Intraoperative electron radiation therapy combined to external beam radiation therapy and limb sparing surgery in extremity soft tissue sarcoma: a retrospective study of 182 cases in a single specialized center.

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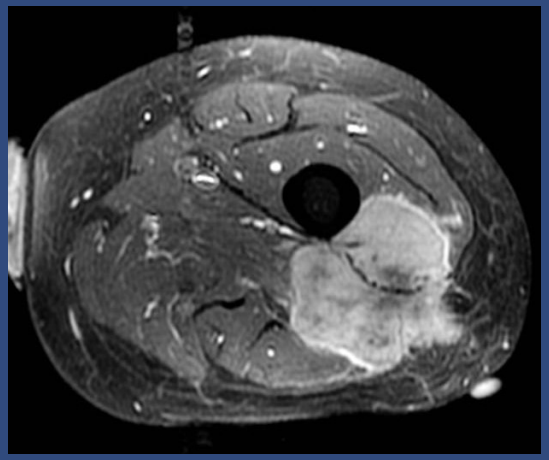
Disclosures and Conflicts of Interest

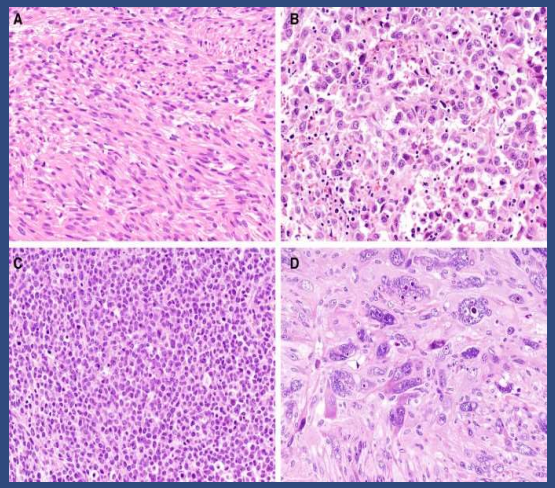
- No conflicts of interest to declare
- This study is a retrospective analysis and has not received any funding

Agenda

- Introduction and Objectives
- Methodology
- Results
- Discussion
- Conclusions

Introduction (I)





- Incidence 1% of the population
- Mesenchymal origin
- Median age of presentation: 65 years
- Unknown etiology
  - Genetic factors
  - Environmental factors: chemical agents, immunosuppression, viruses…
- Multimodal treatment: surgery, RT and/or CHT
- IOERT, in combination with EBRT, allows obtaining a lower locorregional recurrence, preservation of the extremity and good functional outcome

Introduction II

Radiation therapy (RT)

Benefit in T < 5 cm, low grade, superficial (7th ed. TNM AJCC), and R0 ???

External radiotherapy (IMRT/3DCRT) → non-SD in LC or survival; ≠ toxicity

- **Preoperative 50 Gy →↑R0**
- **Postoperative (3-6 weeks) 50 Gy + boost 10-16 Gy (R0/R1)**

➢ **Boost:**

- **Intraoperative radiotherapy (IORT) → 10-20 Gy with LC 97% and OS 70% (Roeder)**
- **Intraoperative brachytherapy (IOBT) → LDR 15-25 Gy / HDR 15-20 Gy with LC 82%**

➢ **Proton Therapy:**

- **In development (dosimetry benefit, LET ionization density for radio-resistance)**
- **Paediatric patients, in recurrences or locally advanced tumours, difficult locations, re-irradiation**

	preoperative RT	postoperative RT
Total radiation dose[1]	50 Gy[2]	60-68 Gy
Target volume	↓	↑
Tumor shrinkage[1,3]	possible	-
Local control[4]	↑?	↓?
Wound complications	↑	↓
Fibrosis	↓	↑
Edema	↓	↑
Joint Stiffness	↓	↑
Functional outcome	↑	↓

Extracted from Radiation Therapy in Adult Soft Tissue Sarcoma – Current Knowledge and Future Directions: A Review and Expert Opinion, by Roeder F. Cancers (Basel). 2020 Nov 3;12(11):3242.

Objectives (I)

To analyze the oncological control, survival and quality of life observed in a homogeneous treatment program, which contains Intraoperative Electron Radiotherapy (IOERT) as radiotherapy intensification, in soft tissue sarcomas of the extremity, analyzing the volumetric impact of the tumor on limb preservation and sarcoma progression patterns, as well as the resulting final functionality

Objectives (II)

The systematization of the widespread use of intraoperative radiotherapy in patients with soft tissue sarcoma of the extremities allows us to study its contribution in terms of sarcoma control and its relationship with functional outcomes, in a context of comprehensive multidisciplinary and multifactorial action

Multifactorial issues:

- Prognostic known factors and efficacy of IOERT
- Multimodal treatments
- Evolutionary patterns
- Volumetry, Functionality and Safety

Scenario in maximum local intensification...

- Intraoperative radiotherapy (IOERT) with electrons is a feasible local intensification treatment in patients with extremity sarcomas, which has validated its use in international recommendation guidelines

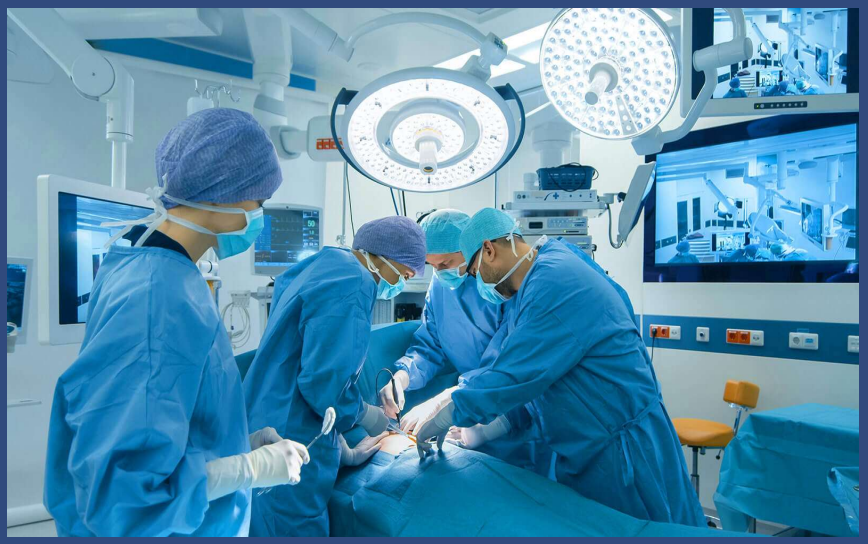
- IOERT incorporation to multimodal treatment, as a component of evidence-based care innovation, allows for the enhancement of various criteria for improvement in the expected oncological outcomes:
  - Maximize limb preservation
  - Promote an acceptable functional outcome
  - Anticipate interventions through rehabilitation and clinical support actions that promote QoL

Methodology

Hospital General Universitario Gregorio Marañón. Madrid
(National Reference Center in the management of Sarcoma)

- n = 182 patients
- SPB of extremities and bordering areas treated with IORT technique at HGUGM Madrid (CSUR)
- Descriptive and prevalence study
- Prospective register of clinical-therapeutic parameters
- Retrospective analysis of oncological and functional evolution data
- Follow-up from 2 to 300 months (median 60 m)
- Exclusion (incomplete records, advanced metastatic stages)
- Toronto Extremity Salvage Score (TESS): Functionality Questionnaire
- Descriptive and analytical statistics (Kaplan-Meier, Cox regression)
- Volume $\mathrm{V} = \frac{\pi}{6} x \cdot y \cdot z$ (cm^3)

