Sarcomi dei Tessuti Molli

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Consiglio Nazionale delle Ricerche

I declare to have no conflict of interests

The majority of sarcomas arise from the soft tissue (close to 75%), with 15% gastrointestinal stromal tumours (GISTs) and 10% bone sarcomas

Casali PG et al. (ESMO guidelines) Annals of Oncology 29 (Supplement 4): iv51–iv67, 2018

Soft Tissue Sarcomas

< 1% of all malignancies

About 40% eventually die for the disease

1.8 to 5 cases per 100,000 individuals per year

Age 15-19 = 1.2/100,000

Age 45-49 = 6/100,000

Age > 80 = 20/100,000

Toro JR et al. Int. J. Cancer:119,2922–2930 (2006); Xiaocheng W et al. Cancer Causes and Control (2005) 16:309–320

Risk Factors

- previous radiation therapy
- chronic lymphedema (lymphangiosarcoma)
- Thorotrast, vinyl chloride, and arsenic (hepatic angiosarcomas)
- The HIV and human herpes 8 (Kaposi sarcoma)

Genetic Factors

- Gardner syndrome (*APC* mutation)
- Li-Fraumeni syndrome (*TP53* mutation)
- Nevoid basal cell carcinoma syndrome (Gorlin syndrome: *PTC* gene mutation)
- Tuberous sclerosis (Bourneville disease: *TSC1* or *TSC2* mutation)
- von Recklinghausen disease (neurofibromatosis type 1: *NF1* mutation)
- Werner syndrome (adult progeria: *WRN* mutation)

Singer S et Al. and Malawer MM et Al. In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2011, pp 1522-1609

Diagnosis

Careful planning of the initial biopsy

Adequate tissue should be obtained

Core-needle or incisional biopsy for microscopic examination

Experienced pathologist

Ordonez N et Al. In: Fletcher CDM, Bridge JA, Hogendoorn P, et al., eds.: WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. Lyon, France: IARC Press, 2013, pp 218-20

Adipocytic tumors

- Atypical lipomatous tumor
- Well-differentiated liposarcoma
- Liposarcoma, not otherwise specified
- Dedifferentiated liposarcoma
- Myxoid/round cell liposarcoma
- Pleomorphic liposarcoma.

Fibroblastic/myofibroblastic tumors

- Dermatofibrosarcoma protuberans.
- Fibrosarcomatous dermatofibrosarcoma protuberans.
- Pigmented dermofibrosarcoma protuberans.
- Solitary fibrous tumor, malignant.
- Inflammatory myofibroblastic tumor.
- Low-grade myofibroblastic sarcoma.
- Adult fibrosarcoma.
- Myxofibrosarcoma.
- Low-grade fibromyxoid sarcoma.
- Sclerosing epithelioid fibrosarcoma.

So-called fibrohistiocytic tumors.

- Giant cell tumor of soft tissues.

Smooth muscle tumors.

- Leiomyosarcoma (excluding skin).

Pericytic (perivascular) tumors.

- Malignant glomus tumor.

Skeletal muscle tumors.

- Embryonal rhabdomyosarcoma (including botryoid, anaplastic).
- Alveolar rhabdomyosarcoma (including solid, anaplastic).
- Pleomorphic rhabdomyosarcoma.
- Spindle cell/sclerosing rhabdomyosarcoma.

vascular tumors of soft tissue.

- Retiform hemangioendothelioma.
- Pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma.
- Epithelioid hemangioendothelioma.
- Angiosarcoma of soft tissue.

Chondro-osseous tumors.

- Extraskeletal osteosarcoma

Nerve sheath tumors.

- Malignant peripheral nerve sheath tumor.
- Epithelioid malignant peripheral nerve sheath tumor.
- Malignant Triton tumor.
- Malignant granular cell tumor.

Raut CP et al. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp 517-21.

Soft Tissue Sarcomas

> 80 different entities (W.H.O. 2013 classification)

Most frequent histologies

- Liposarcoma
- Leiomyosarcoma
- Undifferentiated pleomorphic sarcoma (UPS/PMFH)

Singer S et Al. In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2015, pp 1253-1291

Soft Tissue Sarcomas

extremities (50%)

trunk and retroperitoneum (40%)

head and neck (10%).

Wibmer C et Al. Ann Oncol 21 (5): 1106-11, 2010

MANAGEMENT OF PATIENTS AFFECTED BY SOFT TISSUE SARCOMA

Complete staging and treatment planning by a multidisciplinary team of cancer specialists

Prognostic Factors

- age of the patient
- size of the tumor
- pathologic stage at the time of diagnosis
- histologic grade
- margins status

Singer S et Al. and Malawer MM et Al. In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2011, pp 1522-1609

Coindre JM et Al. Cancer 91 (10): 1914-26, 2001; Zagars GK et Al. Cancer 97 (10): 2530-43, 2003

