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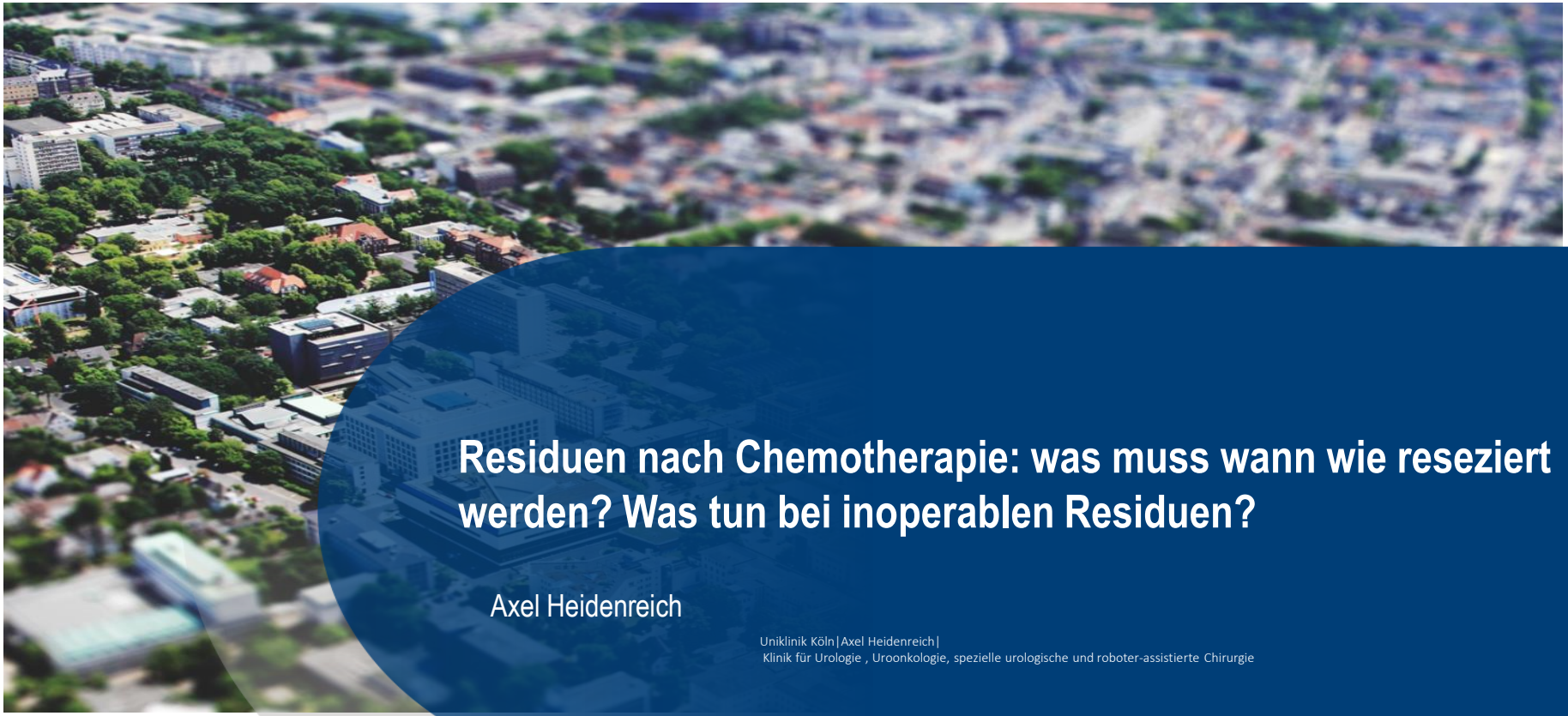

Residuen nach Chemotherapie: was muss wann wie reseziert werden? Was tun bei inoperablen Residuen?

Axel Heidenreich

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Klinik für Urologie , Uroonkologie, spezielle urologische und roboter-assistierte Chirurgie

Interessenskonflikte

Advisory board
Amgen, Astellas, AstraZeneca, Bayer, BMS, Clovis, Janssen-Cilag, MSD, Novartis

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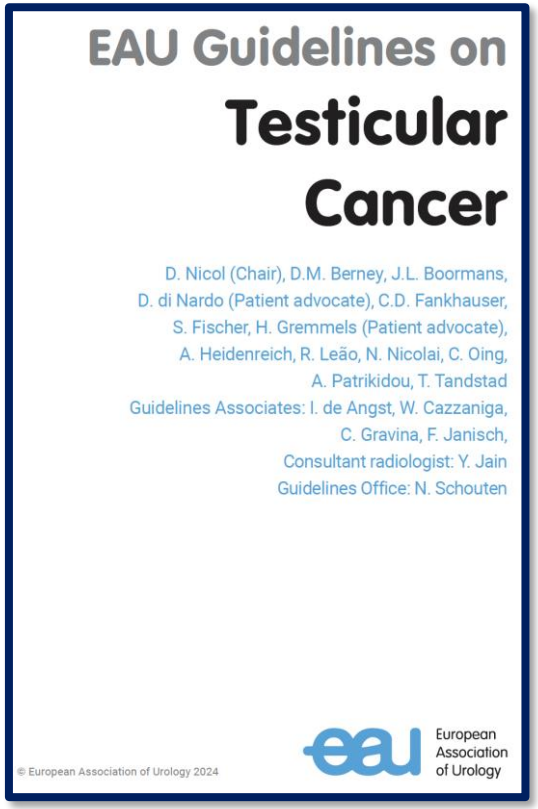
Research grant
Amgen, Astellas, AstraZeneca, BMS

Agenda

- Indikation für die Residualtumorresektion (RTR)
  - Seminom versus Nichtseminom
- anatomische Ausdehnung der RTR

- Vorgehen der RTR in Abhängigkeit der Lokalisation
  - retroperitoneal
  - retrocrural
  - Leber
  - Lunge
- was tun bei inoperablen Befunden?
- Zukunftsperspektive

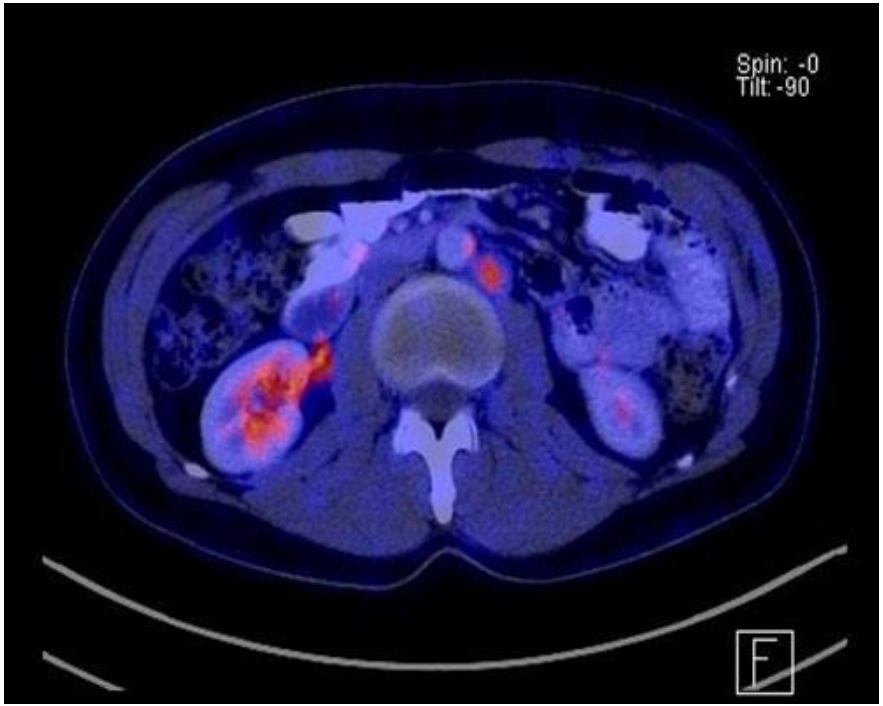
Einleitung



Residualtumor > 3cm bei metastasiertem Seminom nach Chemotherapie

- Monitoring mit Bildgebung und Tumormarkern
- evtl. FDG-PET/CT 2 Monate nach Abschluss Chemotherapie
  - NPV > 90%
  - PPV 23-69%
- positives FDG-PET/CT => Kontrolle nach 6-8 Wochen
- Persistenz => histologische Sicherung oder RPLA
- radiologischer markernegativer Progress => RPLA

Patienten und Methodik



FDG-PET/CT

paraaortaler Residual-tumor,
SUV 29

Histologie

vitales Seminom

Heidenreich A et al., ASCO 2024

Patienten und Methodik

Parameter	Wert
Medianes Alter, (IQR)	40 (31-68) Jahre
Klinisches Stadium	
I	8 (7.3%)
IIA	4 (0.9%)
IIB	27 (25%)
IIC	50 (46%)
III	20 (18%)
IGCCCG	
gut	88 (81%)
intermediär	21 (19%)
präop. Durchmesser, (IQR), cm	3.8 (2.1-14.9)