RESULTS



Summary of main descriptive statistical data (I)

Age (years)		
Median	54	
Range	2–91	
Sex	**n**	**%**
Male / Female	95 / 87	52 / 48
Localization	**n**	**%**
Upper extremity	41	23
Lower extremity	**141**	**77**
Histological Subtype	**n**	**%**
Liposarcoma	**45**	**25**
MFH/UPS	25	14
Sarcoma synovial	19	10
Leiomyosarcoma	18	10
NOS / Others	75	41

Volume (cm^3)		
Median	**118**	
Range	0.75 – 2,848	
ø major (cm)		
Median	8.8	
Range	1.5 - 30	
Status	**n**	**%**
Primary	**138**	**76**
Recurrent	44	24
Ki-67 (%)	**n = 115**	
Median	40	
Range	0-90	

Summary of main descriptive statistical data (II)

Grading (FNCLCC)	n	%
G1	30	17
G2	64	35
G3	**87**	**48**
Stage N	**n**	**%**
0	**176**	**97**
1	6	3
Stage (8 ed.) AJCC TNM	**n**	**%**
IA	7	4
IB	24	13
II	32	18
IIIA	**50**	**27**
IIIB	**58**	**32**
IV	11	6

Multimodal Treatment	n	%
EBRT preoperative + IOERT	41	23
IOERT + EBRT postoperative	**100**	**55**
IOERT ± CHT	41	22

Surgery	n	%
Wide excision	**152**	**84**
Compartmental	22	12
Others	8	4
Surgical resection margins	**n**	**%**
R 0 (negative or > 0.5 cm)	**135**	**74**
R 1 (≥ 1 and ≤ 5 mm)	13	7
R 1 mic + (< 1 mm)	30	17
R 2 mac + (affected)	4	2

Summary of main descriptive statistical data (III)

EBRT	n	%
Preoperative	41	23
Post-operative	100	55
EBRT doses (Gy)	**n**	**%**
Median	50	
Range (cGy)	**2,520-6,040**	
≤ 45 Gy	38	21
> 45 Gy	**103**	**57**

Functionality TESS	n = 93	% = 52
75 - 100 (very good)	**53**	**57**
50 - 74 (good)	**31**	**33**
< 50 (insufficient)	9	10

Follow-up (months)	
Median	60
Range	2 - 300

IOERT energy (MeV)	n	%
Median	8	
Range	4 - 18	
IOERT applicator (cm)	**n**	**%**
< 12	**111**	**61,6**
≥ 12	71	38,4
RIO doses (Gy)	**n**	**%**
7.5 - 10	68	37
12.5	**107**	**59**
15	7	4

CHT	n	%
Yes	53	29
No	**129**	**71**

ONCOLOGICAL SURVIVAL AND PROGRESSION PATTERNS

Progression Pattern Analysis (5 years) (*)

	Local Control - LC		Distant Control - DC		Disease Free Survival - DFS		Metastases		OS	
	%	p	%	p	%	p	%	p	%	p
	68		73		57		33		76	
Surgical Margins (n = 135 / 13 / 30 / 4)										
R 0 (clear or > 0,5 cm)	73	0.03	77	0.04	63	0.005	31	0.04	80	0.042
R 1 (≥ 1 & ≤ 5 mm)	62		69		54		38		69	
R 1 micro + (< 1 mm)	57		57		37		33		60	
R 2 macro + (affect.)	0		0		0		100		50	
Staging TNM AJCC (n = 7 / 24 / 32 / 50 / 58 / 11)										
IA	100	0.002	100	0.001	86	0.001	14	0.001	100	0.001
IB	83		100		83		4		92	
II	78		88		69		22		88	
IIIA	68		62		46		44		72	
IIIB	60		69		52		38		69	
IV	18		27		50		73		36	

(*) Univariate analysis of dichotomous vs. polytomous categorical variables. Pearson Chi-square test
Univariate analysis of both dichotomous categorical variables – Fisher exact test

	LC		DC		DFS		MTS		OS	
	%	p	%	p	%	p	%	p	%	p
Histological Grading (n = 30 / 64 / 87); no classified: 1										
Grade 1	100		100		87		3		93	
Grade 2	80	0.001	84	0.001	70	0.001	25	0.001	83	0.001
Grade 3	48		56		25		51		63	
Mitosis Grading (n = 23 / 86 / 30 / 36); no classified: 7										
Non-mitosis	87		91		65		17		83	
Low (HFP 0-9)	79	0.001	78	0.018	65	0.005	30	0.038	83	0.023
Medium (HFP 10-19)	53		70		47		37		67	
High (HFP > 19)	39		50		33		53		64	
Ki-67 factor (n = 115)										
Index < 40%	81	0.009	85	0.001	71	0.001	19	0.001	87	0.003
Index ≥ 40%	46		54		38		48		62	
Stage Primary vs. Recurrent (n = 138 / 44)										
Primary	78	0.001	78	0.028	65	0.001	30	0.027	80	0.008
Recurrent	30		59		32		45		61	

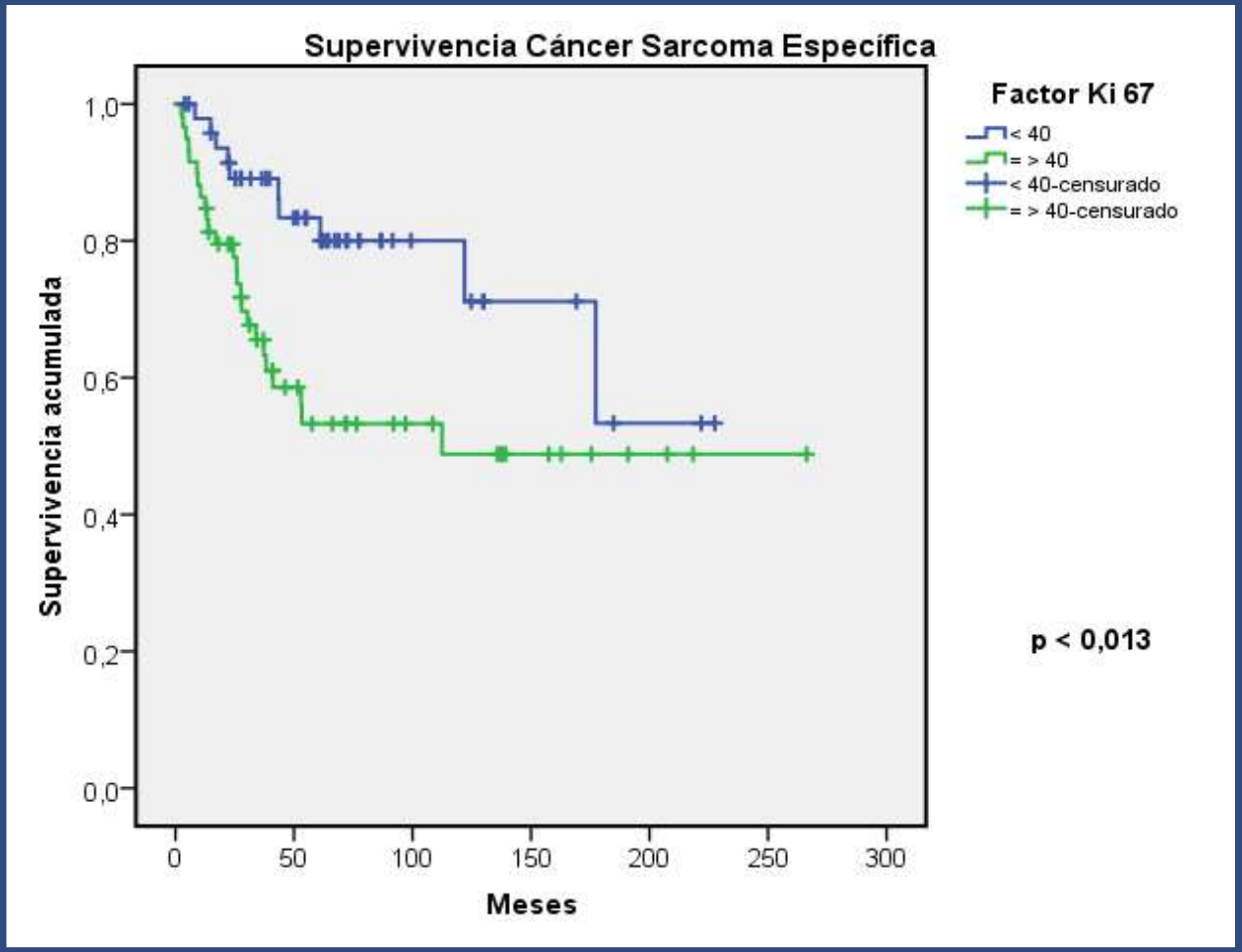
Progression and Survival Resume (%)