Radiation Therapy in Soft Tissue Sarcomas

Strongly individualized

- Tumor size
- Grading
- Deep lesion
- Marginal surgery

Pre-operative

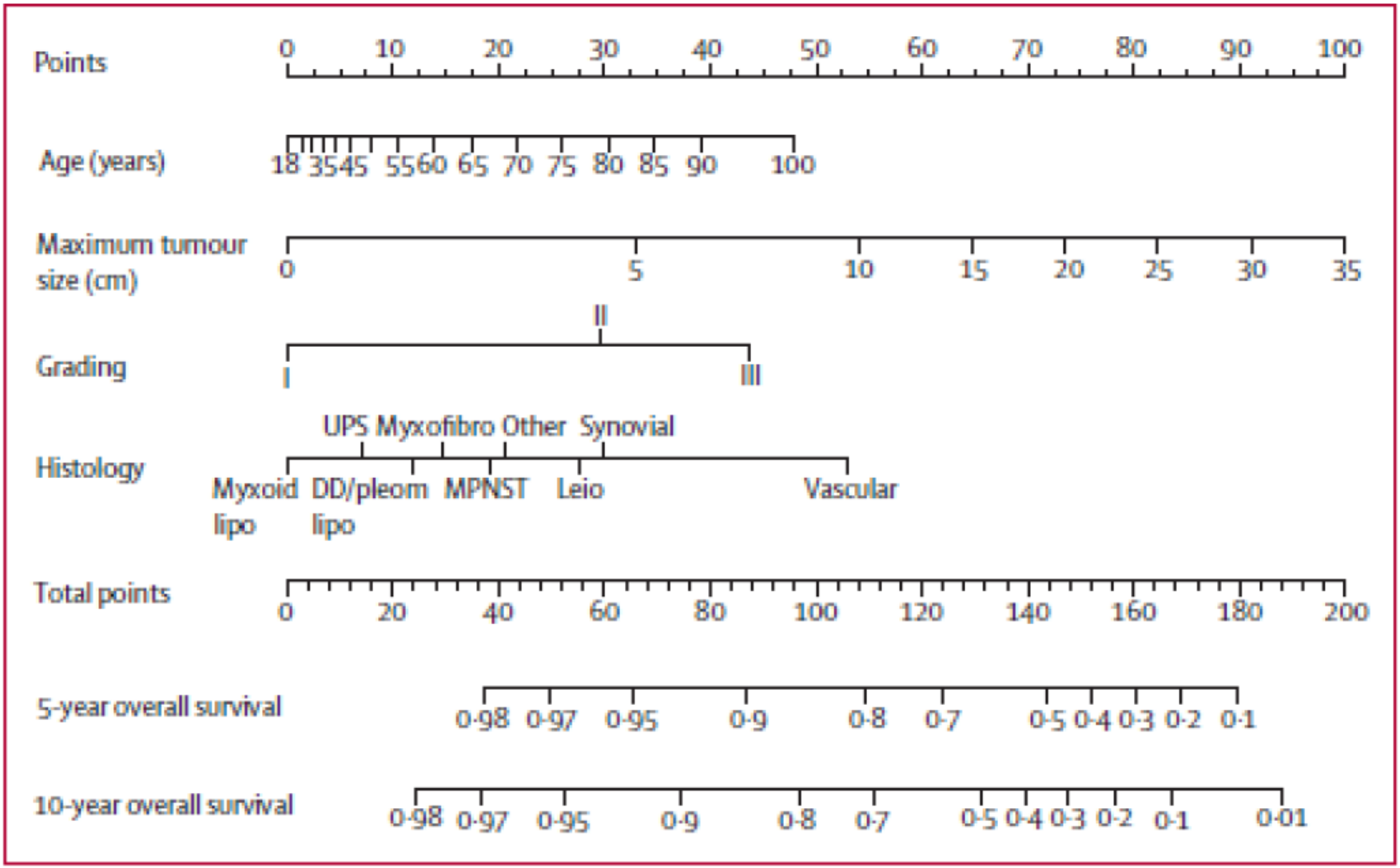
3D-CRT or IMRT

Post-operative

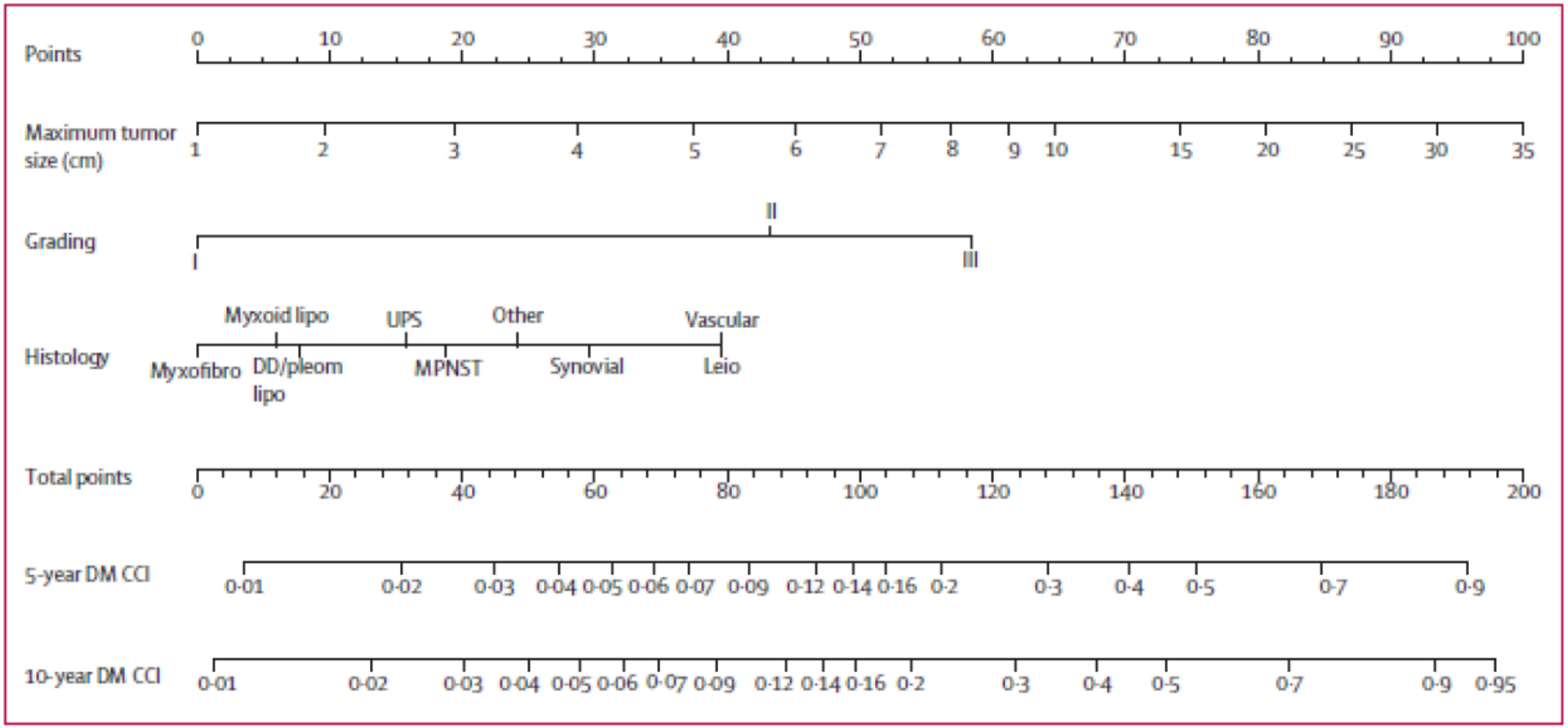
Doses

45-50 Gy pre-operative