Parameter	Wert
Orchiektomie	
rechts	37 (34%)
links	56 (51%)
bilateral	3 (2.7%)
extragonadal/kA	13 (12%)
Follow-up, median (IQR)	56 (4 – 160) Monate

GESAMT: N = 109

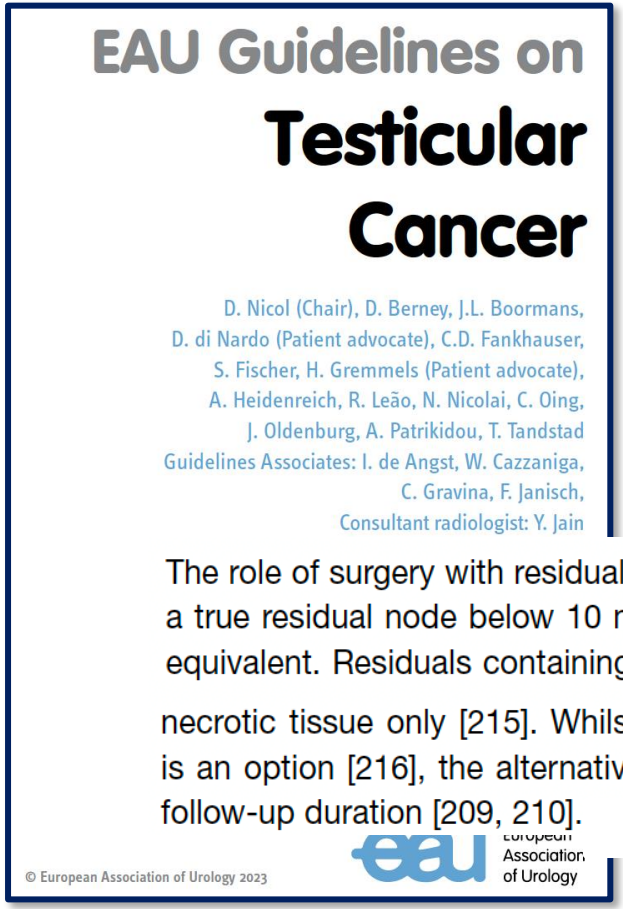
Heidenreich A et al., ASCO 2024

Ergebnisse - perioperativ

Parameter	Wert
Medianer Blutverlust, (IQR)	550 (300-5800) ml
Mediane Hospitalisierung, (IQR)	4 (2-18) Tage
Komplikationen Clavien-Dindo IIIa – V 90 Tage	 10 (11.1%) 4 (3.7%)
Pathohistologie Vitales Seminom Nekrose/Fibrose	 34 (31%) 75 (69%)
FDG-PET/CT Patienten Positive prädiktiver Wert	 52 27%

Ergebnisse - Onkologie

Parameter	Wert
Onkologische Ergebnisse	
Rezidiv, alle	14 (13%)
Rezidiv, Seminom	7 (20.6%)
Rezidiv, Nekrose	7 (9.3%)
Kuration durch Salvage Chemotherapie	11/14 (78.6%)
DOD	3 (2.7%)
Rezidivlokalisation	
Lymphknoten	12 (80%)
Viszeral/skelettal	3 (20%)
Prädiktive Marker vitales Karzinom	
Markernegative Progression	HR 19, $p < 0.001$
FDG-PET/CT SUV > 10	HR 31, $p = 0.004$



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RTR versus Surveillance bei Residuen < 1cm

	Kakiashvilli, 2009	Kollmannsberger, 2010	Ehrlich, 2010
n	129	161	141
Follow-up	7 Jahre	40 Monate	15.5 Jahre
Rezidivrate	8%	6%	9%
DOD	1%	0%	3%
Prädiktoren Rezidiv/DOD	IGCCCG gut vs intermediär/poor	IGCCCG gut vs intermediär/poor 0% versus **6%**	IGCCCG gut vs intermediär/poor 5% versus **27%**

RTR versus Surveillance bei Residuen < 1cm

	Surveillance	RTR
IGCCCG	gut	intermediär/schlecht
Histologie	< 50% Teratom	≥ 50% Teratom
Tumormarker	negativ, Plateau	negativ, Plateau
Radiologie	< 1cm vertikaler **UND** horizontaler Durchmesser	> 1cm in einer Ebene

Oldenburg J et al., J Clin Oncol 2003; 21: 3310; Vergouwe Y et al., Br J Cancer 2003; 88: 843; Albers P et al., J Urol 2004; 171: 1835, Heidenreich A et al., Eur Urol 2005; Vergouwe Y et al., Eur Urol 2006;

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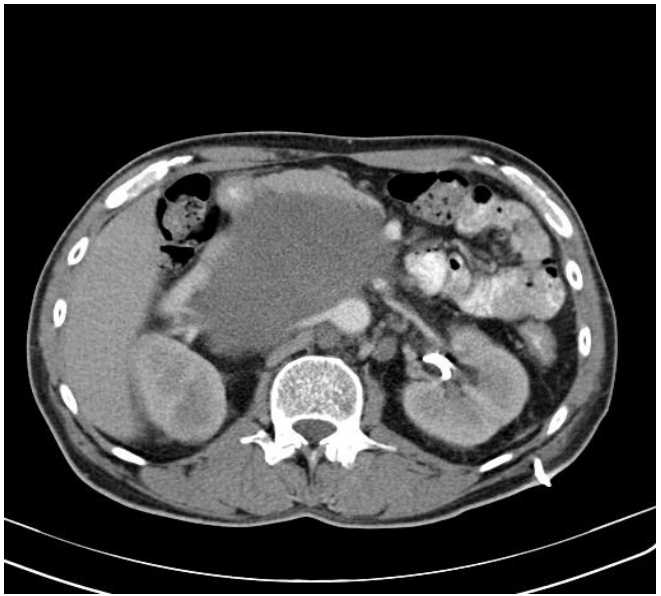
Heterogenes Szenario – individuelles Vorgehen

retroperitoneales Residuum, infrahilär

mediane Laparotomie

retroperitoneales Residuum, suprahilär



Chevron - Inzision

retrocrurales Residuum

thoracoabdominell

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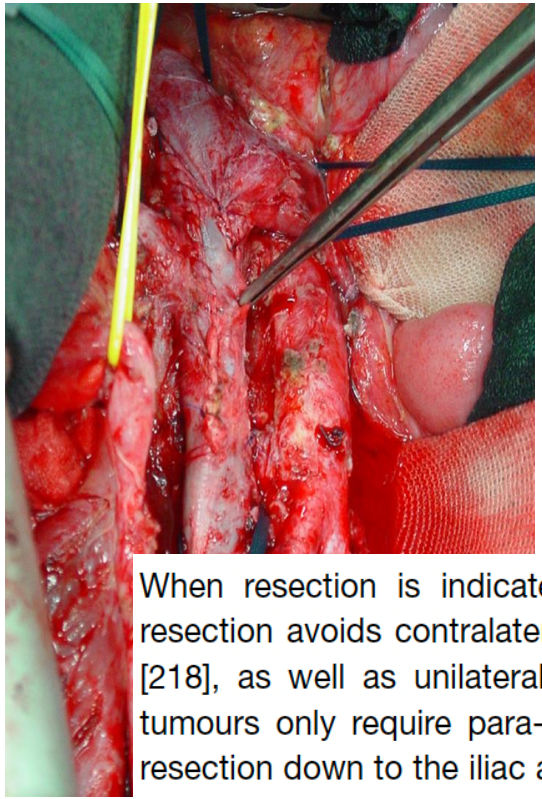
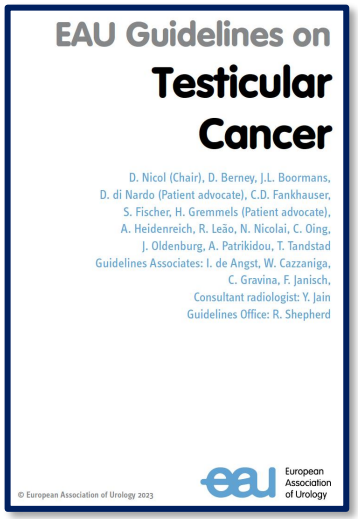
Ausdehnung der PC - RTR





When resection is indicated, bilateral nerve sparing RPLND is the standard option. Ipsilateral template resection avoids contralateral nerve dissection and may be considered for residuals with a diameter < 5 cm [218], as well as unilateral lymph node metastases on pre- and post-chemotherapy CT scans, left-sided tumours only require para-aortic resection whereas right-side tumours need paracaval and inter-aortocaval resection down to the iliac arteries [219, 220]. Mapping studies indicate a potential risk of contralateral disease

