Radio-induced breast sarcomas

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5th MASTERCLASS OF SARCOMA AND RARE CANCERS

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Plan

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3. Clinical presentation
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   - Bevacizumab and TKIs
   - Immunotherapy

1. Introduction

- Approximately one-third of BS, with angiosarcoma being the most common subtype
- Incidence: 1.5-2 cases per million per year[1]
- Cumulative incidence of radiation-induced breast sarcoma (RIBS) at 0.3% at 15 years post-RT[2]
- Radiation-induced breast angiosarcoma (RIBA): MYC gene amplification[3]
- ↑ risk in pts with Li-Fraumeni sd[4]

[1] Karlsson et al., Breast Cancer Res. Treat. 2020; [2] Yap et al., Int. J. Radiat. Oncol. Biol. Phys. 2002; [3] Manner et al., Am. J. Pathol. 2010; [4] Le et al., Breast Cancer Res. Treat. 2020

Definition

Modified criteria for RI-bone sarcomas by Cahan et al.

- different histological features between the primary tumor and the present sarcoma
- the development of sarcoma in a previously irradiated field
- a latent period typically >5 years
- histological confirmation of the second malignancy as sarcoma

Further modified by Arlen et al.

- including tissues adjacent to the irradiated field
- a shorter latency period (3–4 years)

Cahan et al., Cancer 1948
Arlen et al.,, Cancer 1971

2. Pathophysiology

RT is likely the main causative factor

- But: a clear dose-dependent relationship has not yet been established (only in some studies[1])
- Different hypotheses: direct effect of RT due to tissue damage, central role of lymphedema (lymphatic channels obstruction from RT or surgery), cases of out-of-field sarcomas (?), role of female hormones (radiation-induced AS in female reproductive organs (?)

Table 4. Odds ratio (OR) of soft tissue and bone cancer as a function of the dose of radiation

Dose of radiation to the site of soft tissue or bone cancer[a]	Cases/ Controls	Mean dose in controls (range)	OR (95% CI)	*p*-value[b]
≤ 14	4/65	1.1 (0–14.0)	1 (ref)	
14–44	2/22	26.8 (14.8–44.9)	1.6 (0.2–11.0)	$P < 10^{-3}$
≥ 45	8/11	53.0 (45.2–79.8)	30.6 (4.9–611)	

[1] Rubino et al., Breast Cancer Res. Treat. 2005

3. Clinical presentation of RIBS

	Primary Breast Sarcoma	Radiation-Induced Breast Sarcoma
Frequency	Rare	Rare
Age	5th–6th decade	Depends on first cancer age and latency period
Risk factors	Unknown, genetic predisposition	Young age of RT, long latency period, high radiation dosage, alkylating agents, genetic predisposition
Clinical presentation	Unilateral breast lump	Unilateral breast lump, discoloration, purplish-red nodules, thickening or elevation of the skin, and a diffuse pattern of extension
Histology	UPS, FS, AS	AS
Prognosis	Poor	Poor

- RIBS: painless unilateral lump
- RIBA: discoloration, purplish-red nodules, thickening f the skin (can be misdiagnosed as benign skin changes)

Kokkali et al., IJMS 2022

- Surgical mammary specimen of RIBA. Note violet, congestive skin and subcutaneous tumoral infiltration

(Prof. Theocharis, Medical School of Athens)

Author	Year of Publication	Treatment Period	Total N	AS (%)	Median Age (Years)	Latency Period (Years)	Median T (cm)
Karlsson	1998	1958–1992	67	47.8	NA	NA	NA
Lagrange	2000	1975–1995	14	42.9	65.5	NA	NA
Blanchard	2002	1975–2001	34	35.3	62.3 (mean)	12.7 (mean)	NA
Billings	2004	<2004	27	100	70	4.9	4
Kirova	2005	1984–2005	18	72.2	66.5	7.3	NA
Sher	2007	1965–2002	13	100	72	7	NA
Hodgson	2007	1981–2000	31	100	72.9 (mean)	5.2 (mean)	NA
Palta	2010	1997–2006	14	100	66.5	7.7	NA
Pencavel	2011	1996–2006	19	78.9	61 (mean)	NA	NA
Seinen	2012	1990–2009	35	100	67	7	4
Fraga-Guedes	2012	1999–2009	20	100	66	7.5	2.8
Torres	2013	1993–2011	95	100	71	7	5
Linthorst	2013	2000–2011	23	100	70	8.8	NA
D'Angelo	2013	1982–2011	79	100	68	7	4.2
Cohen-Hallaleh	2017	2000–2014	49	100	72	7.5	5
Gervais	2017	1994–2014	20	100	71	8	5–10
Yin	2017	1973–2012	173	100	70–74	NA	NA
Abdou	2019	1990–2015	13	100	71	7.8	6.9
Rombouts	2019	1989–2017	209	100	73	8	NM
Gutkin	2020	1998–2019	34	100	72	6.9	5.6 (mean)

