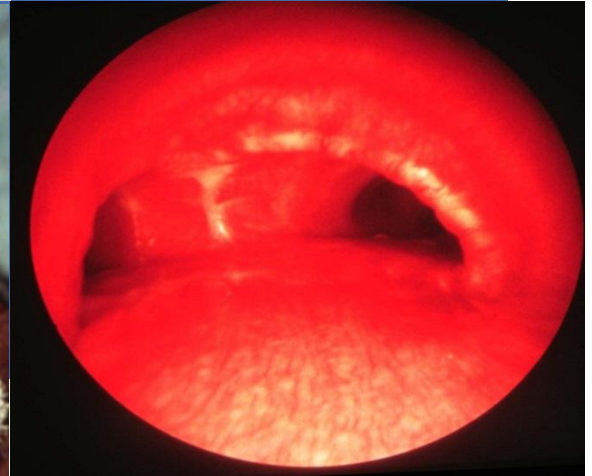
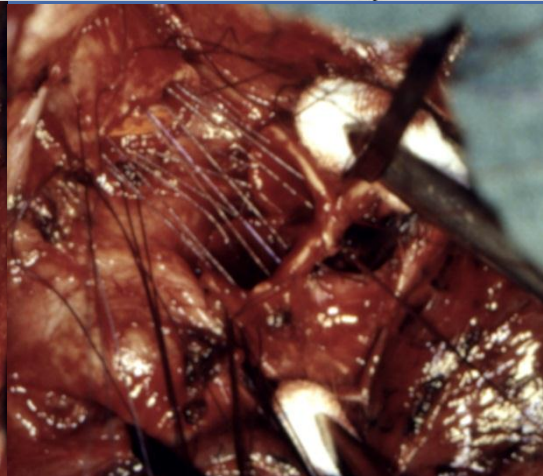
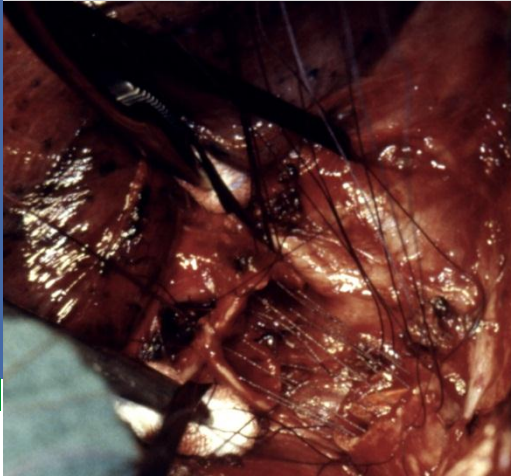
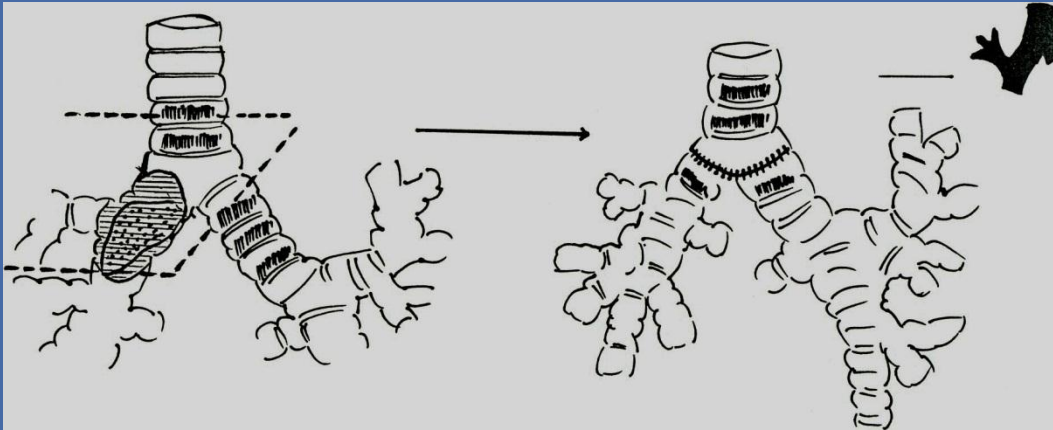