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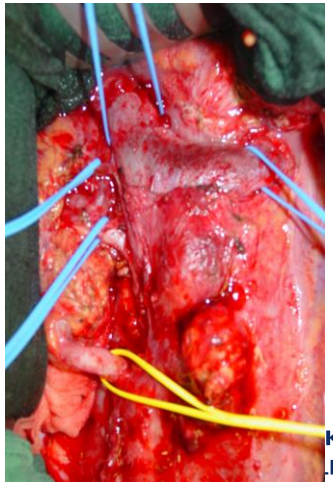
Postchemotherapy retroperitoneal lymph node dissection in advanced testicular cancer: radical or modified template resection. Heidenreich A, Pfister D, Witthuhn R, Thüer D, Albers P. Eur Urol. 2009 Jan;55(1):217-24

Modifiziertes Template bei

- Residualtumor ≤ 2cm,
- Residualtumor 2-5cm wenn initial in der primären Landungszone des tumortragenden Hodens

Radikale bilaterale Resektion

- initiales Bulcky Disease
- Residualtumor > 5cm
- Lokalisation außerhalb der primären Landungszone



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Postchemotherapy retroperitoneal lymph node dissection in advanced testicular cancer: radical or modified template resection. Heidenreich A, Pfister D, Witthuhn R, Thüer D, Albers P.Eur Urol. 2009 Jan;55(1):217-24

Onkologische und funktionelle Daten

- Narbe/Nekrose in 84 (55.2%), Teratom in 45 (29.6%) und vitales Karzinom in 23 (15.1%) **=> keine** Unterschiede modifiziert versus radikal
- Rezidive n=8 (5.2%): 1 Rezidiv in-field; 7 Rezidive außerhalb Feldgrenzen einer radikalen RPLA

- **2-Jahre Rezidivfreiheit** 92.8% für modifiziertes und 78.6% für bilaterales Template
- antegrade Ejakulation in 85% nach modifizierter RPLA und 25% nach radikaler RPLA (p=0.02)

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Modified retroperitoneal lymph node dissection for post-chemotherapy residual tumour: a long-term update. Cho JS et al., BJU Int 2017; 120: 104 - 108

Fig. 1 Overall survival of modified RPLND patients (Kaplan–Meier).

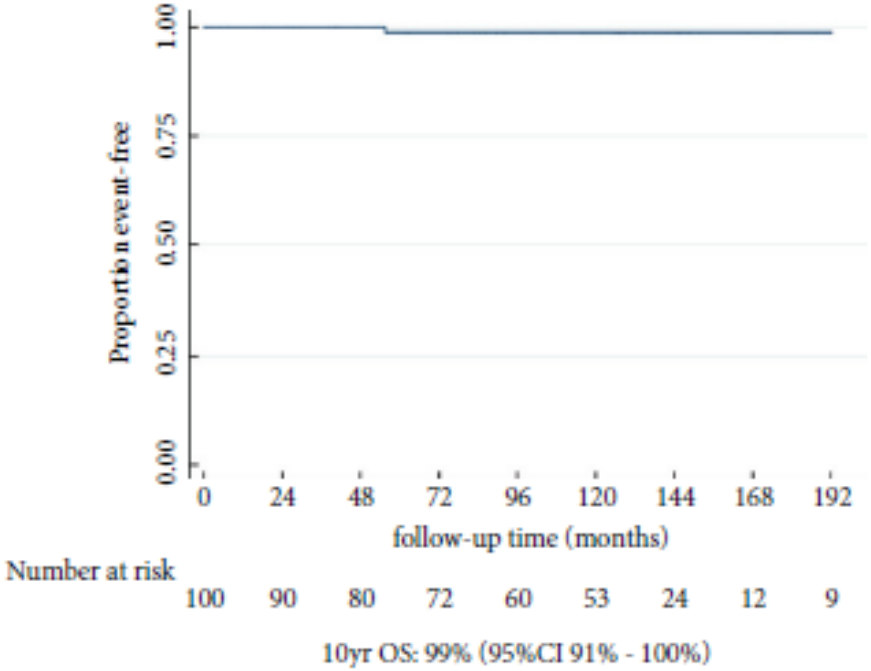
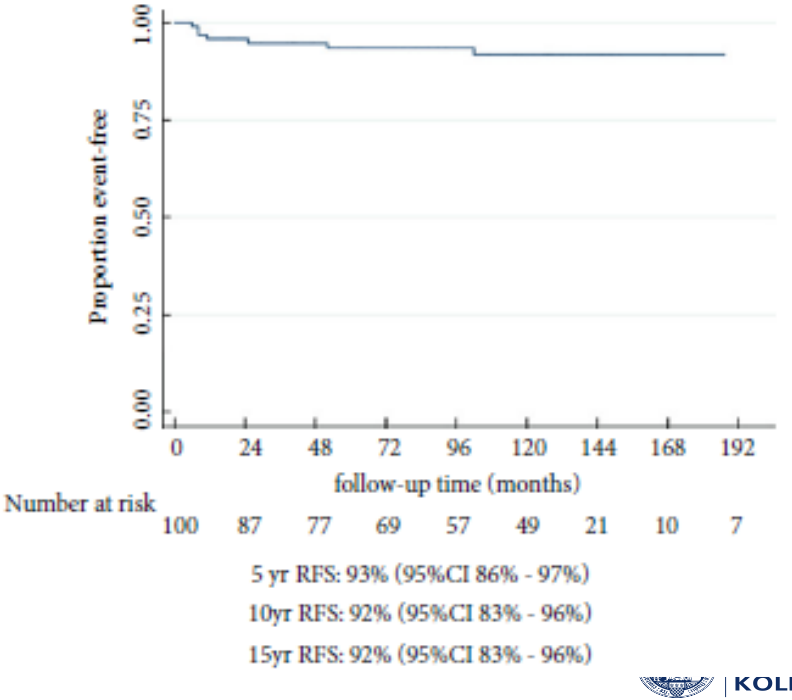
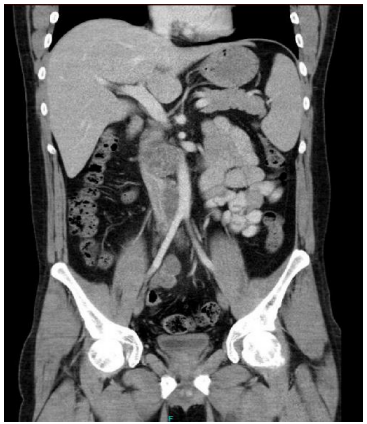


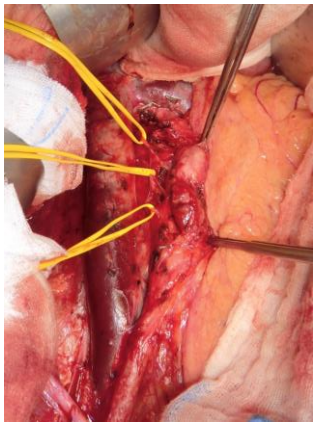
Fig. 2 RFS of modified RPLND patients (Kaplan–Meier).



Ausdehnung der PC - RTR

unilaterales Template

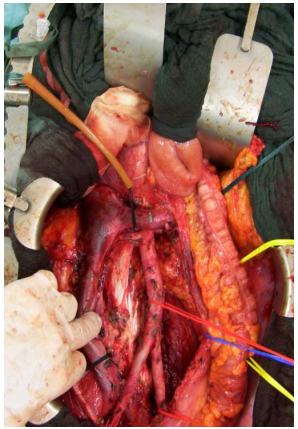




- < 5cm in der primären Landungszone

- **links:** prä- und paraaortal, retro-aortal, A. iliaca comm.
- **rechts:** prä-, para- und retrocaval sowie interaortocaval, A. iliaca comm

bilaterales Template



- bulcky disease
- außerhalb der primären Landungszone

- prä- und paraaortal, retroaortal, prä-, para- und retrocaval sowie interaorto-caval, Aa. iliacae comm.