- Shorter latency period compared to other RI-sarcomas (≥1 year), also for RIBA compared to other RI-angiosarcomas (approximately 7 years versus 10–30 years)

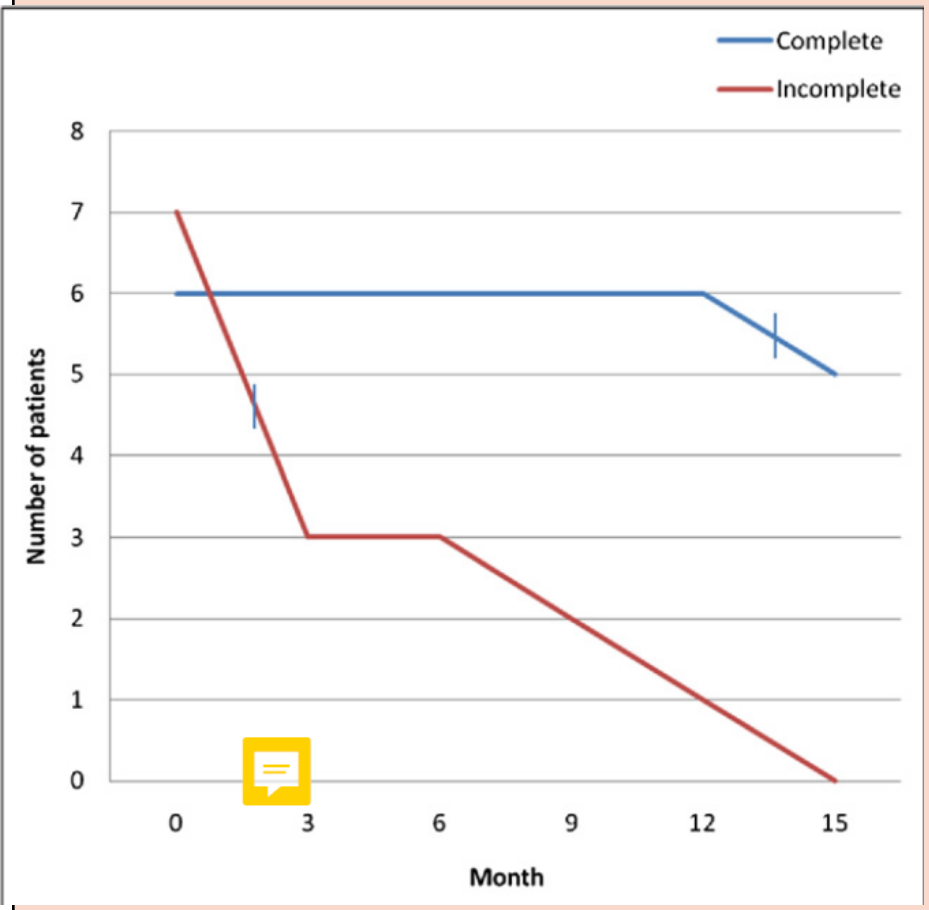
Kokkali et al., IJMS 2022

4. Management of the early disease

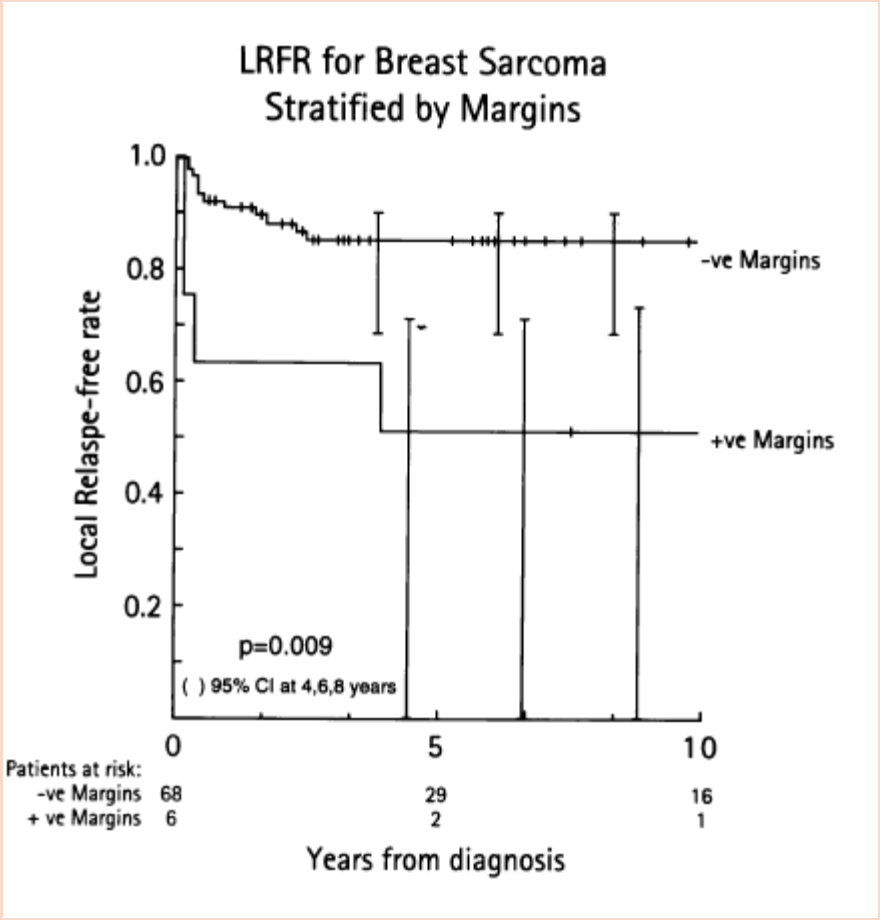
- Multidisciplinary team discussion (tumor growth pattern, involvement of the surrounding tissues, previous treatment modalities..)
- Surgery: the cornerstone of treatment
  - Surgical margins=the most important prognostic factor (local recurrence and OS)
  - Wide margins 2-5 cm (tendency for satellite deposits of RIBA)
  - Challenging surgery for RIBA (diffusively infiltrative margins) → better outcome when primary surgery in a high-volume tertiary sarcoma center versus referral after primary surgery
  - Mastectomy versus wide local excision (T<5 cm): more often R0
  - SLN/lymphadenectomy not indicated

Cohen-Hallaleh et al., Clin. Sarcoma Res. 2017
Pencavel et al., Eur. J. Surg. Oncol. 2011

Detrimental effect of positive surgical margins



OS



Jallali et al., Am J Surg 2012
McGowan et al., Int. J. Radiat. Oncol. Biol. Phys. 2000

Radiation therapy in the early disease ?