Follow-up (years)	OS	DFS	MFS	LC	DC	OS Primary	OS Recurrent
5	76	57	67	68	73	78	57
10	72	54	64	62	68	72	49

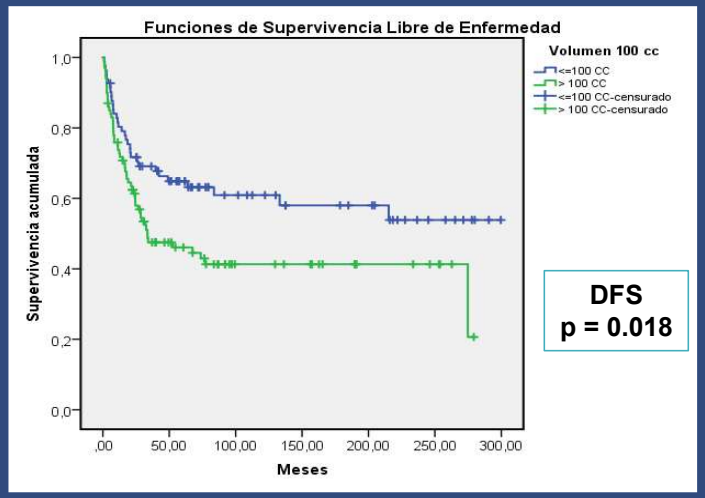
	Alive	Deceased	p < 0.05
Ki 67 (media)	37.53	50.86	p = 0.007
Number of cases	73	35	
Tumor Volume (media)	241.92	430.19	p = 0.045
Number of cases	114	54	

IA	IB	II	IIIA	IIIB	IV	p=0.003
Staging TNM AJCC vs. ALIVE						
100%	95%	74%	64%	60%	36%	