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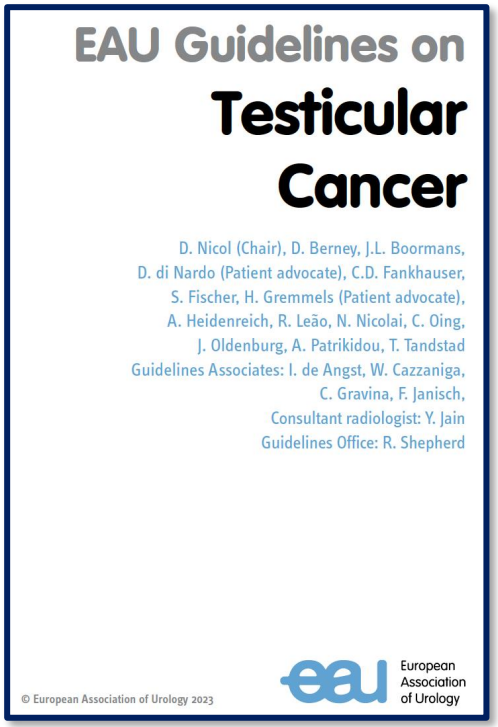

Recommendations	Strength rating
Perform surgical resection of residual masses after chemotherapy in NSGCT in the case of visible residual masses and when serum levels of tumour markers are normal or normalising.	Strong

When surgery is indicated, all areas of primary metastatic sites must be completely resected within two to six weeks of completion of chemotherapy. If technically feasible, a bilateral nerve-sparing procedure should be performed. There is growing evidence that template resections with unilateral preservation of nerves in selected patients yield equivalent long-term results compared to bilateral systematic resections in all patients. The mere resection of the residual tumour (so called lumpectomy) should not be performed [213, 219, 222-225].

eigene Erfahrung: 122/395 (30.8%

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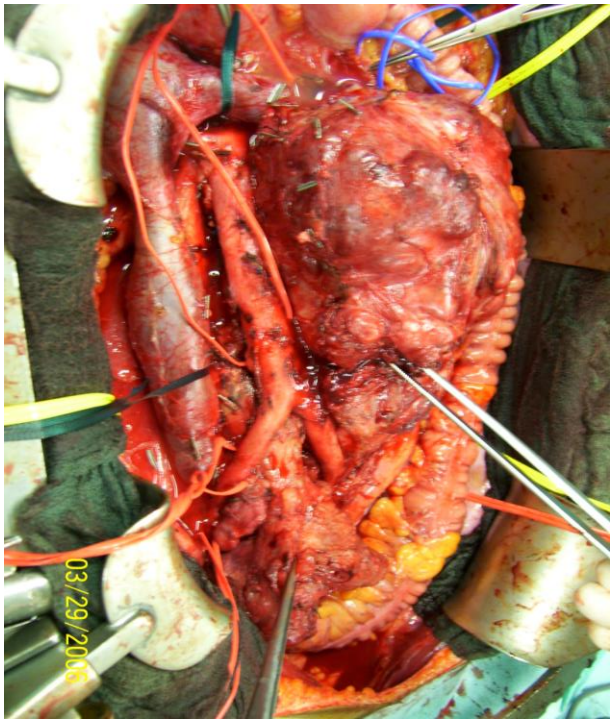
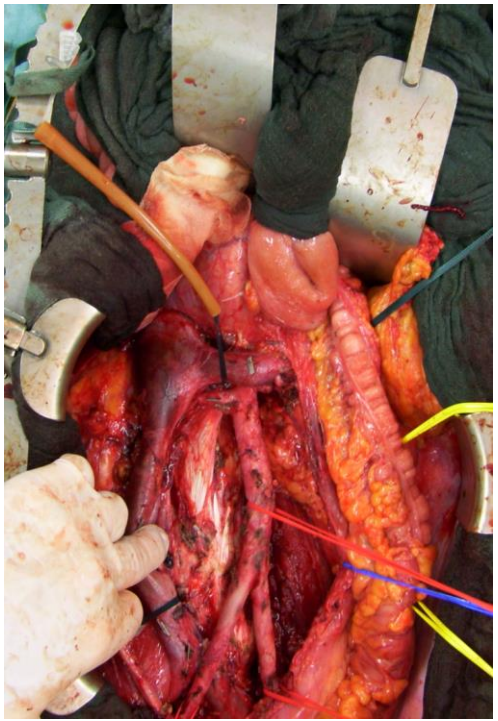
retroperitoneale RTR: groß, aber einfach

Bulcky Tumor (25 x 13cm), solide & zystische Morphologie





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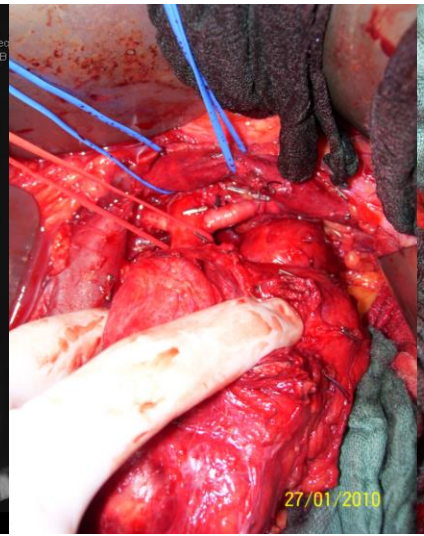
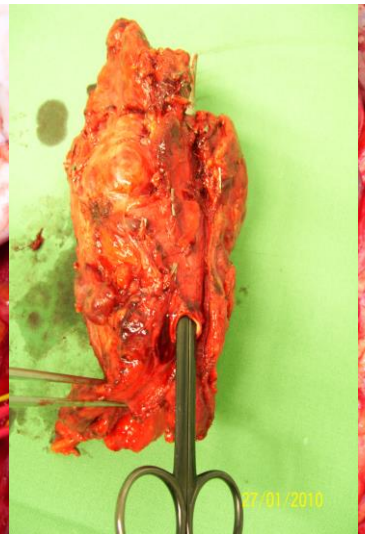
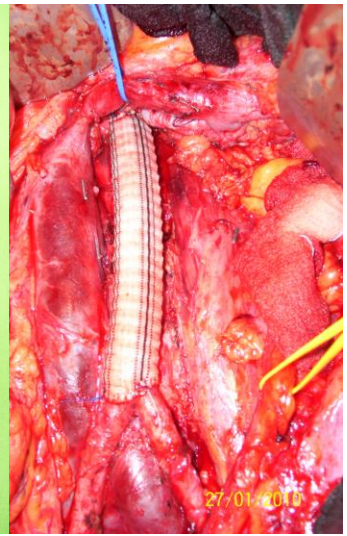
Retroperitoneal und komplex