Adenoidcystic Ca Trachea/Carina



LCNEC RUL/R main bronchus

T4 Carina/Trachea

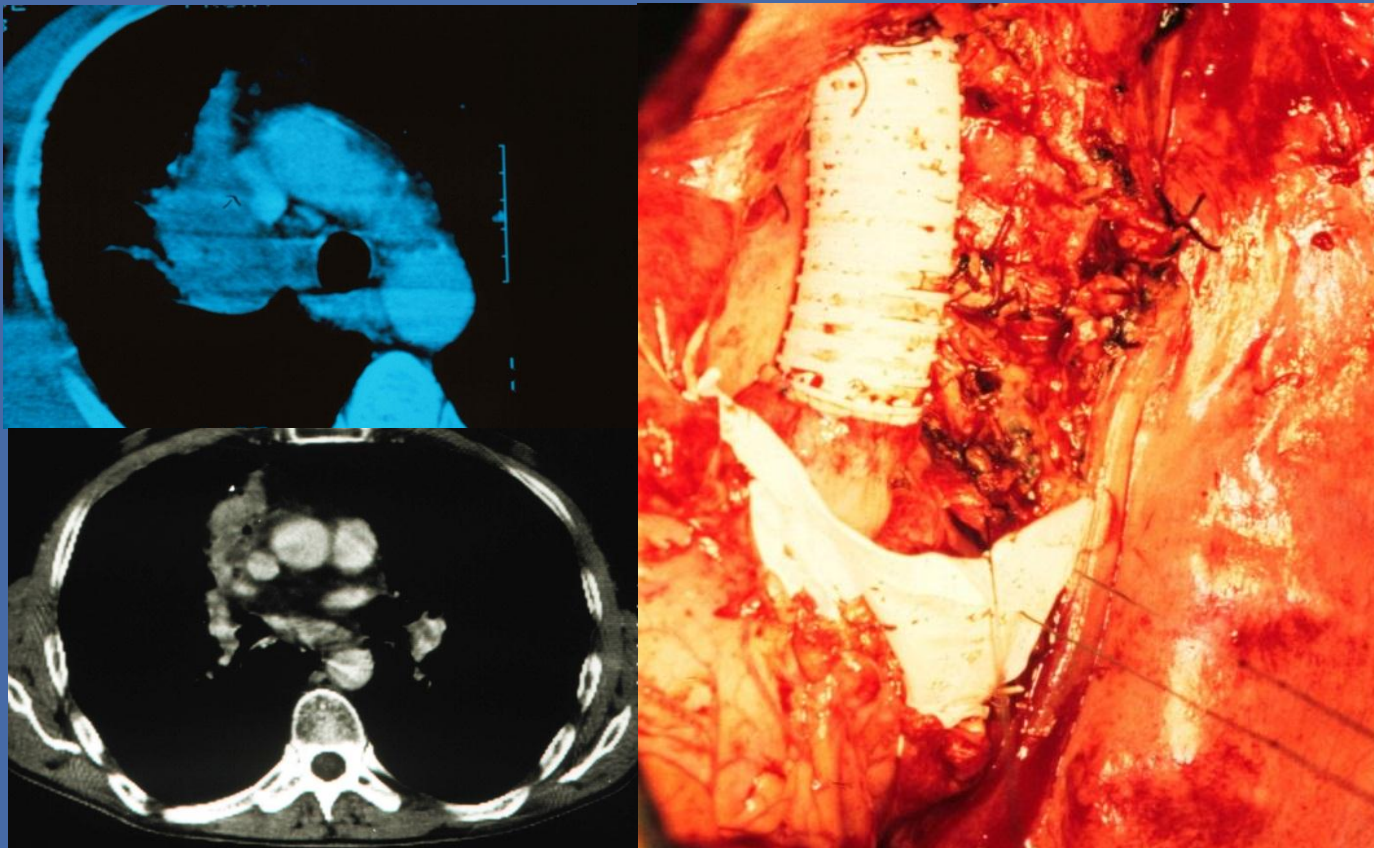


T4 Carina/Trachea

Author	n	Induction	Letality	5J Survival
Liu (2009)	32	no	9,4%	40,6%
Jiang (2009)	41	no	2,4	26,8%
Rea (2008)	49	CTx (19P)	6,1%	27,5%
Yamamoto (2007)	35	no	8,5%	28,3%
Macchiarini (2006)	50	CTx/RTX (18P)	4%	51%
De Perrot (2006)	119	no	7,6%	44%
Regnardt (2005)	65	no	7,7%	26,5%
Mathisen (2004)	60	no	15%	42%

- Publications with large experience
- Not exactly define between T3 and T4 Tumoren
- Not only patients with lung cancer
- Induction treatment not acceptable because of healing complications
- Good long term results by R0-Resection und N0/N1 pathology