CSS & Ki-67 factor

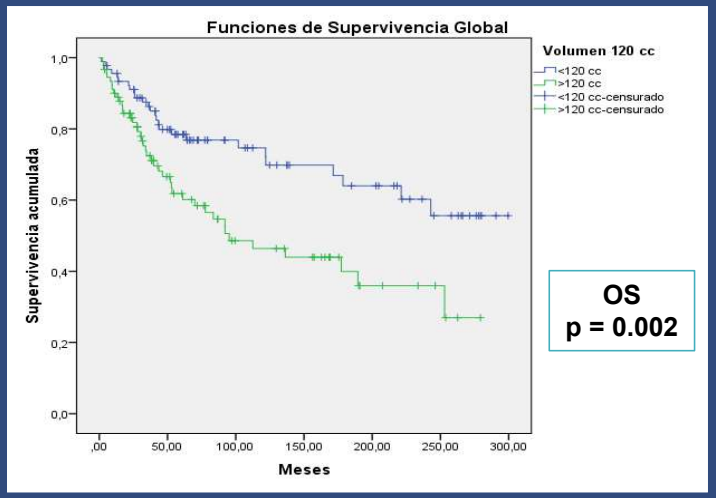


Volumetry & Survival: potential as a staging variable

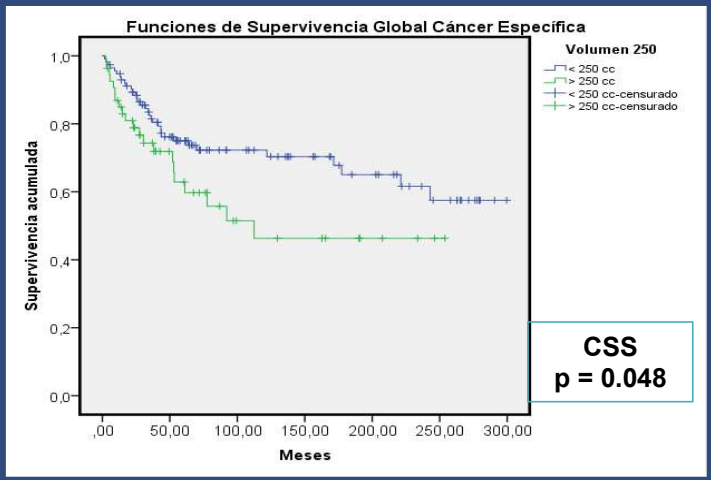


DFS
p = 0.018

Kaplan-Meier

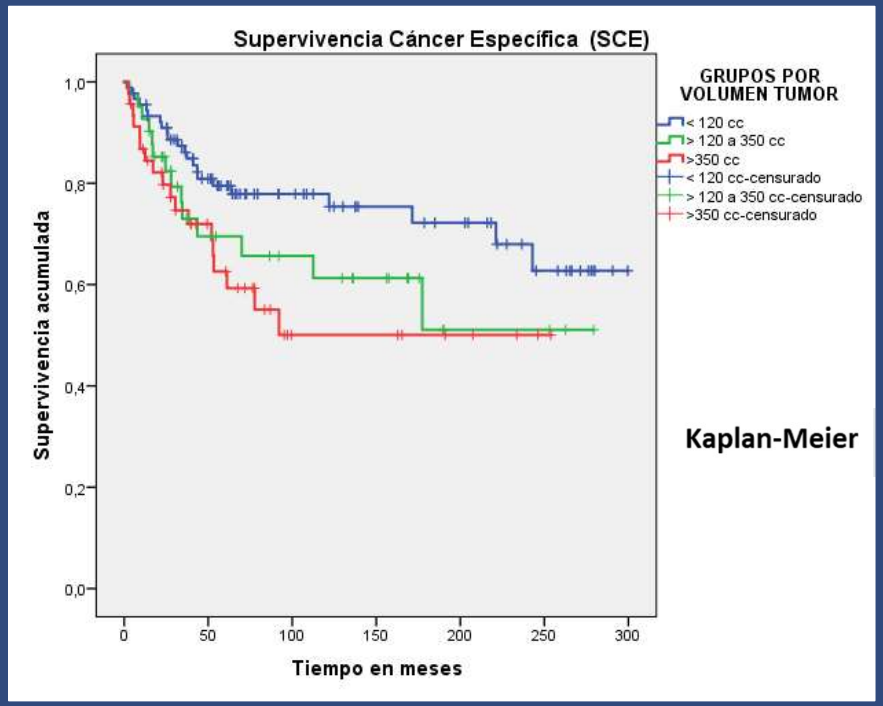


OS
p = 0.002

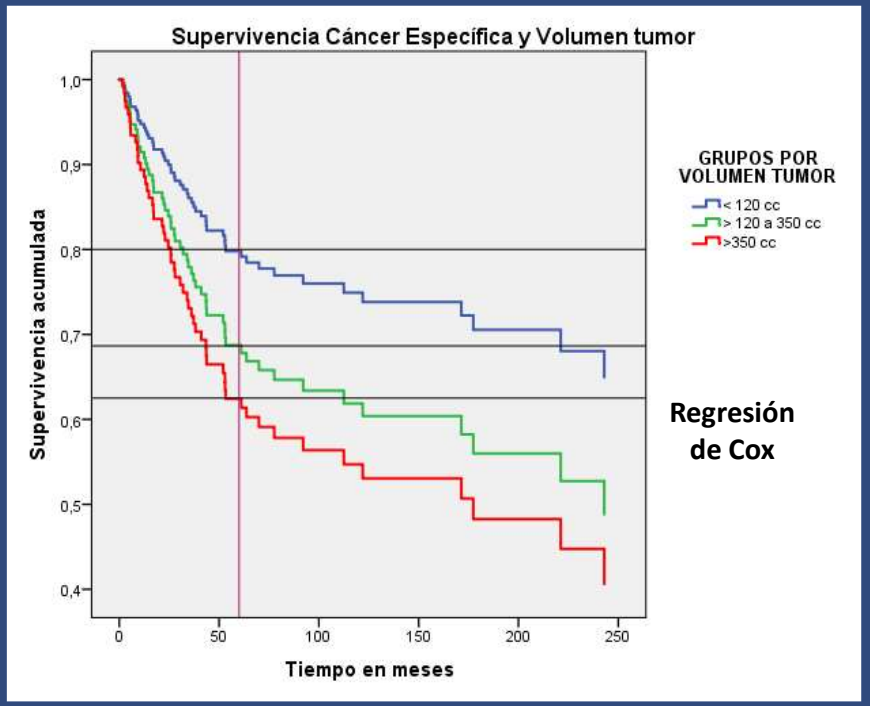


CSS
p = 0.048

Tumor Volumetry and CSS



Kaplan-Meier

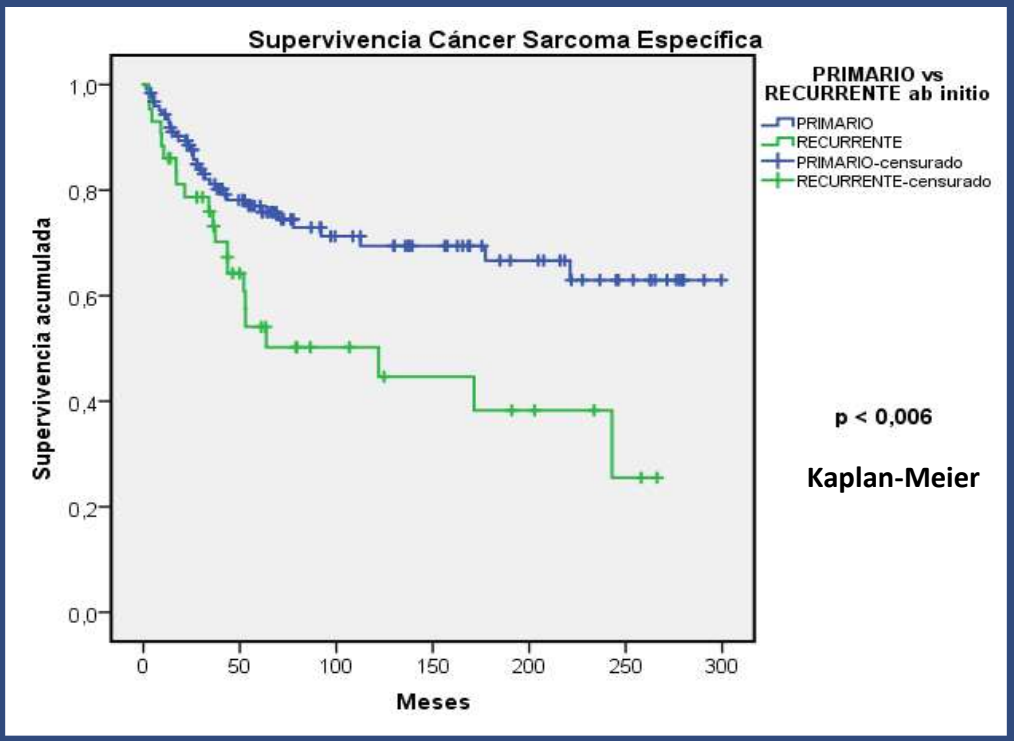


Regresión de Cox

Volume	n	CSS - 5 years	CSS – 10 years	p
< 120 cc	87	80%	79%	0.01
120-350 cc	37	70%	65%	
> 350 cc	44	66%	59%	

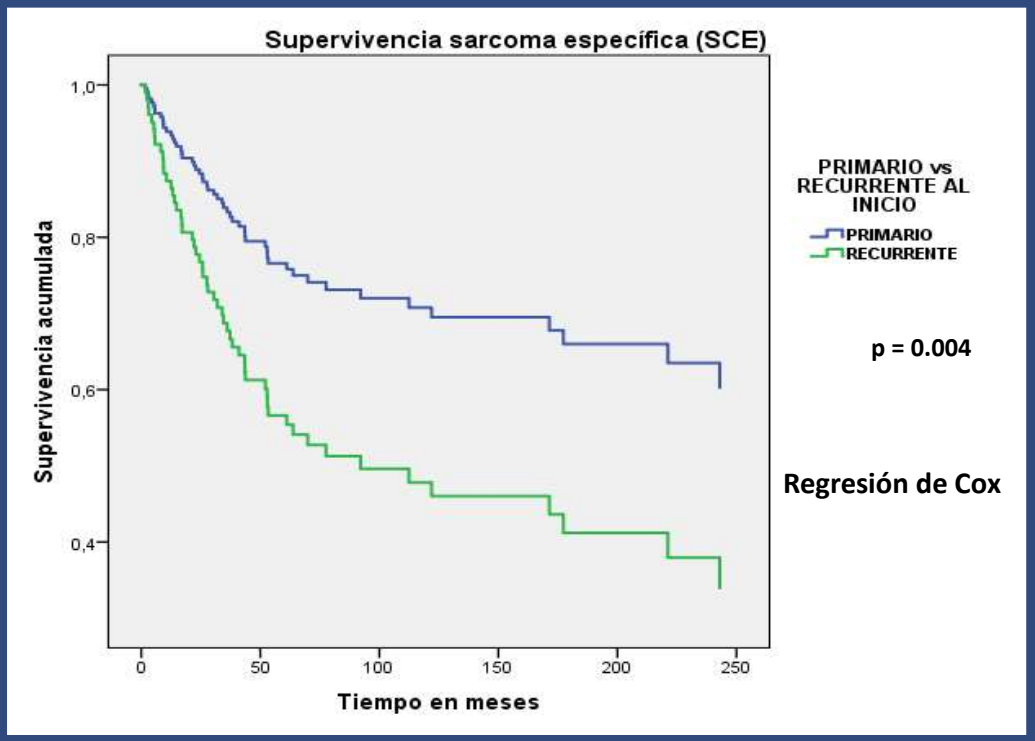
Volume	n	CSS – 5 years	HR
< 120 cc	87	80%	1
120-350	37	69%	1.90
> 350	44	63%	2.14