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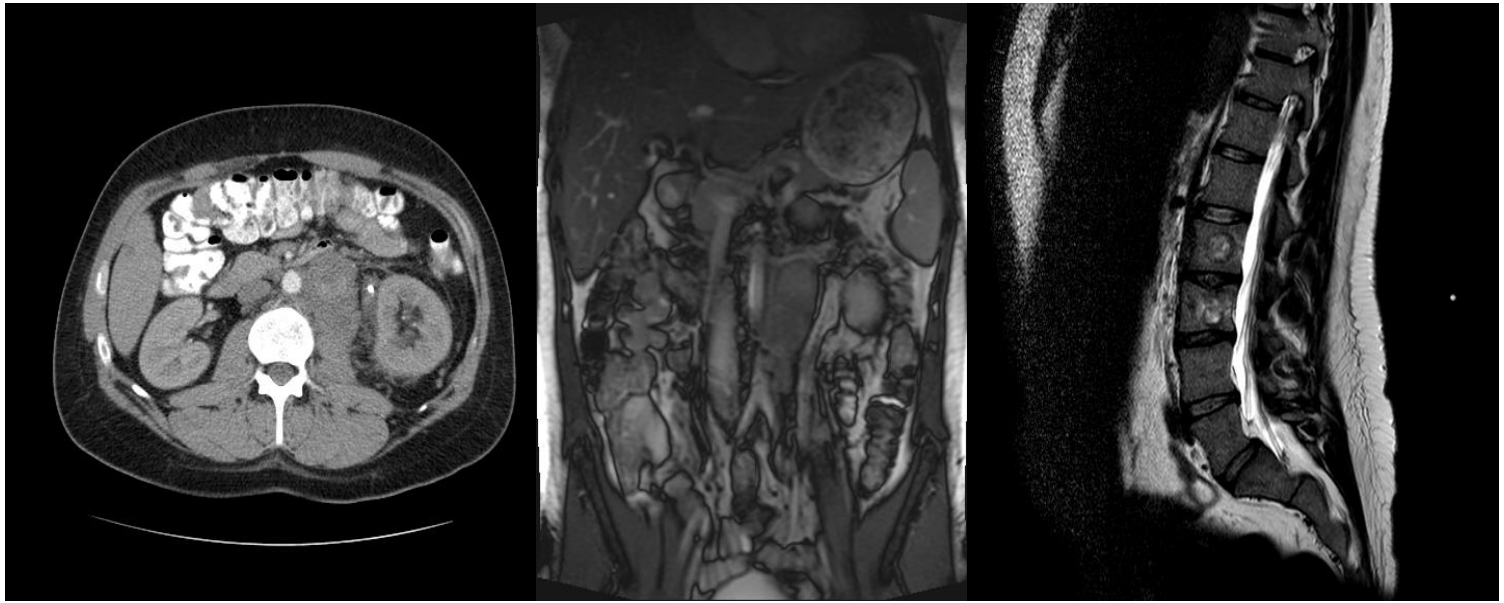
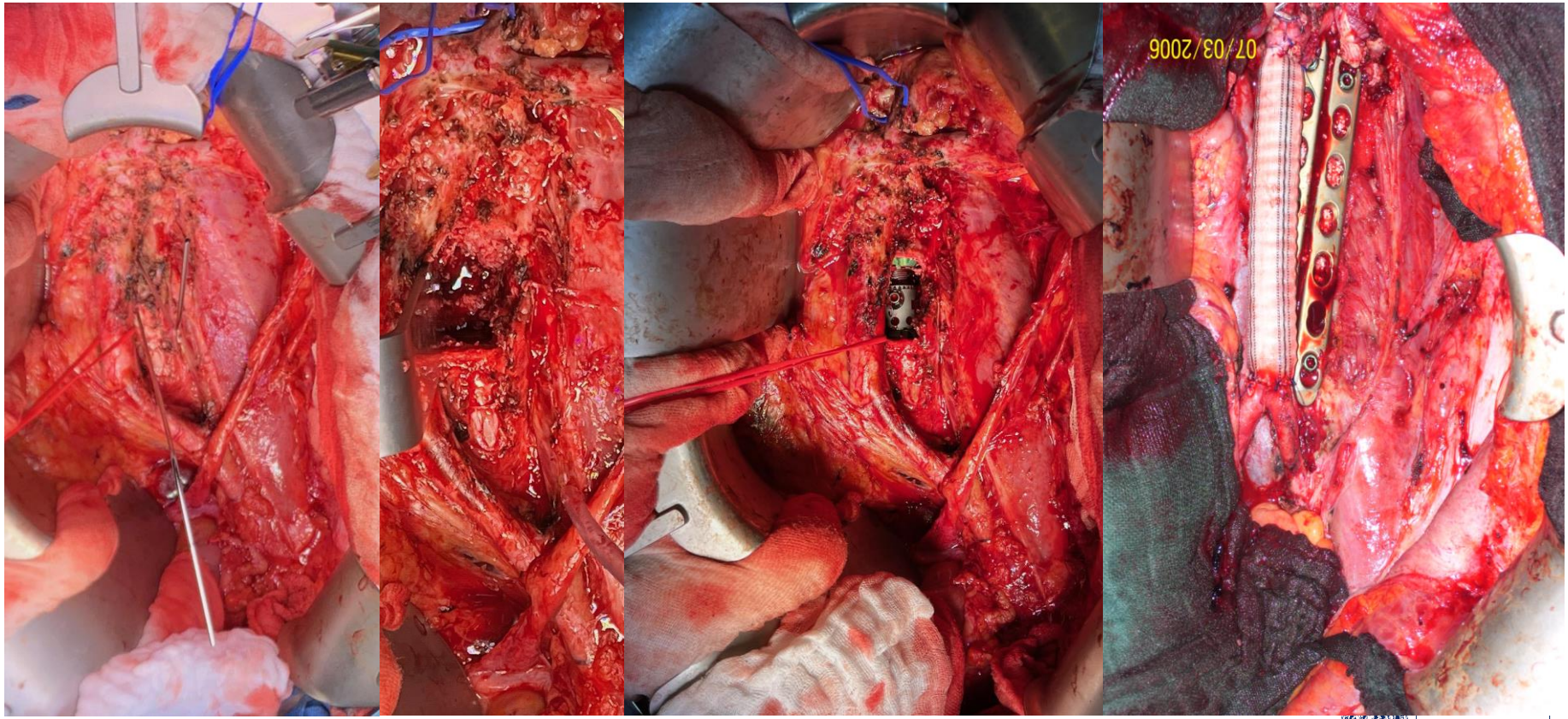
Retroperitoneal und schwierig



Retroperitoneal und schwierig



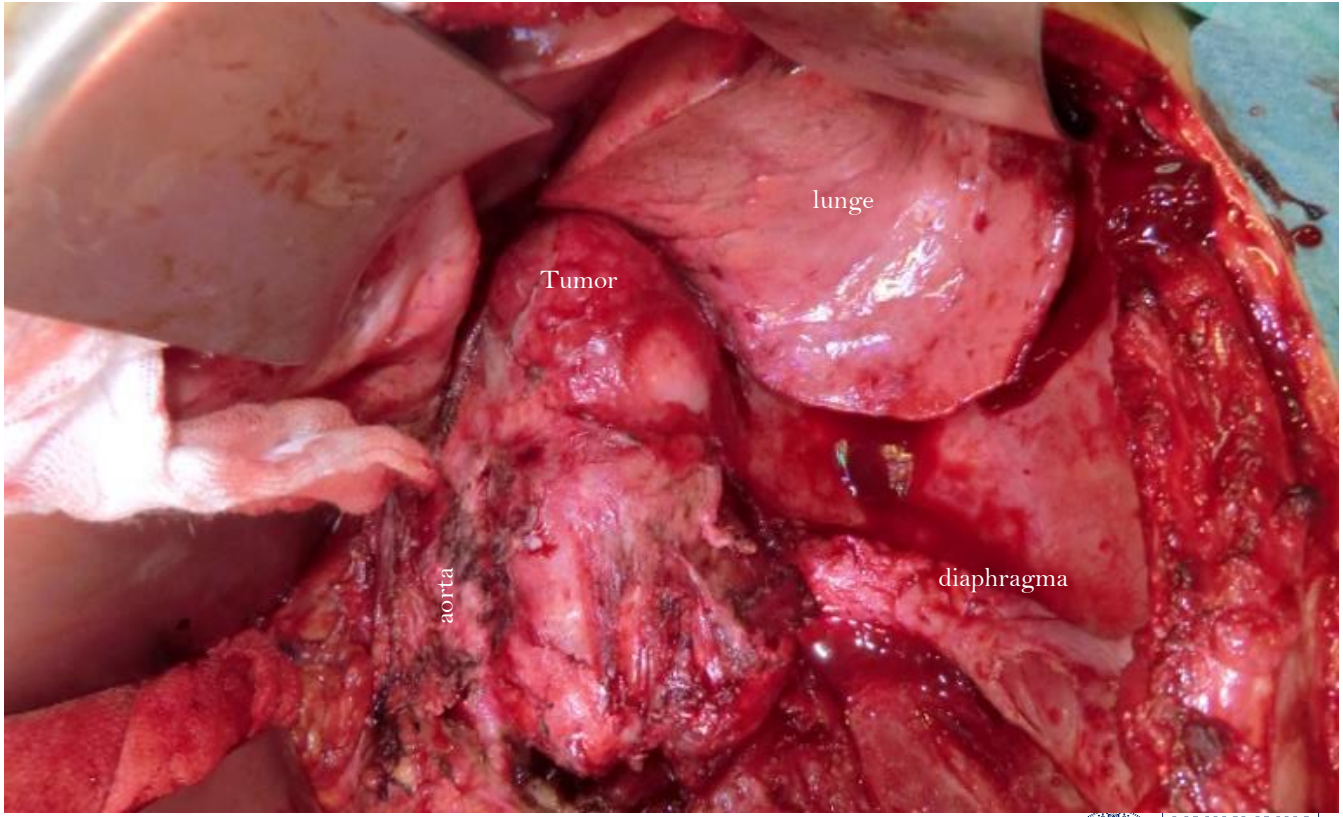
Surgical management of complex residual masses following systemic chemotherapy for metastatic testicular germ cell tumours. Heidenreich et al., Ann Oncol 2017; 28: 362 - 367

Table 2. Surgery-associated complications classified according to Clavien–Dindo depended on type of adjunctive surgeries; multiple listing are possible

	Vascular surgery	Skeletal surgery	Pancreatico-duodenal surgery	PC-RPLND w/o adjunctive surgery	*P*
N	15	5	4	138	
Grad I	0	0	0	0*	ns
Grad II	2 (13.3%)	2 (40%)	2 (50%)	5 (3.6%)	0.03**
Grad IIIa	2 (13.3%)	0	1 (25%))	3 (2.2%)	0.03***
Grad IIIb	0	0	2 (50%)	0	ns
Grad IVa	1 (6.7%)	0	1 (25%)	2 (2.2%)	0.01***
Grad IVb	0	0	0	0	ns
Grad V	0	0	0	0	ns
Time of hospitalisation	7.5 (6–11)	13.9 (9–32)	18.5 (14–45)	6.1 (4–12)	0.03

*Perioperative pain medication was necessary in all patients.
**Statistically significant between vascular surgery/no adjunctive surgery versus skeletal/pancreaticoduodenal surgery.
***Significantly more frequent only for pancreaticoduodenal resections.