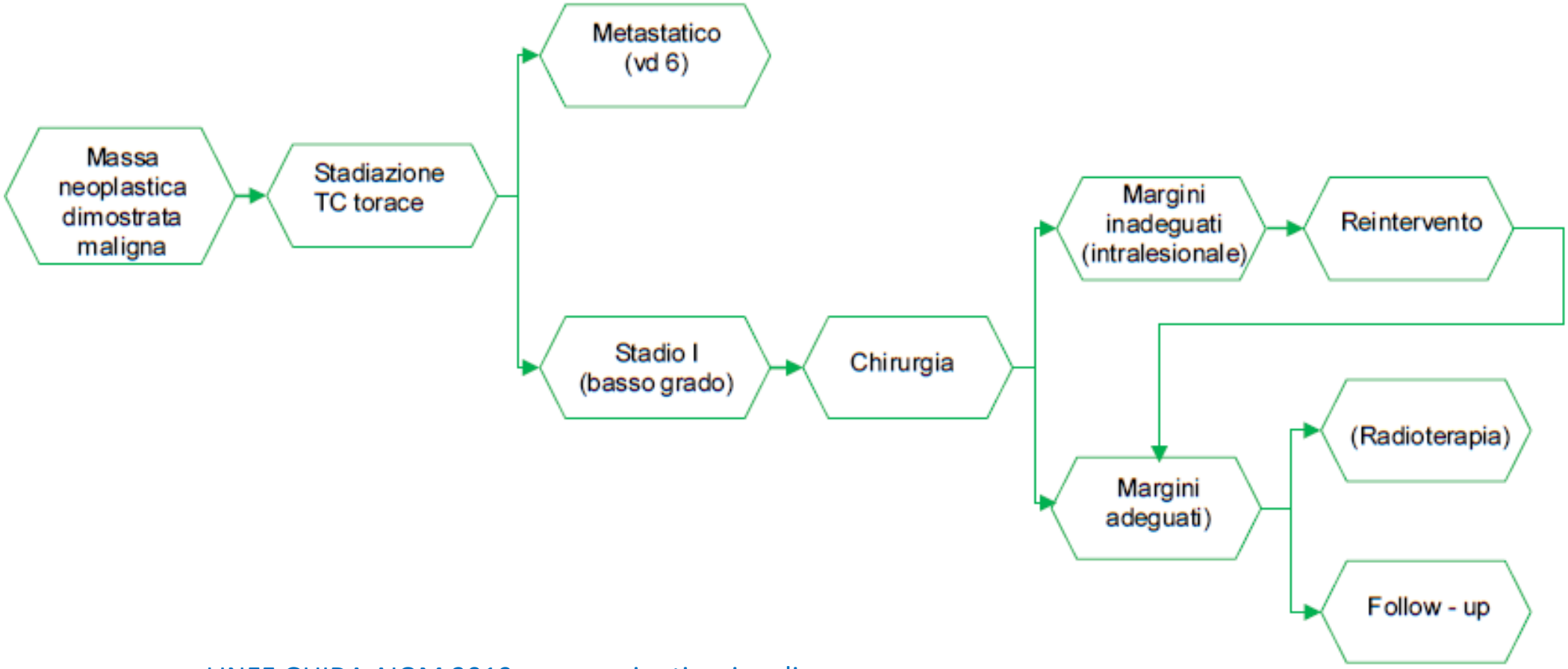
54 – 66 Gy post-operative



Overall survival nomogram



Distant metastases nomogram



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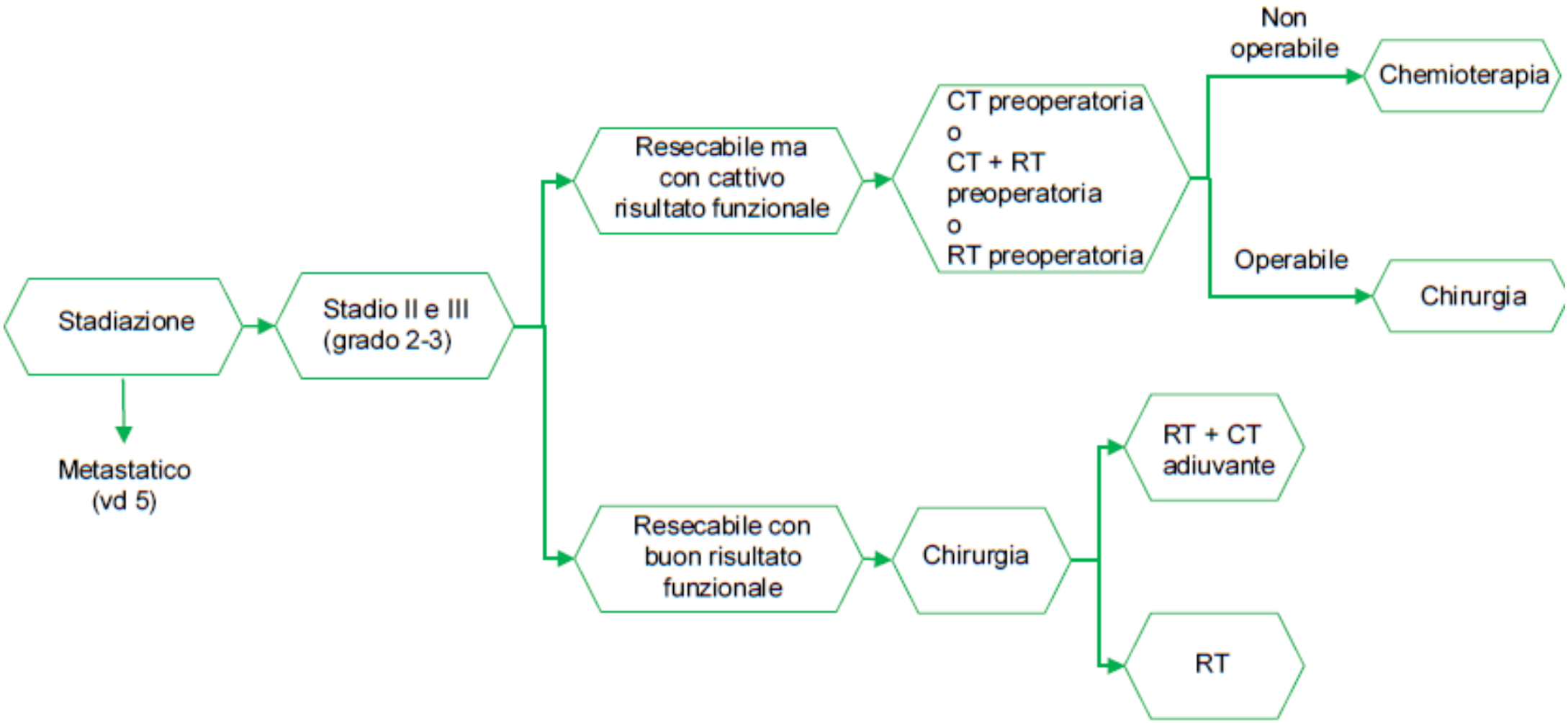

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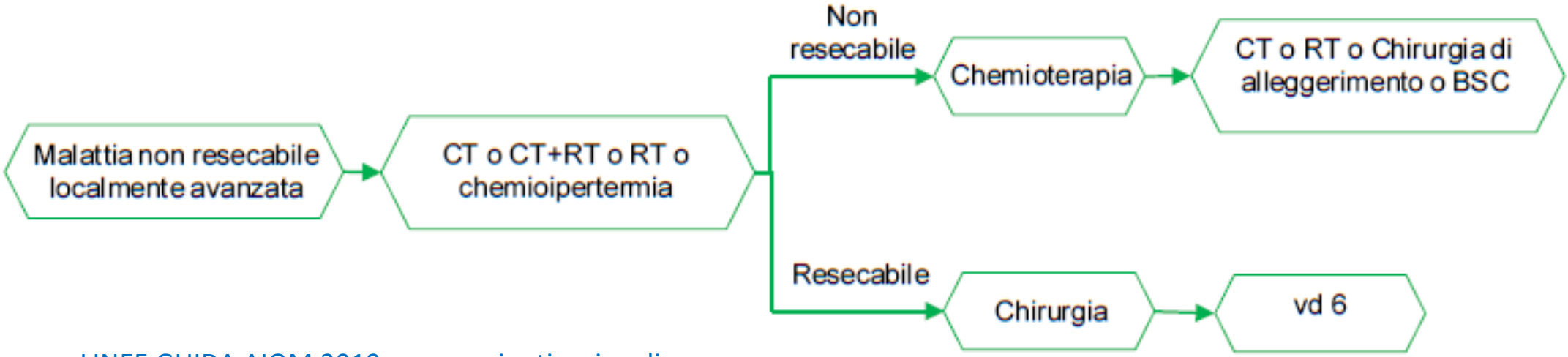