CSS - Cancer-Specific Survival (Primary vs. Recurrent)



p < 0,006

Kaplan-Meier



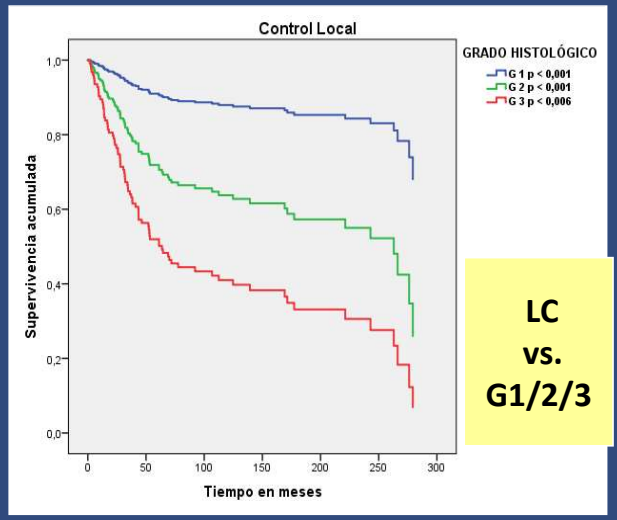
p = 0.004

Regresión de Cox

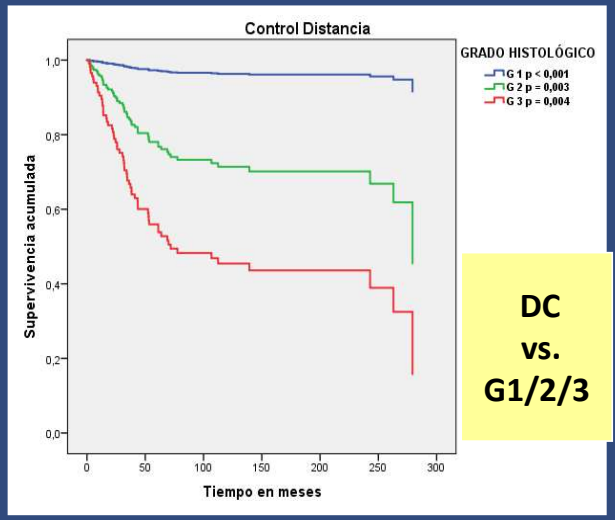
Hazard Ratio (HR) : 0.445

Primary tumours have a 55% lower risk of sarcoma death (95% CI: 23%-75%) compared to recurrent tumours

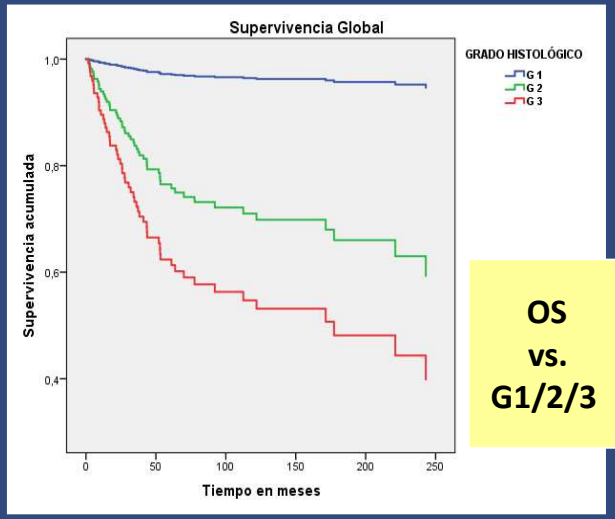
Patterns of Survival and Progression vs. Histological Grading