T4 Vena cava



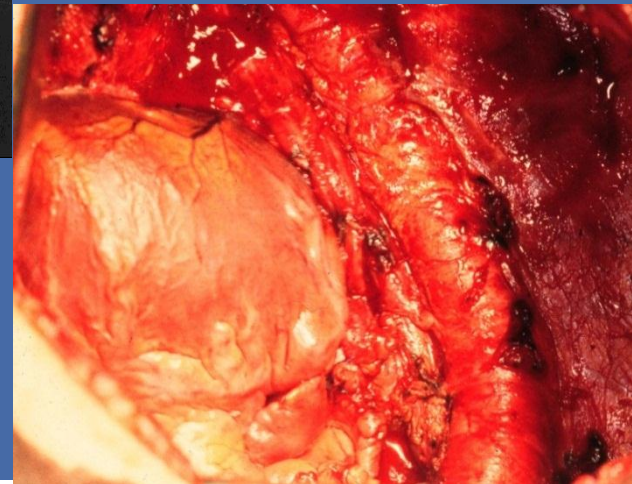
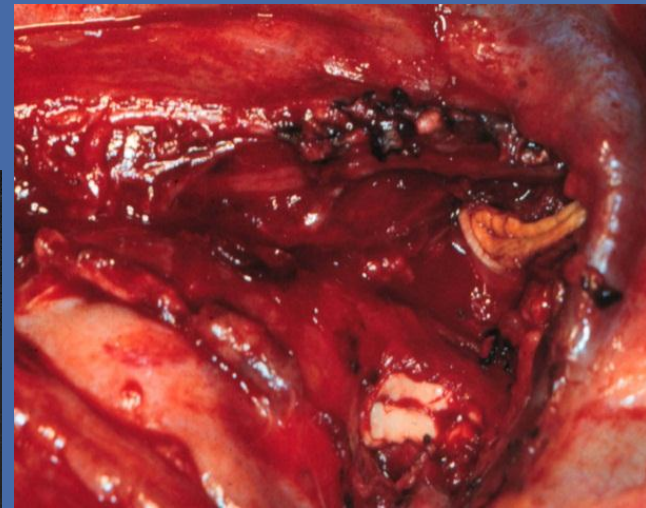
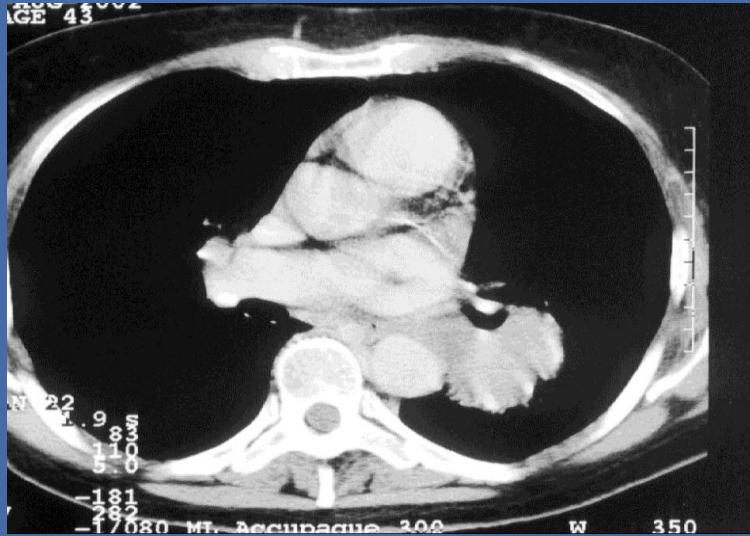
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T4 Vena cava

Author	n	Induction	Letality	5J Survival
Lanuti (2009)	9	CTx/RTx	11,1%	30%
Politi (2007)	16	CTx	6,25%	20 months
Spaggiari (2007)	52	CTx	7,7%	31% (52%N0-1, 21%N2)
Redina (1999/2007)	9/140	CTx	11,1%	30,5%

- Series with small number of cases
- Technical feasibility also without extracorporeal circulation
- Induction treatment is recommended
- For the prognosis important the R0 Resektion und N0/N1 pathology