Thoracoabdominell bei großen Residuen



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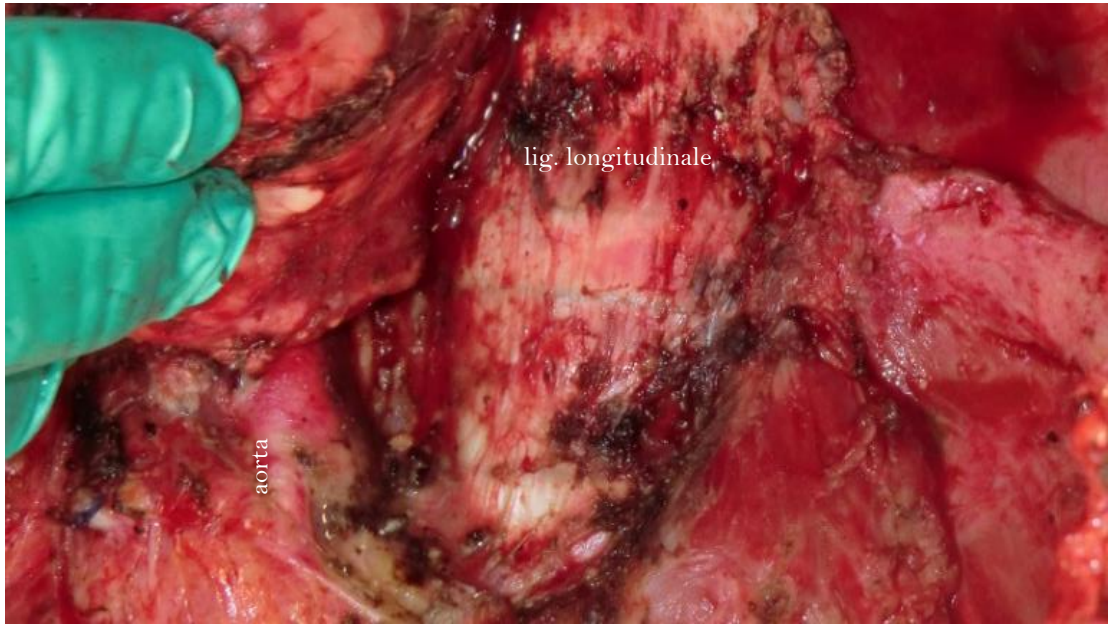
Thoracoabdominell bei großen Residuen



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PC - RTR retrocruraler Residualtumoren

Retrocrurale Metastasen und Histologie

Narbe/Nekrose	42-48%
Teratom	45-55%
Vitales Karzinom	8-15%

=> komplette Resektion aller retrocruralen Residuen
=> eine Sitzung mit RPLA
=> große chirurgische Expertise erforderlich

PC - RTR hepatischer Residualtumoren

	Liver resection histology (95% confidence interval)		
RPLND histology	**Necrosis/fibrosis (n=27)**	**Viable GCT (n=4)**	**Teratoma (n=5)**
Fibrosis/necrosis (n=19)	79% (54–94%)	5.3% (0.13–26%)	16% (3.4–40%)
Viable GCT (n=5)	60% (15–95%)	40% (5.3–85%)	0% (0–52%) *
Teratoma (n=8)	63% (24–91%)	13% (0.32–53%)	25% (3.2–65%)
Teratoma and viable GCT (n=4)	100% (40–100%)	0% (0–60%) *	0% (0–60%) *

4/36 (11%) mit divergenter Histologie

- geringe Diskordanz der Histologie zwischen RP und Leber
- individuelle Entscheidung zur Lebermetastasenresektion

Pietzak EJ et al., Urology 2018; 118: 114 - 118

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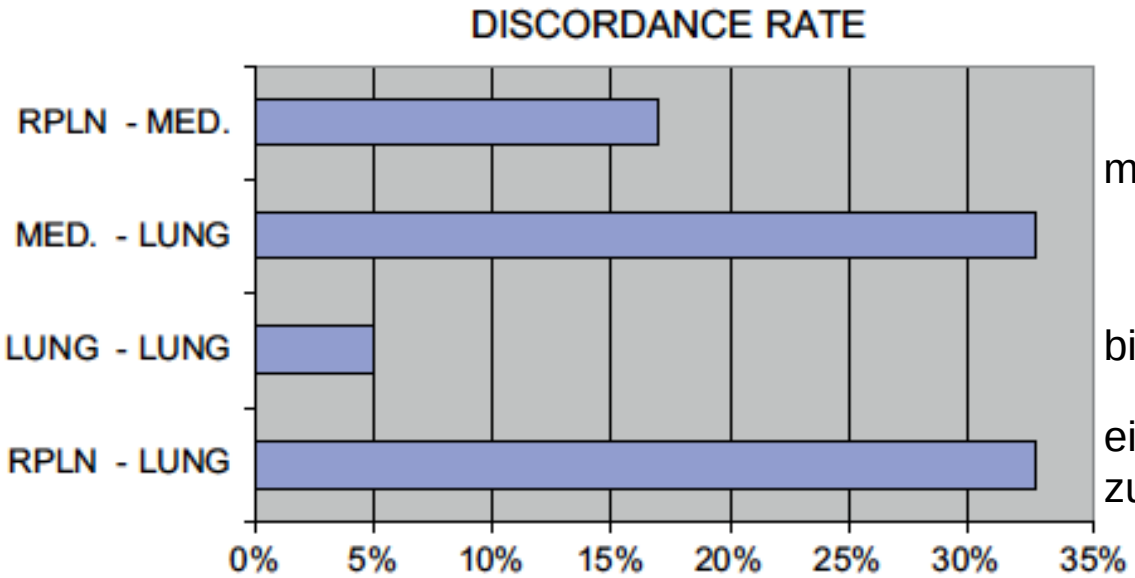
PC - RTR pulmonaler Residualtumoren



mediastinal immer

bilateral bei Teratom/Karzinom

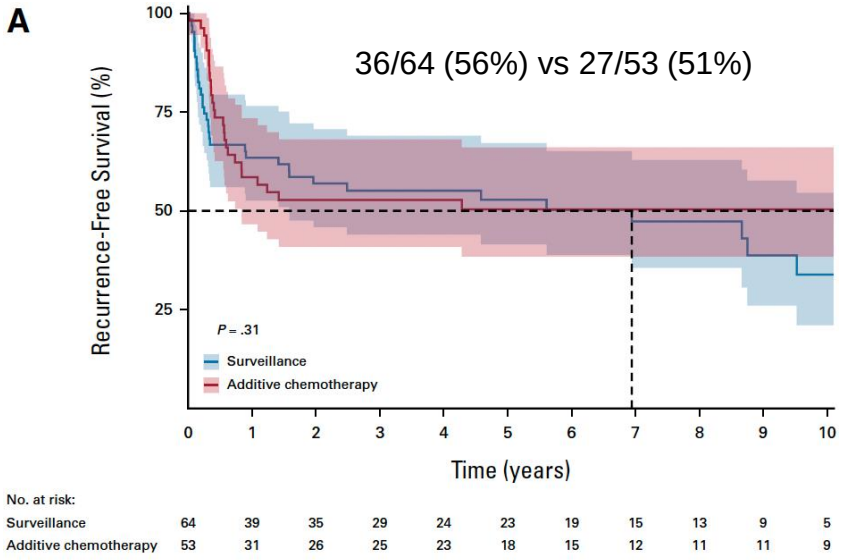
eine Seite immer; die einfachste zuerst

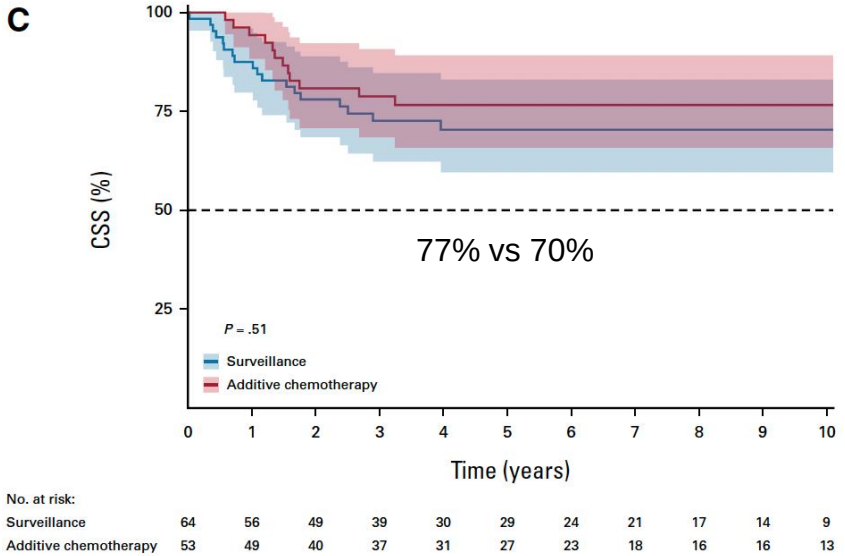
Besse B et al., J Thorac Cardiovasc Surg 2009; 137: 448 - 452

Risk Factors for Relapse in Nonseminomatous Testicular Cancer After Postchemotherapy Retroperitoneal Lymph Node Dissection With Viable Residual Cancer

Luca Antonelli, MD[1,2]; Davide Ardizzone, MD[3]; Isamu Tachibana, MD[4]; Nabil Adra, MD[5]; Clint Cary, MD[4]; Lee Hugar, MD[6]; Wade J. Sexton, MD[6]; Aditya Bagrodia, MD[7,8]; Michal Mego, MD[9]; Siamak Daneshmand, MD[10]; Nicola Nicolai, MD[11]; Sebastiano Nazzani, MD[11]; Patrizia Giannatempo, MD[11]; Andrea Franza, MD[11]; Axel Heidenreich, MD[12,13]; Pia Paffenholz, MD[12]; Ragheed Saoud, MD[14]; Scott Eggener, MD[14]; Matthew Ho, MD[14]; Nathaniel Oswald, MD[15]; Kathleen Olson, MD[15]; Alexey Tryakin, MD[16]; Mikhail Fedyanin, MD[16]; Natacha Naoun, MD[17]; Christophe Javaud, MD[17]; Walter Cazzaniga, MD[18]; David Nicol, MD[18,19]; Axel Gerdtsson, MD[20,21]; Torgrim Tandstad, MD[22,23]; Karim Fizazi, MD[17]; and Christian Daniel Fankhauser, MD[1,3,24]; in collaboration with the EAU-YAU Penile and Testis Cancer Working Group

J Clin Oncol 2023; 41: 5296 - 5305





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Was tun bei inoperablen Befunden?