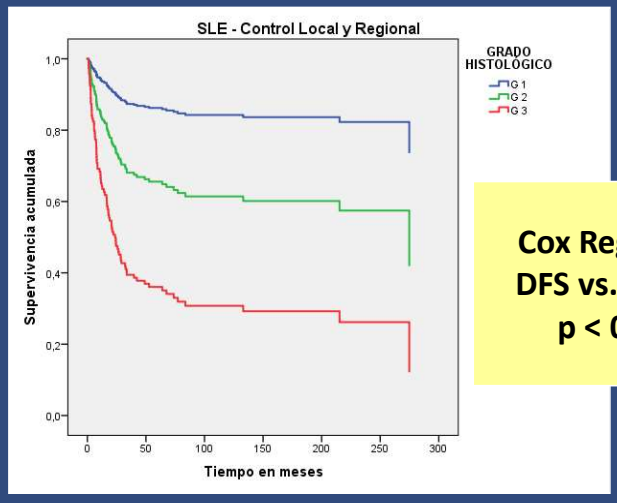
LC vs. G1/2/3



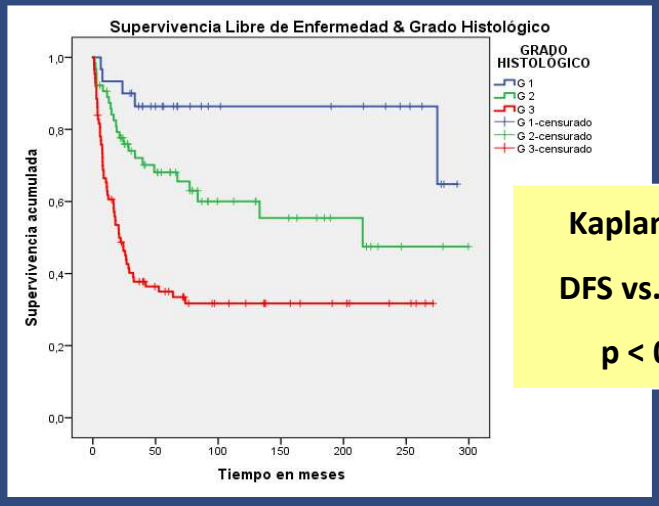
DC vs. G1/2/3



OS vs. G1/2/3

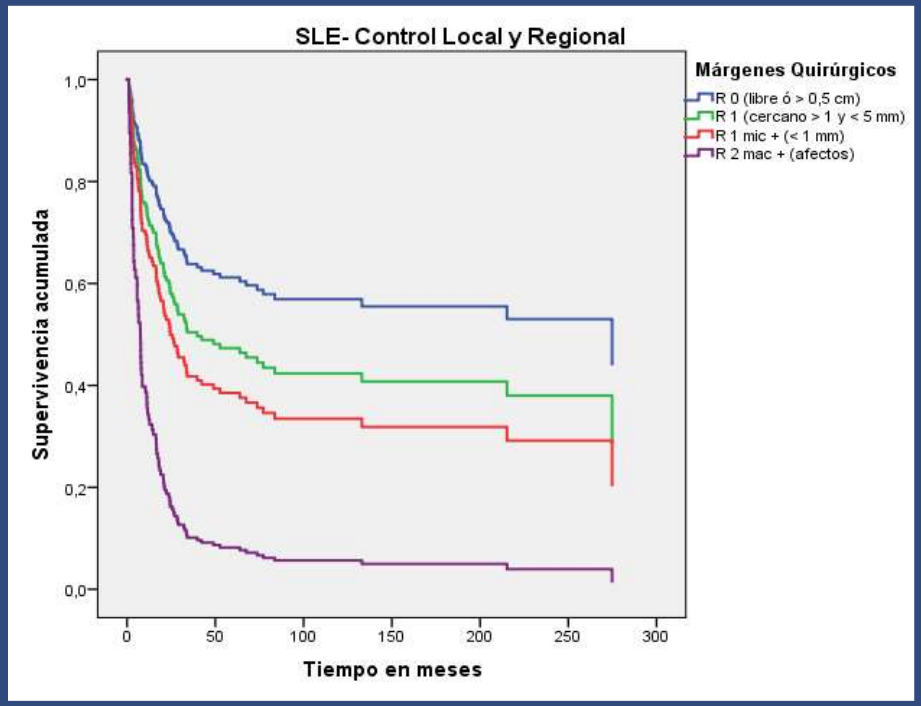


Cox Regression
DFS vs. G1/2/3
p < 0.001

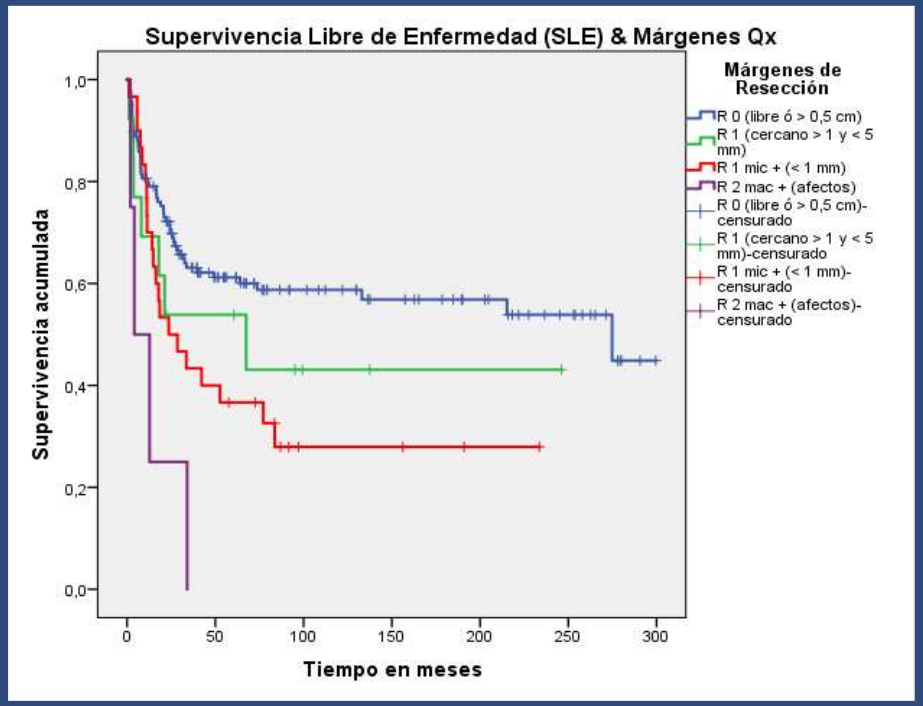


Kaplan-Meier
DFS vs. G1/2/3
p < 0.001

Survival Patterns vs. Surgical Margins

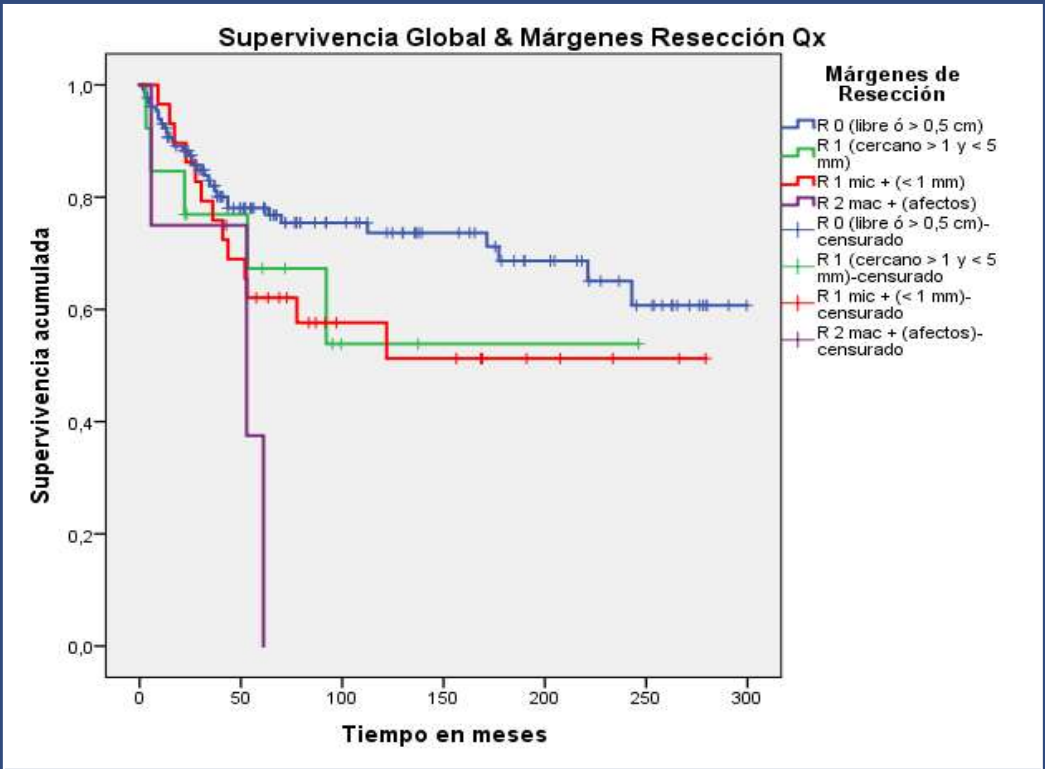


Cox Regression
DFS vs. Surgical Margins



Kaplan-Meier
DFS vs. Surgical Margins
R0 / R1, p = 0.01

Survival Patterns vs. Surgical Margins



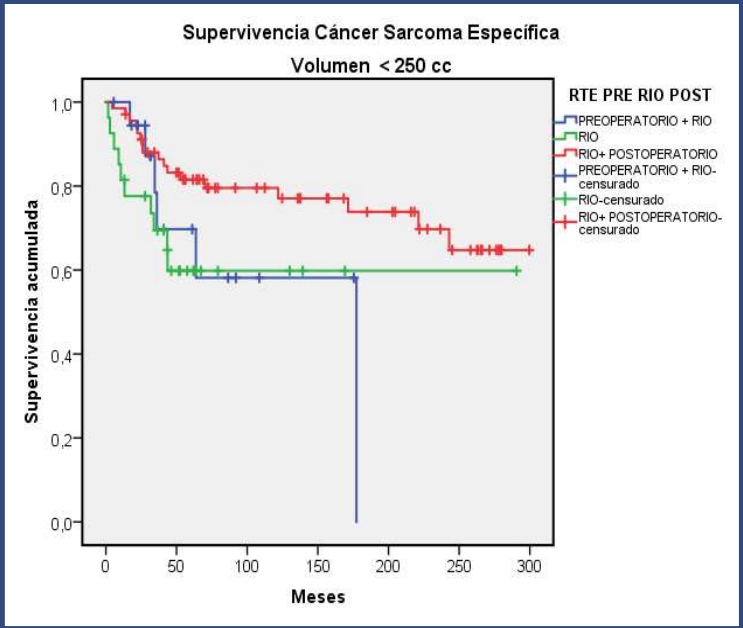
OS vs. Surgical Margins
R0 / R1; p = 0.02