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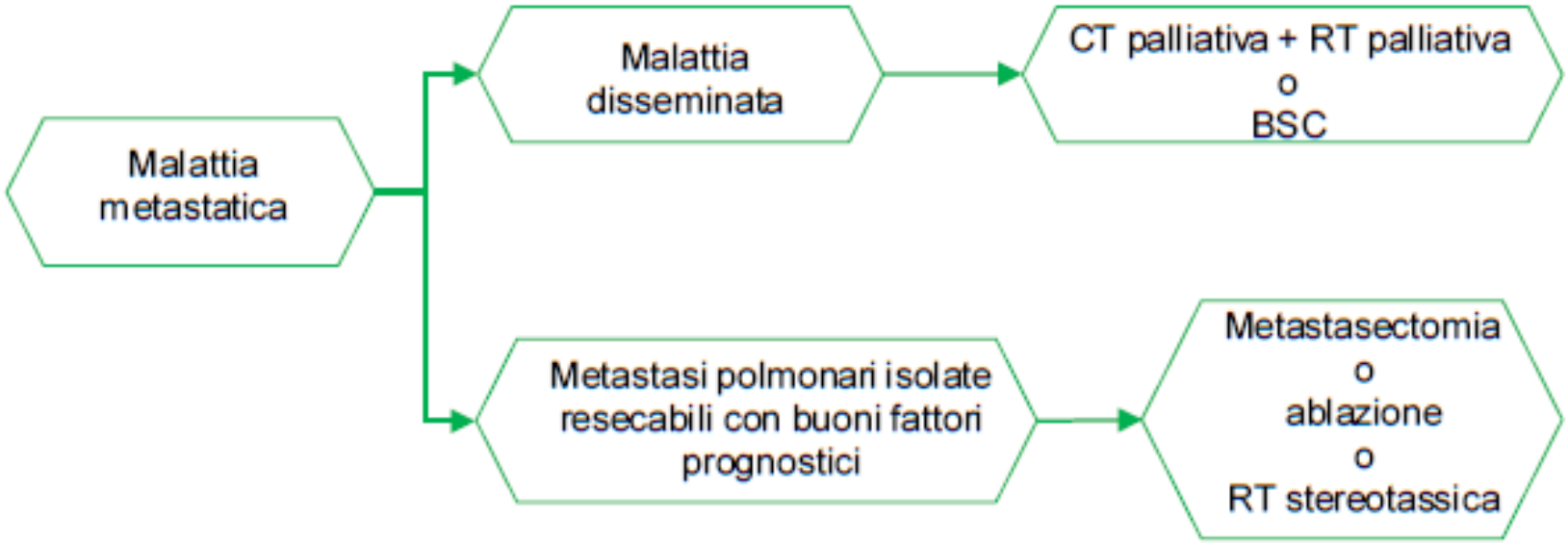
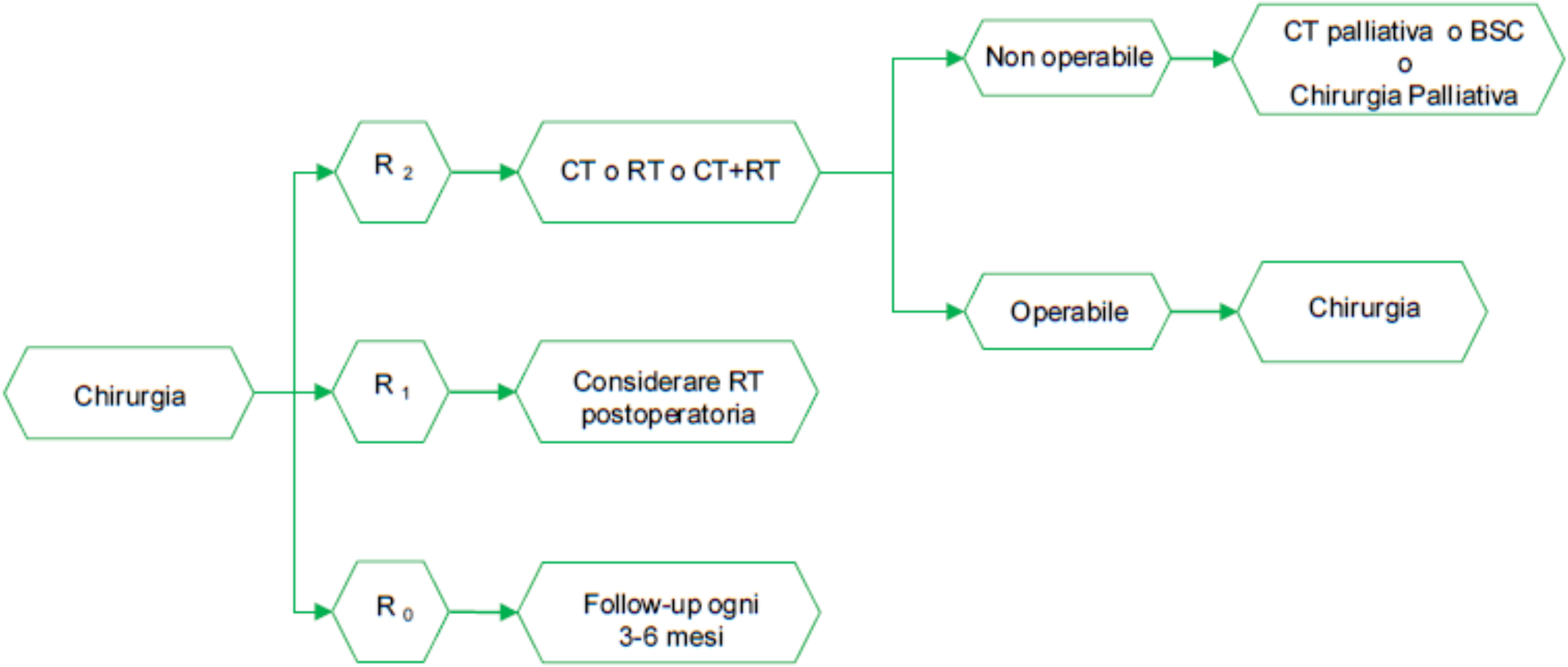
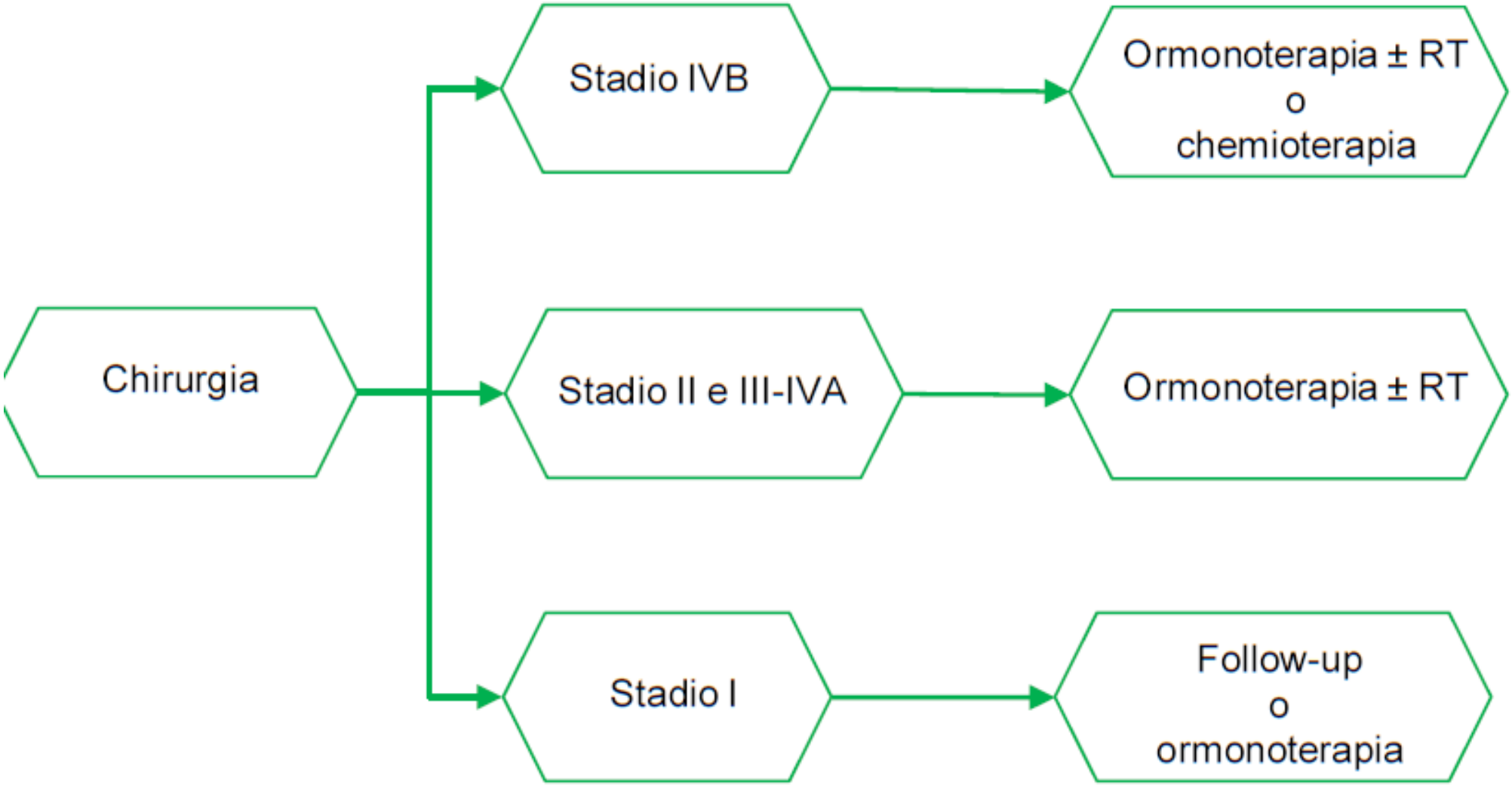




LINEE GUIDA AIOM 2019 – sarcomi retroperitoneali



LINEE GUIDA AIOM 2019 – sarcomi uterini

EClinicalMedicine 17 (2019) 100215

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Research Paper

Development and external validation of a dynamic prognostic nomogram for primary extremity soft tissue sarcoma survivors

Dario Callegaro[a], Rosalba Miceli[b], Sylvie Bonvalot[c], Peter C. Ferguson[d], Dirk C. Strauss[e], Veroniek V.M. van Praag[f], Antonin Levy[g], Anthony M. Griffin[d], Andrew J. Hayes[e], Silvia Stacchiotti[h], Cecile Le Pèchoux[g], Myles J. Smith[e], Marco Fiore[a], Angelo Paolo Dei Tos[i], Henry G. Smith[e], Charles Catton[j], Joanna Szkandera[k], Andreas Leithner[l], Michiel A.J. van de Sande[f], Paolo G. Casali[h,m], Jay S. Wunder[d], Alessandro Gronchi[a,*]