- ist der Befund inoperabel?
  - nur für mich oder tatsächlich?
- warum ist der Befund inoperabel?
  - kann ich das Problem interdisziplinär lösen?
- verursacht der Residualtumor Symptome?
  - Resektion nur des symptomatischen Befundes
- gibt es eine nicht-chirurgische Option?
  - molekulare Testung, klinische Studie

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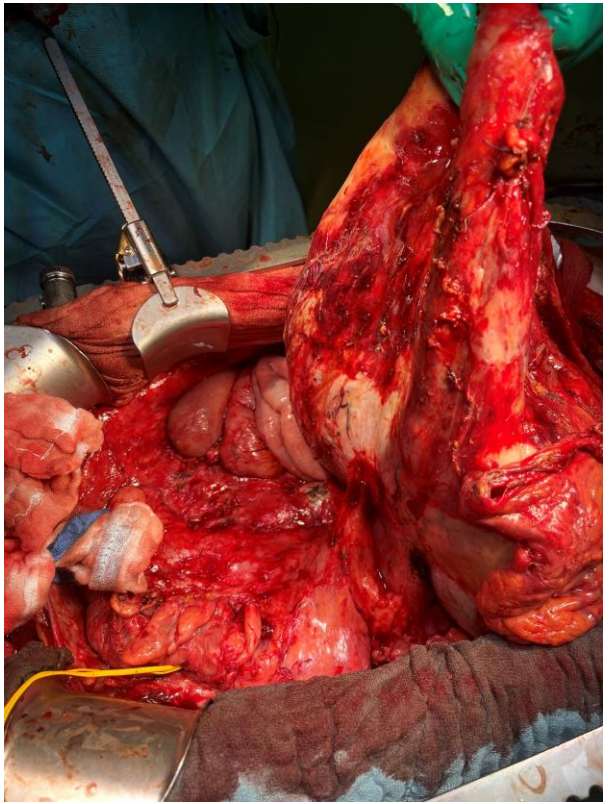
Individuelle Fälle brauchen individuelle Lösungen...



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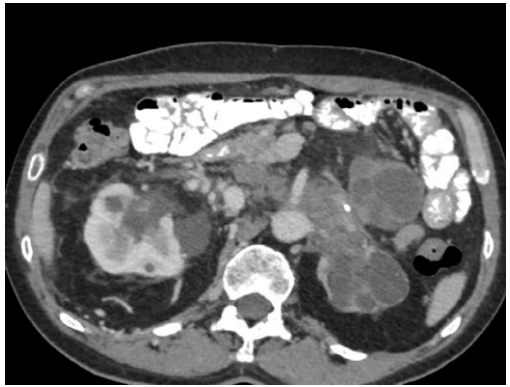
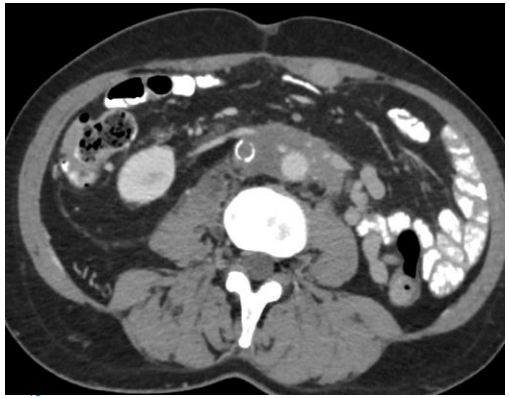
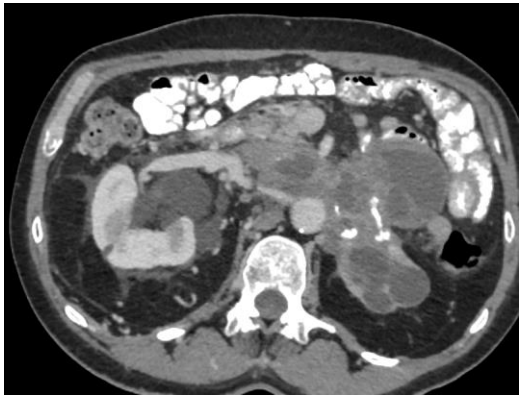


Truncus Coeliacus
AMS

Hydronephrose re
Einzelniere



RPLA extern
Cavaprothese



Aorta > 50%
A. renalis

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Individuelle Fälle brauchen individuelle Lösungen...

Redo – RPLA (all urology)

retroperitoneale & retrocrurale bilaterale RPLA
Cholecystectomie, partielle Resektion des Duodenums
Aortenprothese
OP-Dauer: 19.5 Stunden, Hospitalisation 6 Tage

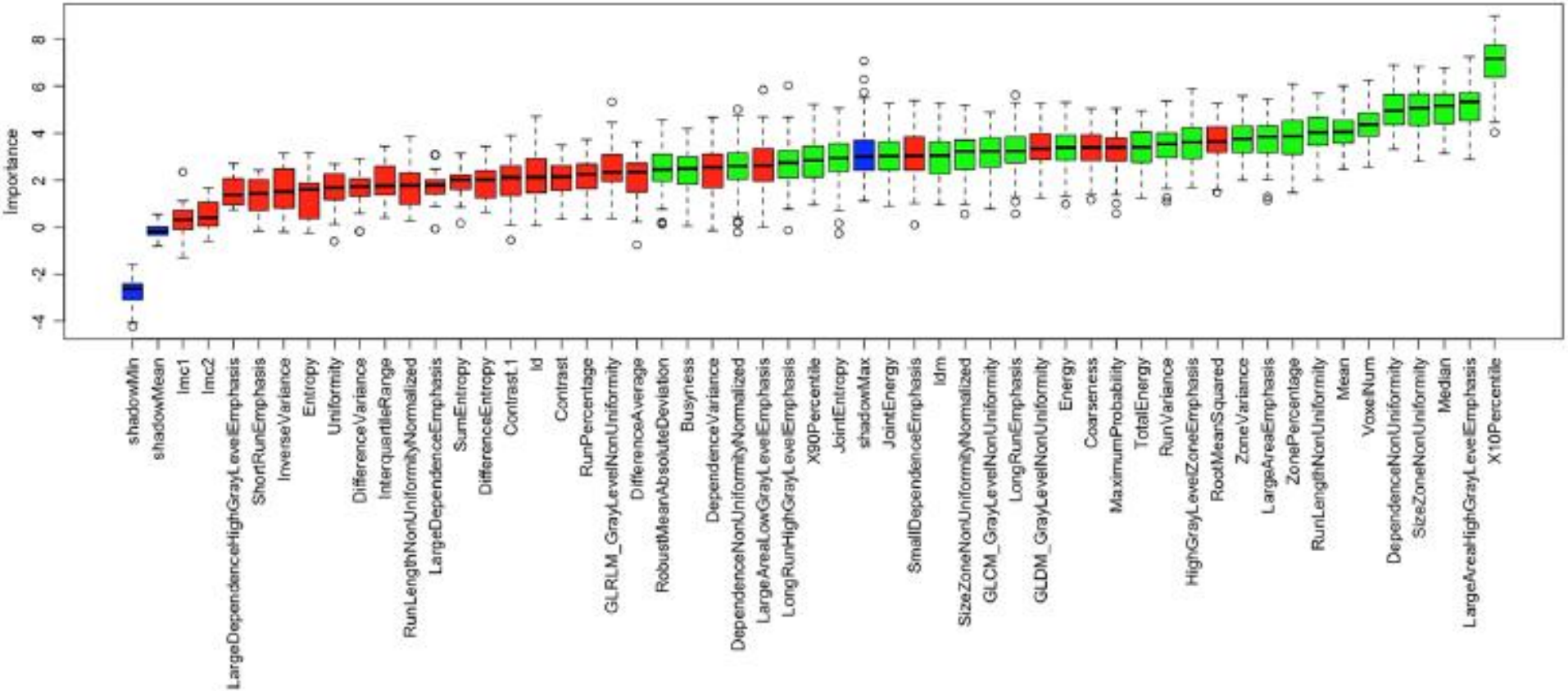
Agenda

- Indikation für die Residualtumorresektion (RTR)
  - Seminom versus Nichtseminom
- anatomische Ausdehnung der RTR