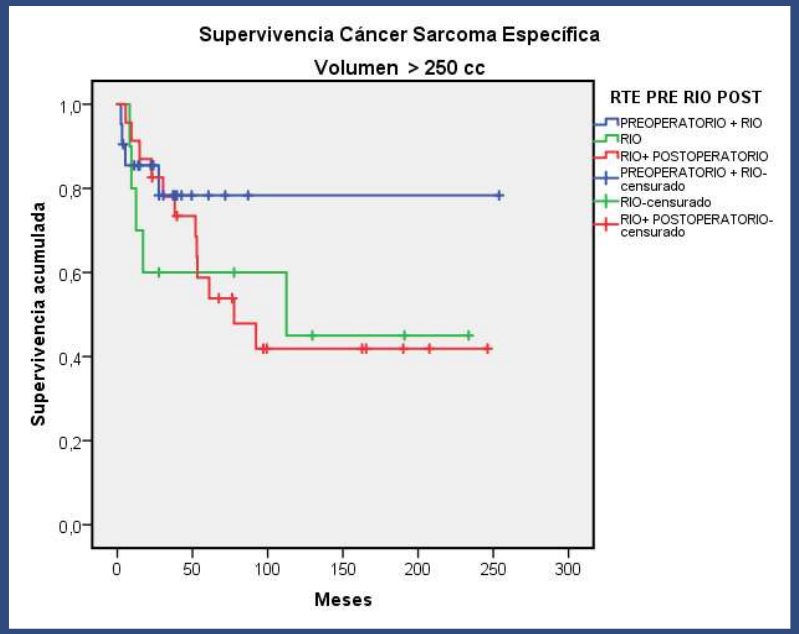
Survival, Progression patterns vs. EBRT pre/postoperative

	LC (%)		DC (%)		OS (%)		DFS (%)		MFS (%)	
Follow-up (years)	5	10	5	10	5	10	5	10	5	10
EBRT Pre + IOERT	66	59	68	61	80	76	56	54	61	59
IOERT	51	46	66	63	56	54	44	42	63	61
IOERT + Post EBRT	75	69	78	73	78	70	62	59	70	68
p	0.002		0.004		0.053		0.038		0.032	

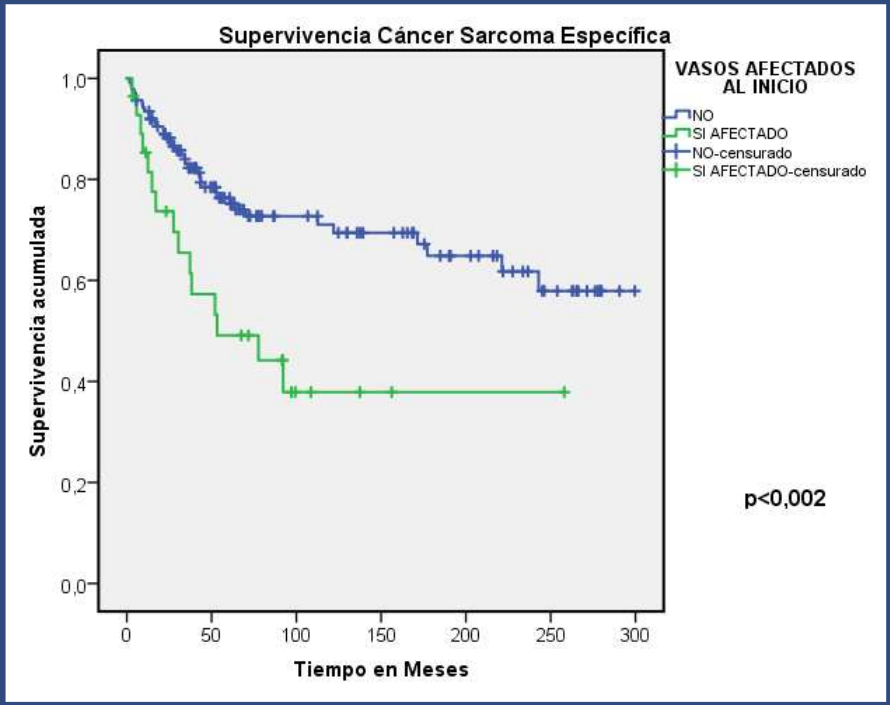
CSS vs. EBRT PRE / POSTOPERATIVE (Volume 250 cc)

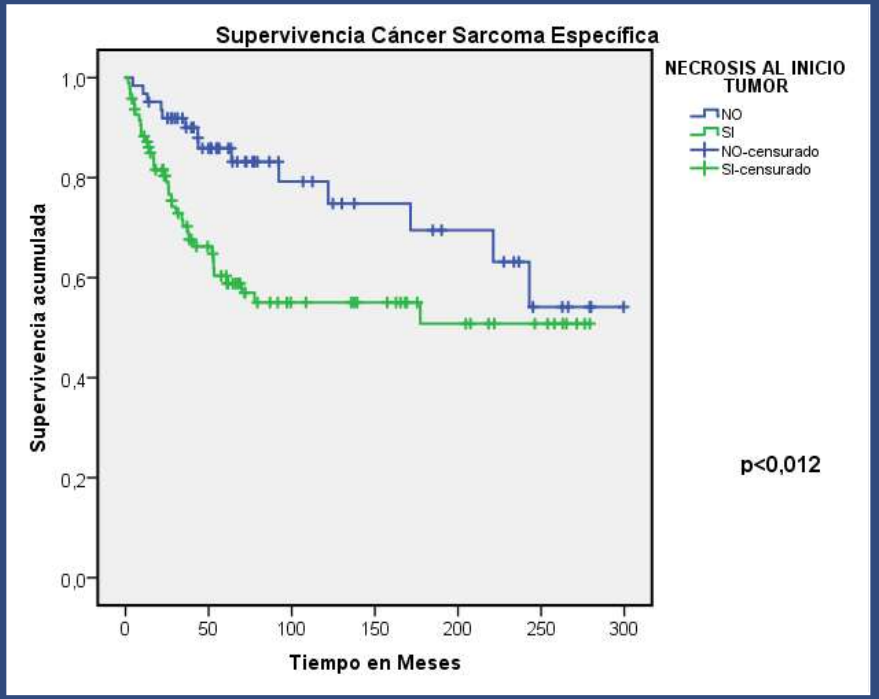
CSS vs. v < 250 cc
EBRT pre/post
p = 0.046





CSS vs. Vessels and Necrosis





Functionality

TESS	n	(%)
TESS test	93	51
Functionality 0 to < 50	9	10
Functionality ≥ 50 to < 75	31	33
Functionality → ≥ 75-100	53	57
Non-TESS (deceased)	68	37
Amputation	14	8
Non-located	6	3

FUNCTIONALITY 75 vs. Volume 120 cc					
p = 0.002			Volume 120		Total
			< 120 cc	> 120 cc	
FUNCTIONALITY	< 75	n	16	24	40
		%	40.0	60.0	100.0
	≥ 75	n	38	15	53
		%	71.7	28.3	100.0
Total		n	54	39	93
		%	58.1	41.9	100.0

FUNCIONALITY 75 vs. Volume 250 cc					
p = 0.045			Volume 250		Total
			< 250 cc	> 250 cc	
FUNCTIONALITY	< 75	n	25	15	40
		%	40.0	60.0	100.0
	≥ 75	n	43	10	53
		%	81.1	18.9	100.0
Total		n	68	25	93
		%	73.1	26.9	100.0