T4 PA/ Atrium



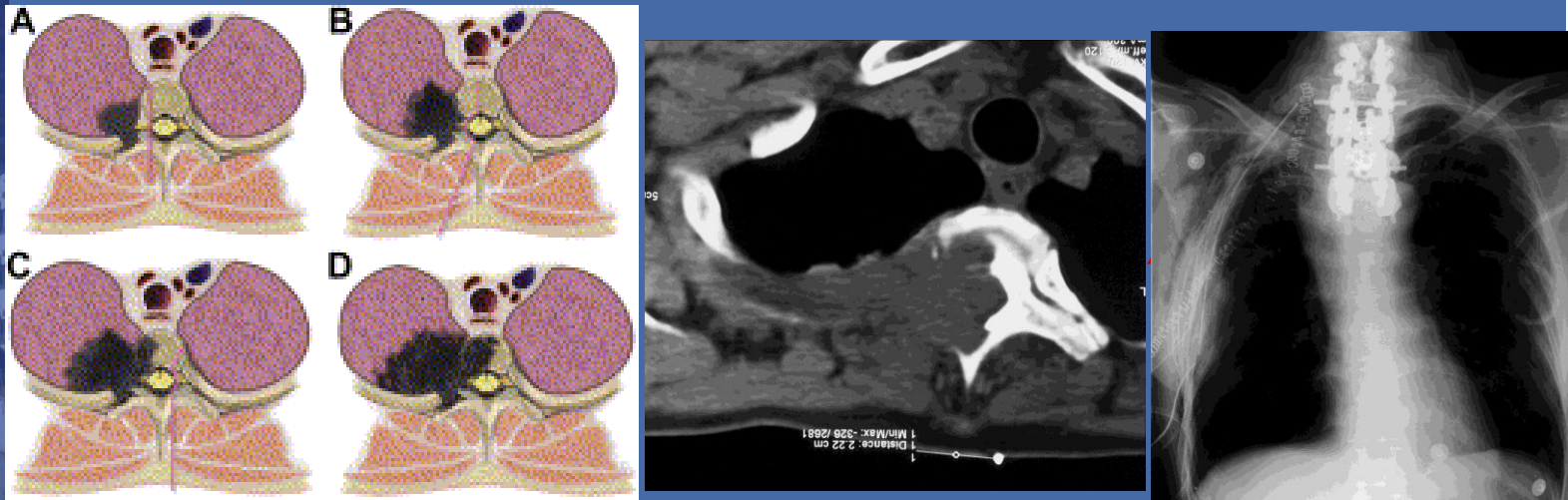
T4 PA/ Atrium

Author	n	Resection	Letality	5y survival
Wu (2009)	46	30Pn/16Lo	0%	22%(23%N1, 18%N2)
Mu (2008)	32	22Pn/10Lo	6,2%	43%(70%N0, 45%N1, 15%N2)
Akopov (2007)	28	16Pn/2Lo	3,5%	17% /23 Months
Spaggiari (2005)	15	15Pn	0%	39% (at 3 years)
Bobbio (2004)	23	22Pn/1Lo	8,7%	10%

- Small number of cases
- Induction treatment is necessary
- Technical feasibel, often with extracorporal circulation
- Letality low but high rates of morbidity
- Important for the prognosis R0 Resection and N0/N1 pathology

T4-vertebral body

(A) Right non-small cell lung cancer (NSCLC) invading thoracic inlet (TI) and the transverse processes. (B) Right NSCLC invading the TI and the intervertebral foramina. (C) Right NSCLC invading the TI and the cancellous bone. (D) Massive invasion of the vertebral body by a right NSCLC preventing en bloc resection
(From Fadel et al. Ann Thorac Surg 2011;92:1024-30)



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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

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

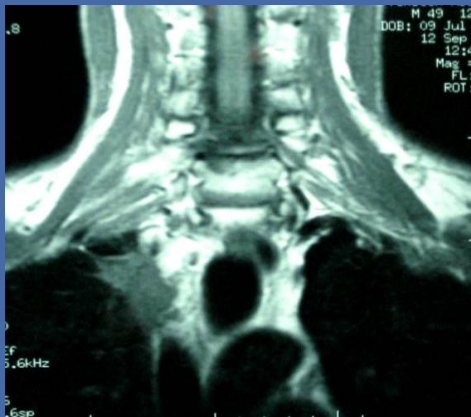
Wich are the candidates for surgery in T4 Tumors ?