Development cohort:
Primary extremities STS having surgery between 1994 and 2013 in 3 european and 1 canadian reference center

Validation cohort
FNLCC II-III eSTS having surgery between 2000 and 2016 in 7 other european reference centers

Development cohort 3740 patients and validation 893

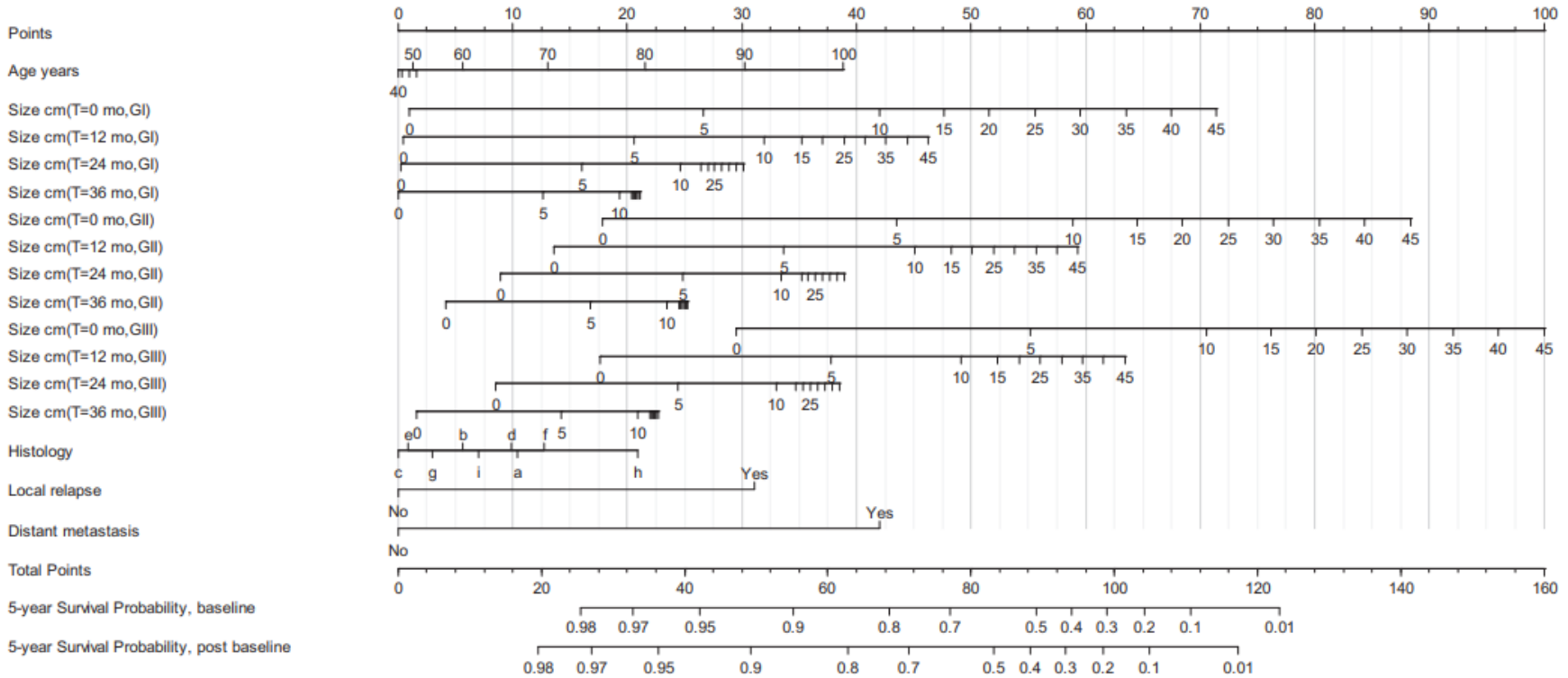

Fig. 1. Overall survival dynamic nomogram. Dynamic nomogram for 5-year overall survival (OS) in patients with primary resected eSTS. The nomogram allows the user to compute the 5-year survival probability on the basis of patient's age, tumor size, tumor grade, histology, occurrence of distant metastasis or occurrence of local recurrence as first events. The prediction can be calculated at baseline (time 0, at surgery) or post baseline (at 1 year, 2 years or 3 years after surgery). The prediction window is fixed at 5 years. Importantly, the choice of the proper size axis depends upon tumor grade and time at which the prediction is computed. For example, (i) to predict at time 0 (surgery) the 5-year OS of a 60 year-old patient with a 5 cm G3 MPNST, the user should locate patient's tumor size on the axis 'Size cm (T = =0 mo, GIII)' and draw a line straight upward to the "Points" axis to determine the score associated with that size and grade (55 points). Then repeat the process for patient's age at surgery (60 years = 6 points), histologic subtype (10 points), and sum the scores achieved for each covariate (sum=71 points). Locate this sum on the "Total Points" axis. Draw a line straight down to the "5-year survival probability, baseline" axis to find the predicted probability (about 78%). (ii) to predict 5-year OS of a patient with the same clinical characteristics as above but who had been operated two years before and has not had any events during the first two years of follow-up, the user should locate patient's tumor size on the axis 'Size cm (T = =24 mo, GIII)' and draw a line straight upward to the "Points" axis to determine the score associated with that size and grade (24 points). Then repeat the process for patient's age at surgery (60 years = 6 points), histologic subtype (10 points), local relapse (0 points), distant metastasis (0 points) and sum the scores achieved for each covariate (sum=40 points). Locate this sum on the "Total Points" axis. Draw a line straight down to the "5-year survival probability, post baseline" axis to find the predicted probability (about 94%). Histology abbreviations: (a), leiomyosarcoma; (b), pleomorphic/DD liposarcoma; (c), myxoid liposarcoma; (d), MPNST; (e), myxofibrosarcoma; (f), other; (g), synovial sarcoma; (h), UPS; (e), vascular sarcoma.

STRASS (EORTC 62092): A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma.

Sylvie Bonvalot, Alessandro Gronchi, Cecile Le Pechoux, Carol Jane Swallow, Dirk C. Strauss, Pierre Meeus, Frits van Coevorden, Stephan Stoldt, Eberhard Stoeckle, Piotr Rutkowski, Claudia Sangalli, Charles Honoré, Marco Rastrelli, Chandrajit Raut, Peter Chung, Marco Fiore, Saskia Litiere, Sandrine Marreaud, Hans Gelderblom, Rick L.M. Haas

266 pts affected by retroperitoneal sarcoma [198 (74.5%) Liposarcoma]

Patients were randomized 1:1

preoperative RT (3D-CRT or IMRT) 50.4 Gy followed by surgery (RT/S group)

surgery alone (S group)

Primary endpoint abdominal relapse free survival (ARFS)

3-year ARFS 66.0% in RT/S vs. 58.7% in S group (HR = 0.84, p=0.340)

In liposarcoma group 3-year ARFS 71.6% in RT/S and 60.4% in S group (HR = 0.64, p =0.049)

Eur J Cancer. 2013 Mar;49(5):1142-51. doi: 10.1016/j.ejca.2012.10.014. Epub 2012 Nov 10.
The impairment of the High Mobility Group A (HMGA) protein function contributes to the anticancer activity of trabectedin.
D'Angelo D[1], Borbone E, Palmieri D, Uboldi S, Esposito F, Frapolli R, Pacelli R, D'Incalci M, Fusco A.

Oncogene. 2018 Nov;37(45):5926-5938. doi: 10.1038/s41388-018-0394-x. Epub 2018 Jul 6.
HMGA1/E2F1 axis and NFkB pathways regulate LPS progression and trabectedin resistance.
Loria R[1], Laquintana V[1], Bon G[1], Trisciuoglio D[2,3], Frapolli R[4], Covello R[5], Amoreo CA[5], Ferraresi V[6], Zoccali C[7], Novello M[5], Del Bufalo D[2], Milella M[6], Biagini R[7], D'Incalci M[4], Falcioni R[8].