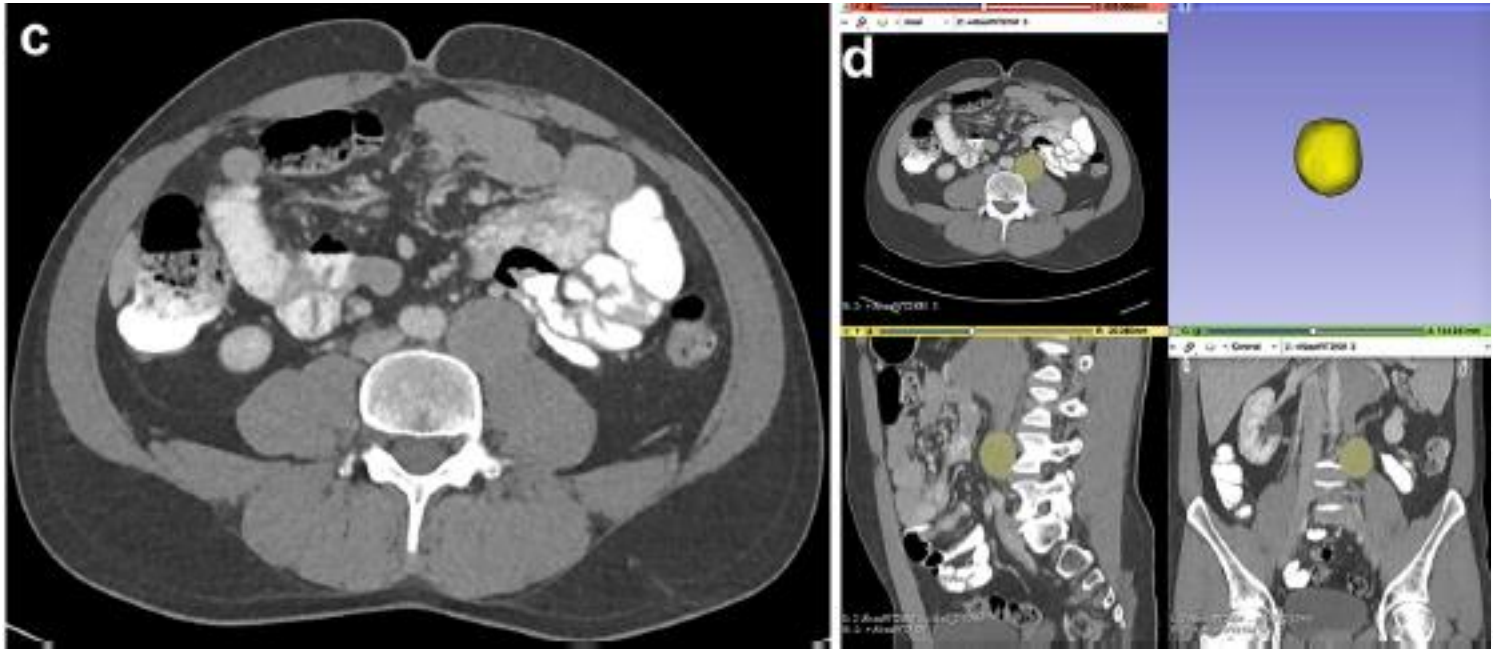
- Vorgehen der RTR in Abhängigkeit der Lokalisation
  - retroperitoneal
  - retrocrural
  - Leber
  - Lunge
- was tun bei inoperablen Befunden?
- Zukunftsperspektive

Feature class/matrix	Radiomics feature
First order/histogram ($n = 19$)	**Energy**, **total energy**, entropy, minimum, **10th percentile**, **90th percentile**, maximum, **mean**, **median**, interquartile range, range, mean absolute deviation (MAD), **robust mean absolute deviation (rMAD)**, root mean square (RMS), standard deviation, skewness, kurtosis, variance, uniformity
Shape ($n = 17$)	Mesh volume, voxel volume, **voxel number**, surface area, surface area-to-volume
NGTDM ($n = 5$)	Coarseness, contrast, **busyness**, complexity, strength

enign and malignant histopathology in germ cell tumors prior to post- node dissection



Radiomics allows for detection of benign and malignant histopathology in patients with metastatic testicular germ cell tumors prior to post-chemotherapy retroperitoneal lymph node dissection



Seminom korrekt vorhergesagt

Baessler B, Nestler T, Pinto Dos Santos D, Paffenholz P, Zeuch V, Pfister D, Maintz D, Heidenreich A. Eur Radiol. 2020 Apr;30(4):2334-2345

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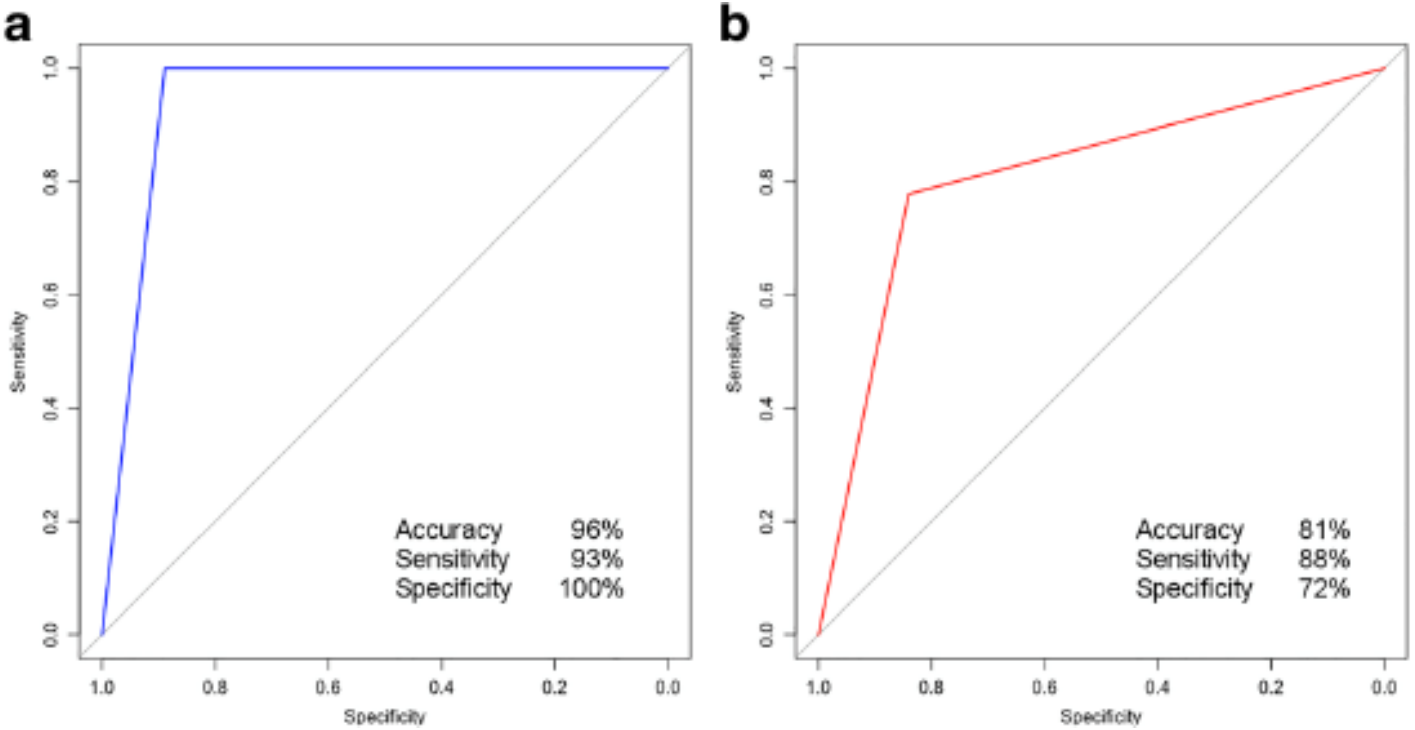

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Zusammenfassung

- PC – RTR ist eine “Experten – Chirurgie”
- aktive Surveillance bei Tumoren < 1cm, gutter Prognose und kein Teratom im Primarius
- Multidisziplinarität (abhängig von den eigenen Fähigkeiten) => sorgfältige preoperative Bildanalyse
- immer noch 40-50% mit Nekrose/Fibrose
    - Radiomics vielversprechend => externe Validierung
    - molekulare Marker für die Zukunft

Thanks a lot for your attention