For T4 disease operability is not always clear defined

Induction treatment is necessary and results in tumor reduction, so that surgery and R0 resection could be reached

For patients with central tumors and carina resection induction treatment is not acceptable because of healing complications

Pancoast tumors



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Pancoast Tumor Stage II-IIIIB

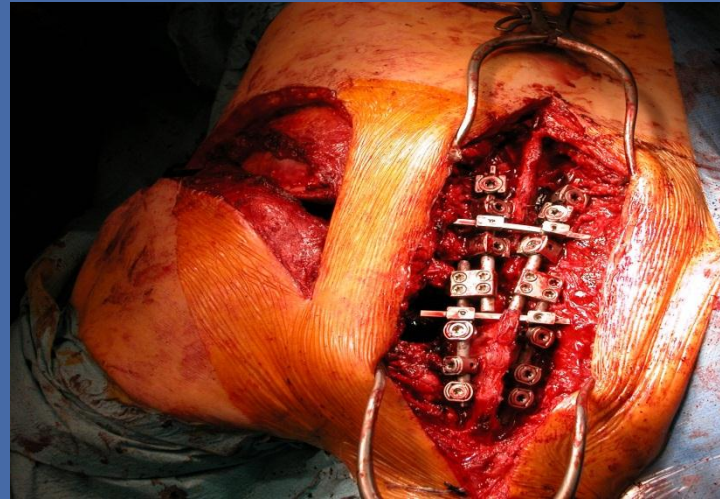
For sulcus superior tumors stage II-IIIIB induction CTx/RTx followed by surgery is recommended (grade A)

Technical or functional inoperable patients should receive a definitive CTx/RTx (grade C)

Pancoast Tumor Stage II-IIIIB



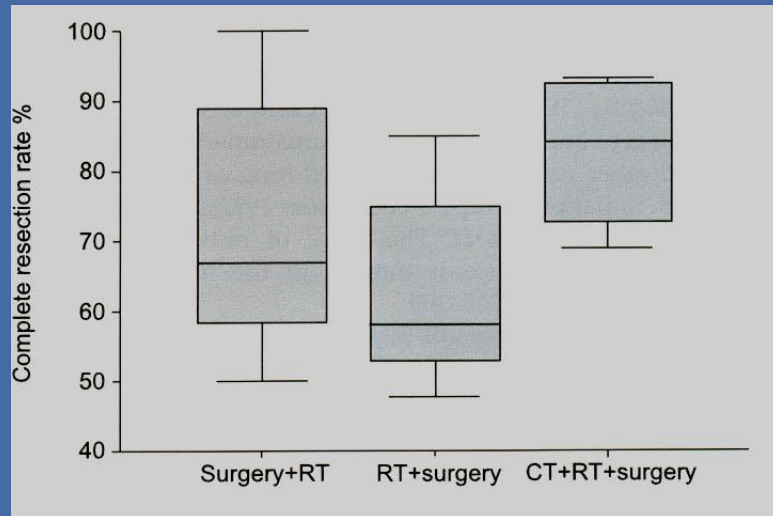
Transmanubrial approach with chest wall resection and vena cave replacement



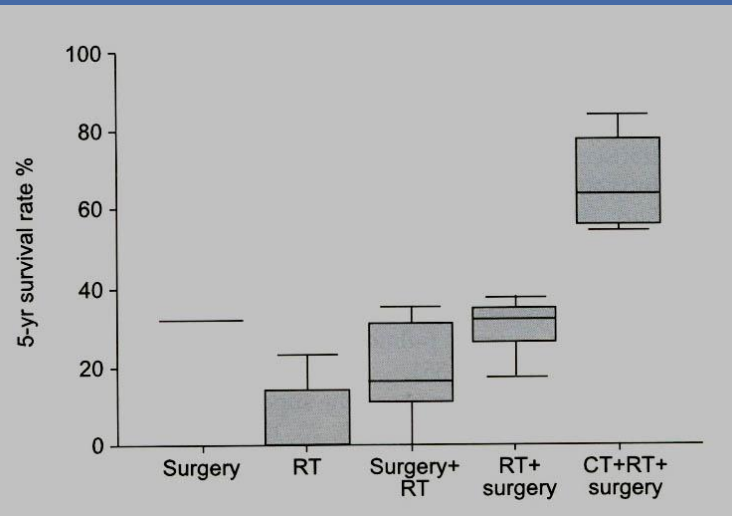
Chest wall resection with vertebral body resection and stabilisation

Role of induction treatment

Mara et al, ERS 2007



R0-resection and treatment concept



Survival and treatment concept



Inderdisciplinary approach of stage IIIA/B
disease is today the basis of successfully treatment
(grade A)



Thank you for your attention

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