EClinicalMedicine 9 (2019) 35–43

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EClinicalMedicine
Published by THE LANCET

Research Paper

Trabectedin and RAdiotherapy in Soft Tissue Sarcoma (TRASTS): Results of a Phase I Study in Myxoid Liposarcoma from Spanish (GEIS), Italian (ISG), French (FSG) Sarcoma Groups

Alessandro Gronchi [a,*], Nadia Hindi [b,c], Josefina Cruz [d], Jean-Yves Blay [e], Antonio Lopez-Pousa [f], Antoine Italiano [g], Rosa Alvarez [h], Antonio Gutierrez [i], Inmaculada Rincón [c], Claudia Sangalli [a], Jose Luis Pérez Aguiar [d], Jesús Romero [j], Carlo Morosi [a], Marie Pierre Sunyach [e], Roberta Sanfilippo [a], Cleofe Romagosa [k], Dominique Ranchere-Vince [e], Angelo P. Dei Tos [l,m], Paolo G. Casali [a,b,c,d,e,f,g,h,i,j,k,l,m,n], Javier Martin-Broto [b,c]

14 patients (7M and 7F) with mixoid liposarcoma of the extremities or the trunk wall
median age 36-years (range 24–70); median tumor size of 12.5 cm (range 7–20 cm)

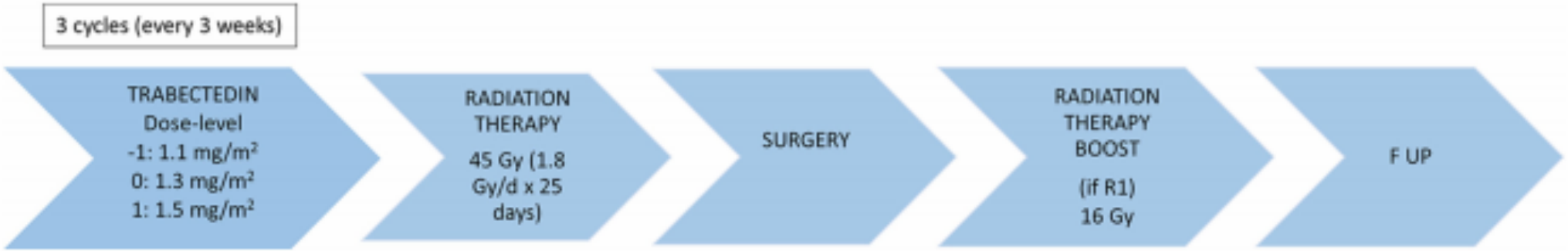


Fig. 1. Outline of the trial design.

Table 2

Tumor Response according to RECIST and Choi Criteria

Response	RECIST Criteria	Choi Criteria
Complete response	Disappearance of all lesions	Disappearance of all lesions
	No new lesions	No new lesions
Partial response	≥30% decrease in the sum of greatest diameters	≥10% decrease in the greatest maximal diameter or a ≥15% decrease in tumor attenuation at CT or contrast enhancement at MR imaging
	No new lesions	No new lesions
Stable disease	Does not meet criteria for complete response, partial response, or progressive disease	Does not met criteria for complete response, partial response, or progressive disease
Progressive disease	≥20% increase in the sum of greatest diameters	≥10% increase in the greatest maximal diameter and does not meet criteria for partial response by using tumor attenuation at CT or contrast enhancement at MR imaging or ≥15% increase in tumor attenuation at CT or contrast enhancement at MR imaging and does not meet the criteria for partial response by using tumor size
	New lesion	New lesion
		New intratumoral nodule or increase in the size of existing intratumoral nodule

Stacchiotti S et al. Radiology, 251(2):447-456, 2009

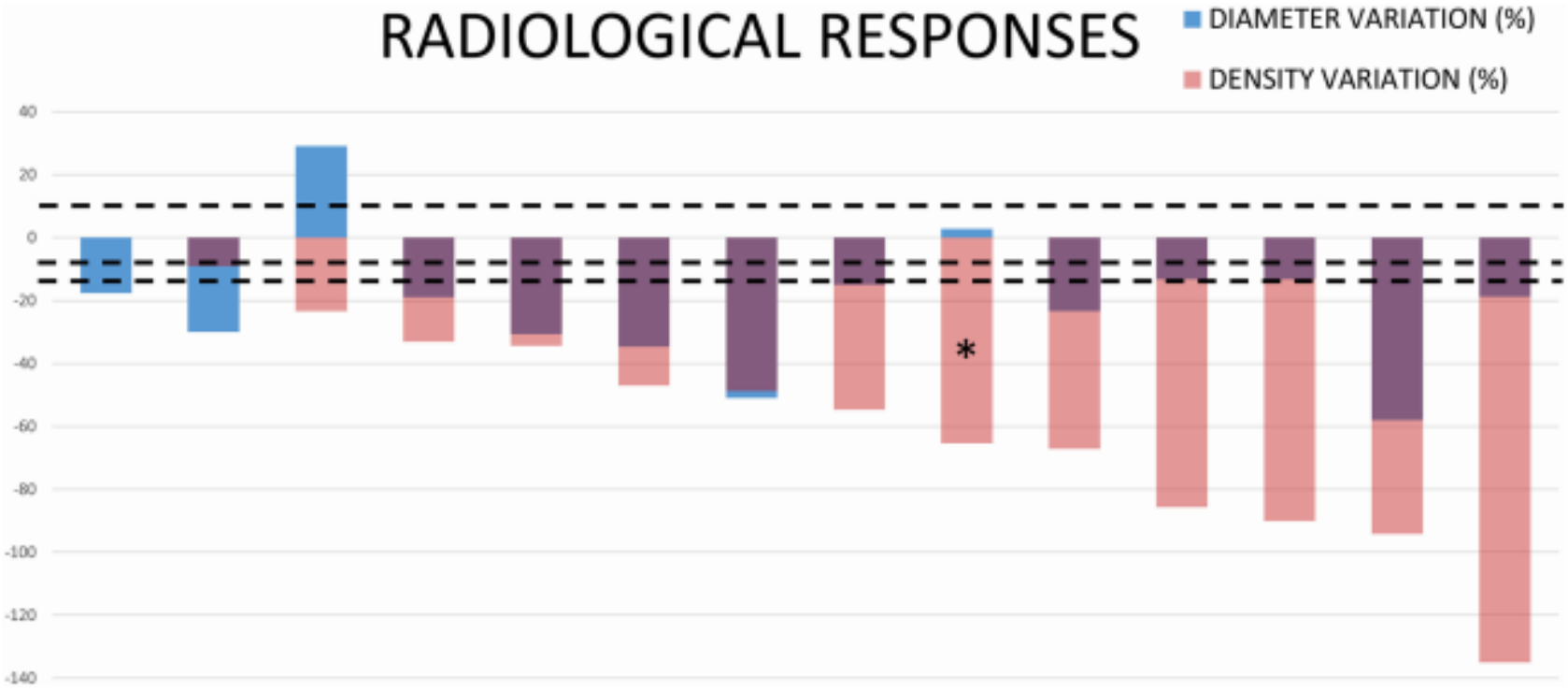


Fig. 2. Waterfall plot of radiological responses after treatment by Choi criteria, including both tumor size and density information. *Patient with progressive disease due to new distant lesions while achieving CHOI partial response on primary tumor.