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DISCUSSION

- Strategic factors for Multimodal Treatment
- Multimodal Treatment
  - Objectives
  - Volumetry Factor
  - Functionality

Strategic factors for Multimodal Treatment I

- Survival and LC: IOERT + EBRT (pre- or post-operative) >>>>> exclusive IOERT
- IOERT dosage:
  - Recommendations ESTRO 2020 (Roeder, Calvo, Ferrer) doses 12-12.5 Gy
  - In our series: chronic PN (15.4%) with doses > 12.5 Gy
- IOERT + EBRT Post-operative: significant OS/CSS improvement for tumor volume < 250 cc
- EBRT Preoperative + IOERT non-significant OS/CSS improvement for tumor volume > 250 cc (future studies)
- EBRT: Neoadjuvant (high volume tumors) and Adjuvant (low volume tumors)
- Innovative treatment strategies (CHT + EBRT) in high-risk patients

Strategic factors for Multimodal Treatment II

- Cellular heterogeneity in SPB, BIOLOGY affected by volume and surgery
- "Discriminatory" volume factor (250 cc) → impact OS / CSS
- Survival and progression patterns (statistical finding):
  - LC / DC / DFS / OS vs. Histological Grading
  - DFS / OS vs. Surgical Margins
  - LC / DC / OS / CSS vs. TNM AJCC staging I - II > 90%
- Increased risk of recurrence:
  - High histological grade (G3) → ↑ metastases and death (66%) vs. G1/G2 (31%)
  - Medium/High Mitotic Index (60% - 69.4%)
  - TNM (stage IIIA, IIIB or IV) (54% - 81.8%)
- Affected or proximate surgical margins (< 5 mm)
- " Discriminatory" Ki-67 factor ≤ 40% → Low grade, Non-recurrent, ↑LC, ↑CSS, reduced mortality rate, ↓volume.
- Treatment of recurrence (CHT, EBRT, IOERT, Surgery)
- Functionality (TESS)

Multimodal Treatment: considerations (I)

- Our study consolidates: Surgery + IOERT (12.5 Gy) + EBRT post-operative (45 – 50 Gy) is a safe and efficient multimodal treatment with high CSS and functionality
  - Grading FNCLCC G1 / G2
  - R0 surgical margins (free or > 5 mm)
  - Tumor volume < 250 cc
  - Ki-67 < 40%
  - Primary
- In other scenarios: G3; Volume > 250 cc; Ki-67 > 40% ; *ab initio* recurrent (other therapeutic sequences and intensities should be assessed → EBRT preoperative, altered fractionations, chemo-irradiation or induction CHT
- IOERT intensification to compensate for adversity due to the condition of the surgical margins
- Future incorporation into studies: Volumetry, functionality measure, Ki-67 factor

Multimodal Treatment: considerations (II)

- Retrospective study with a long period of time in the prospective registration of care action and bio-heterogeneity of the cancer evaluated, influences the methodological quality and interpretation of results.
- Multimodal treatment always associated with IOERT has favourable results in oncological evolutionary patterns.
- Favourable prognostic profiles: **volume < 120 cc, G1, free surgical margins, primary presentation, and Ki-67 ≤ 40%**
- Unfavourable differential prognostic variables: **margins < 5 mm, G3, staging IIIA-IIIB-IV, grade of mitosis, tumor volume > 120 cc, recurrent tumor and number of recurrences, Ki-67 > 40%, limb root SPB, and development of metastases**.
- In volumes up to 250 cc, Radiotherapy must introduce relevant changes in clinical practice with radio-biological innovation: IOERT dose escalation (field-within-the-field), preoperative proton therapy, metabolism-guided dose escalation, altered fractionations, grid dosimetry.
- Limb preservation: achieve limb-sparing surgery and reserve amputation for recurrent or difficult-to-resect cases, or extracompartmental bulky lesions.

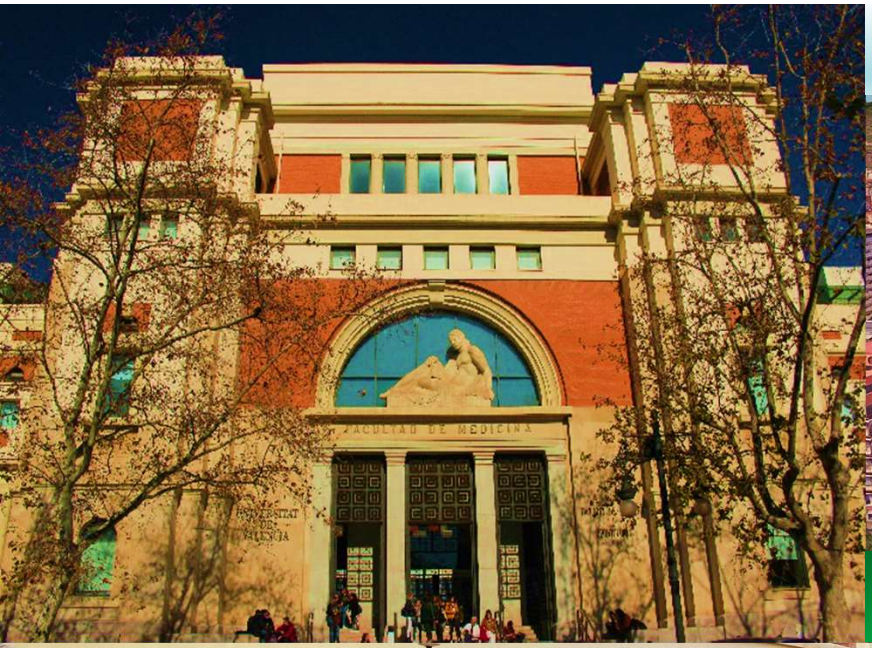
CONCLUSIONS

Conclusions (I)

1. Intraoperative electron radiotherapy, as an innovative and systematized component of local radiotherapy intensification in patients with soft tissue sarcomas of the extremities, contributes significantly to generating patients with **anatomical and functional preservation, minimally toxic local control and majority disability-free survival**, in the context of multimodal treatment, in the mature experience of an expert institution of reference in the treatment of soft tissue sarcomas.
2. The original oncological analysis factors in this study cohort and their impact in relation to prognostic adversity in sarcoma control and patient evolution are **volumetry (> 250 cc) and Ki-67 expression (> 40%)**. Radiotherapy intensity can compensate for the risk of local prognostic adversity up to a volume < 300 cc and a Ki-67 expression factor < 40%. Exceeding these cut-off values does not guarantee oncological control with dose escalation.
3. **Volumetry emerges as a mathematized, recordable risk identification parameter** that should be incorporated into clinical staging elements. In lesions with adverse volumetry, it is an alert to guide personalized treatment proposals with local and systemic intensification criteria.

Conclusions (II)

4. **The study of the functionality of the limb**, using validated methodology and voluntary collaboration by the surviving patients of a homogeneously treated cohort (in terms of intensified radiotherapy intensity and surgical expertise of a reference centre), **identifies a mostly favourable evolution that is negatively compromised by the dimensionality of the original lesion**, due to resections with greater loss of tissues (including muscle structures) and more extensive and irregular radiotherapy volume.
5. The results obtained allow us to have multifactorial oncological and functional predictive information, incorporating **new parameters with objective metrics to improve clinical practice and personalize the treatment of patients with soft tissue sarcomas of the extremities and related areas**, with criteria of intensification in presentations with identifiable oncological prognostic adversity and anticipate rehabilitation care in situations of high risk of dysfunction evolutionary.



THANK YOU FOR YOUR ATTENTION

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