5 achieved PR (36%), 8 SD (57%), 1 distant PD (7%) by RECIST

12 achieved PR (86%), 1 SD (7%) and 1 distant PD (7%) by Choi criteria

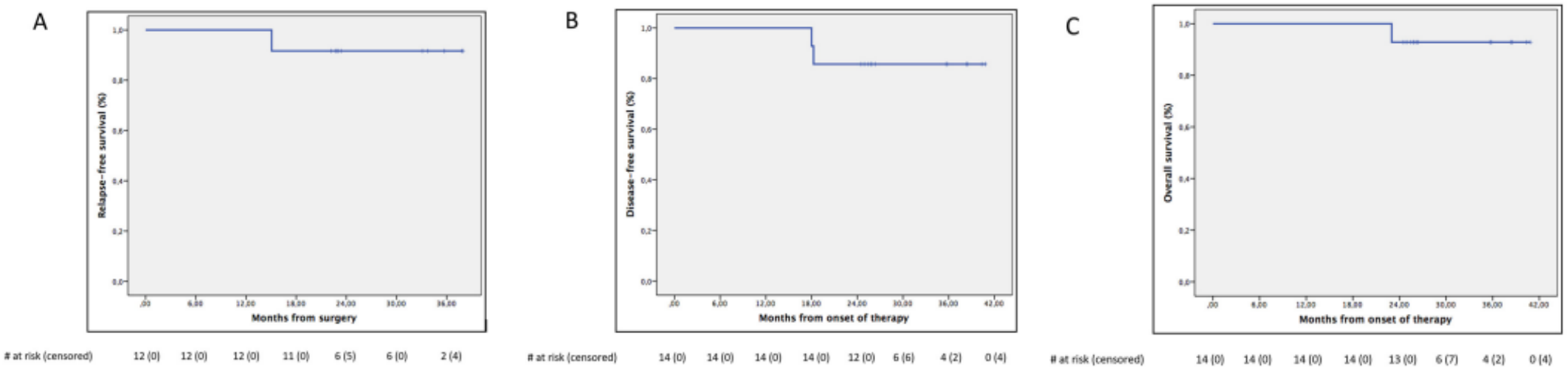
Gronchi A et al. eClinicalMedicine 9:35-43, 2019

Pathology

Median visible residual tumor in the surgical specimen was 5% (0–60)

9/12 patients (75%) with ≤10% visible remaining tumor

3/12 (25%) had a complete pathological response



Gronchi A et al. eClinicalMedicine 9:35-43, 2019

«…. In the 14 patients of this phase 1 component of the trial an impressive activity of Trabectedin with Radiotherapy was observed…»

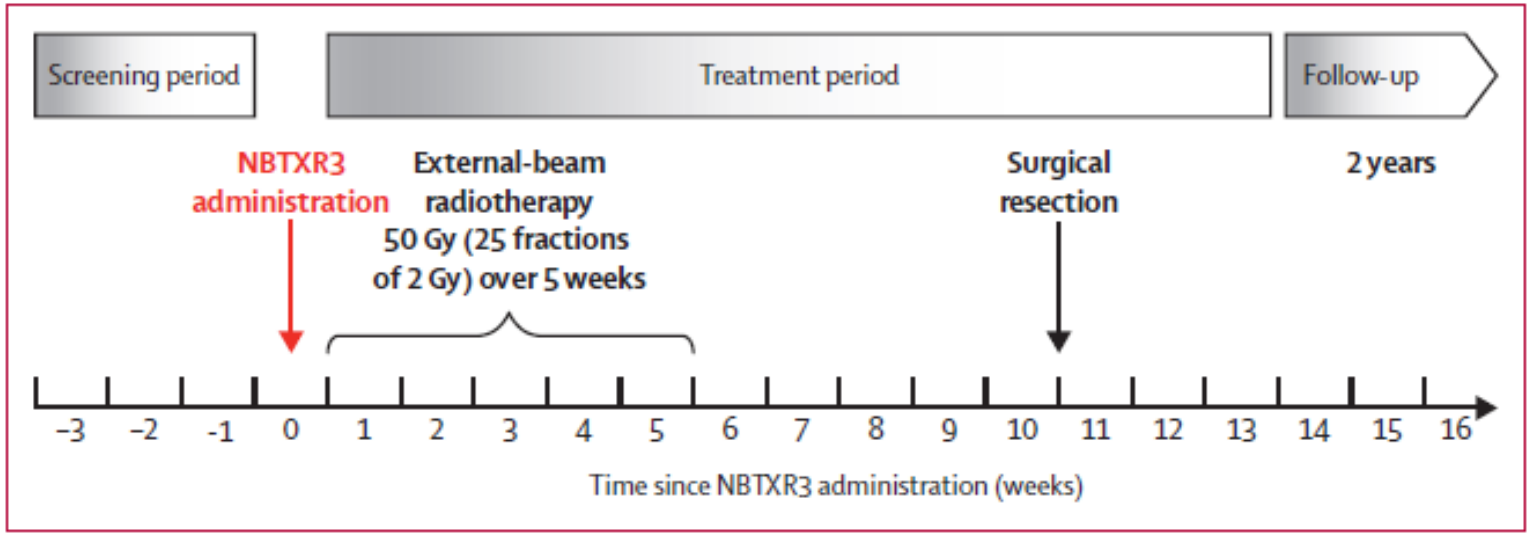
Gronchi A et al. eClinicalMedicine 9:35-43, 2019

NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2–3, randomised, controlled trial

Sylvie Bonvalot, Piotr L Rutkowski, Juliette Thariat, Sébastien Carrère, Anne Ducassou, Marie-Pierre Sunyach, Peter Agoston, Angela Hong, Augustin Mervoyer, Marco Rastrelli, Victor Moreno, Rubi K Li, Béatrice Tiangco, Antonio Casado Herraez, Alessandro Gronchi, László Mangel, Teresa Sy-Ortin, Peter Hohenberger, Thierry de Baère, Axel Le Cesne, Sylvie Helfre, Esma Saada-Bouzid, Aneta Borkowska, Rodica Anghel, Ann Co, Michael Gebhart, Guy Kantor, Angel Montero, Herbert H Loong, Ramona Vergés, Lore Lapeire, Sorin Dema, Gabriel Kacso, Lyn Austen, Laurence Moureau-Zabotto, Vincent Servois, Eva Wardelmann, Philippe Terrier, Alexander J Lazar, Judith V M G Bovée, Cécile Le Péchoux, Zsusanna Papai

179 adult patients with locally advanced soft-tissue sarcoma of the extremity or trunk wall

89 in the NBTXR3 plus radiotherapy group and 90 in the radiotherapy alone group



Bonvalot S et al. Lancet Oncol. 2019 Aug;20(8):1148-1159

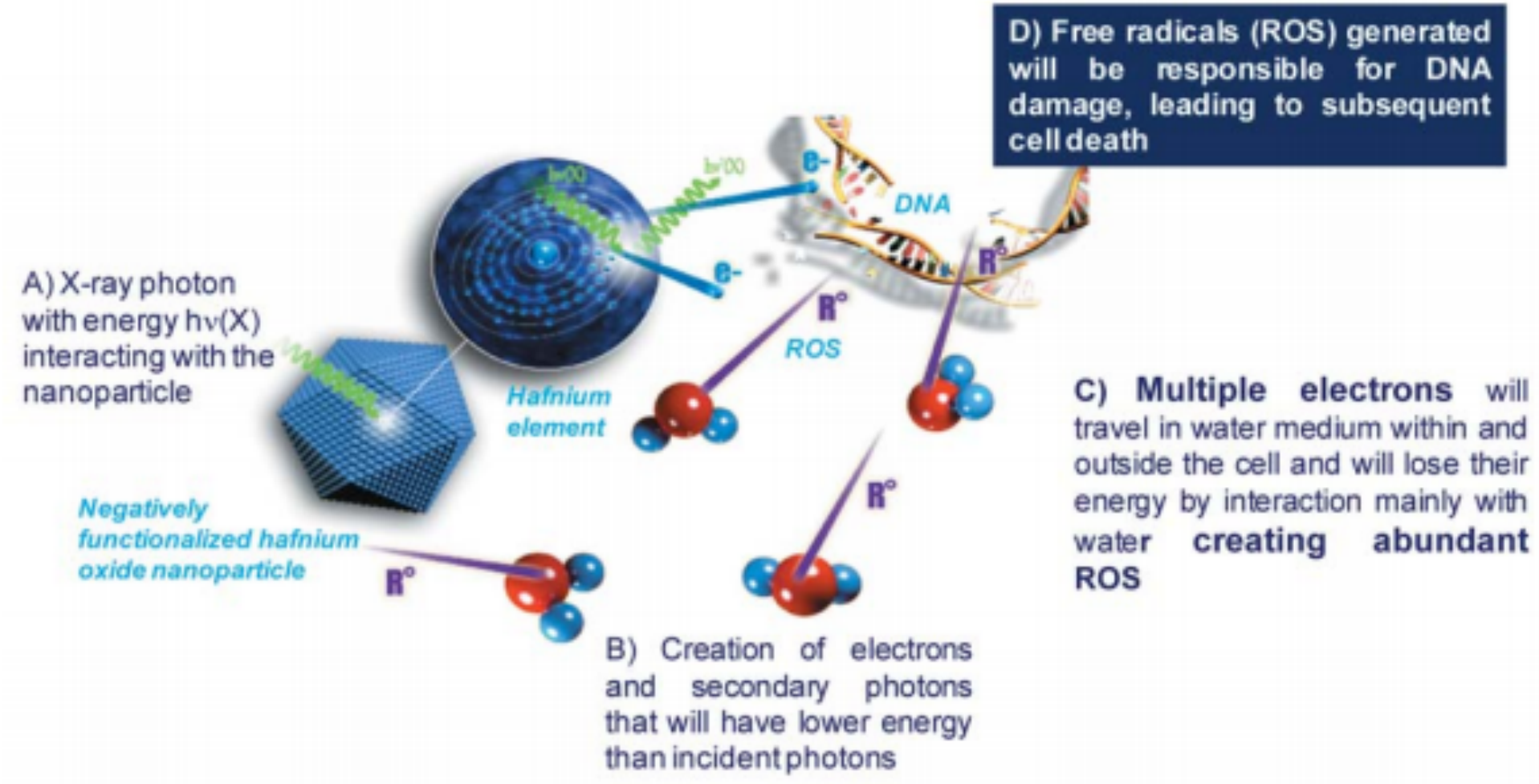


Figure 5. *Mechanism of action of NBTXR3.*

Pottier A. et al. ANTICANCER RESEARCH 34: 443-454 (2014)

	NBTXR3 and radiotherapy group (n=87)	Radiotherapy alone group (n=89)
Patient characteristics		
Sex		
Female	34 (39%)	42 (47%)
Male	53 (61%)	47 (53%)
Age, years*		
Mean (SD)	60·5 (14·1)	60·0 (14·7)
Median; range	63·5; 22–83	64·0; 21–86
Weight, kg†		
Mean (SD)	77·0 (18·0)	75·4 (17·6)
Median; range	76·5; 46–125	72·0; 43–117
WHO performance score		
0	57 (66%)	56 (64%)
1	27 (31%)	29 (33%)
2	3 (3%)	3 (3%)
Disease status		
Primary locally advanced	79 (91%)	83 (93%)
Locally relapsed	8 (9%)	6 (7%)
Synchronous metastasis	2 (2%)	2 (2%)

Bonvalot S et al. Lancet Oncol. 2019 Aug;20(8):1148-1159

Tumour characteristics	NBTXR3 and radiotherapy group (n=87)	Radiotherapy alone group (n=89)
Tumour site		
Upper limb	9 (10%)	9 (10%)
Lower limb	64 (74%)	66 (74%)
Trunk	14 (16%)	14 (16%)
Tumour histological type		
Myxoid liposarcoma	14 (16%)	15 (17%)
Other	73 (84%)	74 (83%)
Undifferentiated or unclassified sarcoma	30 (41%)	28 (38%)
Liposarcoma	13 (18%)	15 (20%)
Adult fibrosarcoma	10 (14%)	9 (12%)
Leiomyosarcoma	8 (11%)	10 (14%)
Myxofibrosarcoma	4 (5%)	5 (7%)
Malignant peripheral nerve sheath tumour	4 (5%)	4 (5%)
Rhabdomyosarcoma	1 (1%)	1 (1%)
Extraskeletal myxoid chondrosarcoma	0 (0%)	1 (1%)
Fibroblastic–myofibroblastic tumours	2 (3%)	0 (0%)
Fibromyxoid sarcoma	1 (1%)	0 (0%)
Synovial sarcoma	0	1 (1%)

	NBTXR3 and radiotherapy group (n=87)	Radiotherapy alone group (n=89)
Histological grade		
1	15 (17%)	16 (18%)
2	36 (41%)	44 (49%)
3	30 (34%)	23 (26%)
Undetermined	6 (7%)	6 (7%)
Tumour longest diameter by MRI, mm		
Mean (SD)	83·1 (34·5)	86·9 (28·3)
Median; range	80·0; 25–191	91·0; 33–152
Target theoretical tumour volume, mL (centralised reading)‡§		
Mean (SD)	904·4 (1127·9)	879·0 (783·0)
Median; range	525·0; 16–6326	717·8; 29–4117

Bonvalot S et al. Lancet Oncol. 2019 Aug;20(8):1148-1159

Grade 3-4 wound complications following resection

	NBTXR3 and radiotherapy group (n=89)		Radiotherapy alone group (n=90)	
	Grade 3	Grade 4	Grade 3	Grade 4
Postoperative wound complication	8 (9%)	0	8 (9%)	0
Postoperative wound infection	5 (6%)	0	7 (8%)	1 (1%)
Postprocedural infection	3 (3%)	0	2 (2%)	0
Postprocedural haemorrhage	2 (2%)	0	1 (1%)	1 (1%)
Seroma	1 (1%)	0	0	2 (2%)
Postoperative abscess	0	1 (1%)	0	0
Postprocedural complication	1 (1%)	0	0	0
Skin flap necrosis	1 (1%)	0	1 (1%)	0
All	19 (21%)	1 (1%)	18 (20%)	2 (2%)

Bonvalot S et al. Lancet Oncol. 2019 Aug;20(8):1148-1159

All grade NBTXR3-related treatment emergent adverse events—all treated population

	All grade	Grade 1–2	Grade 3	Grade 4
Hypotension	10 (11%)	4 (5%)	5 (6%)	1 (1%)
Injection site pain	7 (8%)	6 (7%)	1 (1%)	0
Tumour pain	5 (6%)	5 (6%)	0	0
Feeling hot	3 (3%)	2 (2%)	1 (1%)	0
Oedema peripheral	3 (3%)	3 (3%)	0	0
Radiation skin injury	2 (2%)	1 (1%)	1 (1%)	0
Pain in extremity	2 (2%)	2 (2%)	0	0
C-reactive protein increased	2 (2%)	2 (2%)	0	0
Erythema	2 (2%)	2 (2%)	0	0
Anaphylactic shock	1 (1%)	0	0	1 (1%)
Postprocedural infection	1 (1%)	0	1 (1%)	0
Postoperative wound complication	1 (1%)	0	1 (1%)	0
Apnoea	1 (1%)	0	1 (1%)	0
Hyperhidrosis	1 (1%)	0	1 (1%)	0
All	46 (52%)	35 (39%)	9 (10%)	2 (2%)

Bonvalot S et al. Lancet Oncol. 2019 Aug;20(8):1148-1159

	NBTXR3 and radiotherapy group (n=87)	Radiotherapy alone group (n=89)	p value
Primary endpoint			
Pathological complete responses, n (%)*	14 (16%)	7 (8%)	0·044
Secondary endpoints			
R0 resections†	67 (77%)	57 (64%)	0·042
Resection margin‡			..
NA	2/83 (2%)	4/86 (5%)	
R0	67/83 (81%)	57/86 (66%)	..
R1	9/83 (11%)	19/86 (22%)	..
R2	5/83 (6%)	5/86 (6%)	..

Bonvalot S et al. Lancet Oncol. 2019 Aug;20(8):1148-1159

Conclusions

- Soft tissue sarcoma (STS) are a haeterogeneous setting of rare malignancies
- In STS at the localized stage of disease the possible role of Chemotherapy and Radiotherapy is unclear.
- Surgery is at the present the only modality tu cure localized STS
- Radiation Therapy may help to obtain a more efficient and/or less aggressive surgery
- Preoperative Radiotherapy seems generally more appropriate
- Recent studies suggest that Radiotherapy coupled with Trabectedin or with radioenhancing nanoparticles (NBTXR3) may improve control of STS