Author	Year of Publication	Nodal Involvem.	Type of Surgery (N)	Margin Status (N)	Adjuvant RT (%)	(neo)Adjuvant Chemo (%)	OS/DFS (Years)	Prognostic Association
Karlsson	1998	NA	NA	NA	NA	NA	NA	no
Lagrange	2000	NA	2 MA, 8 WLE	2 R2	28.6	35.7	NA	surgery
Blanchard	2002	NA	30/34 surgery	NA	30	43	NA	size
Billings	2004	NA	10 MA, 10 WLE	NA	10	20	NA	no
Kirova	2005	NA	11 MA, 5 WLE	NA	5.6	5.6	mOS = 22 m	no
Sher	2007	NE	12 MA, 1 WLE	NA	0	NA	NA	size
Hodgson	2007	NA	25 MA, 1 WLE	NA	0	NA	NA	no
Palta	2010	2/14	14 MA	NA	100 (HART)	0	5y-OS = 86%, 5y-PFS = 64%	benefit of HART in addition to surgery
Pencavel	2011	0/3	12 MA, 6 WLE	NA	NA	NA	mDFS = 30 m. 5y-DFS = 26%	surgery at experienced center
Seinen	2012	NA	24 MA, 7 WLE	23 R0, 1R1, 7 R2	3.2	3.2	mDFS = 16 m	amenable to surgery for local recurrence
Fraga-Guedes	2012	0	15 MA	NA	10	50	5y-OS = 28.2%	grade, prior RT
Torres	2013	0	60 MA, 27 WLE	81 RO, 4 R1, 4 R2	0	52	5y-OS = 91%	size
Linthorst	2013	NA	10 MA, 1 WLE	4/11 R0, 6/11 R1, 1/11 R2	34.8	0	mOS = 18 m	reRT + hyperthermia (local control)
D'Angelo	2013	NA	65 MA, 13 WLE	45 R0, 12 R1, 8 R2	NA	11.4	mDSS = 3 y.	age > 68 y, depth
Cohen-Hallaleh	2017	NE	38 MA	32/37 R0	0	19.1	mOS = 37 m (resectable)	size, resectability
Gervais	2017	NA	19 MA, 1 WLE	18 R0	35	50	mOS = 51 m	no
Yin	2017	NA	NA	NA	12.7	NA	mOS = 32 m	age, tumor spread
Abdou	2019	NA	9 MA	NA	7.7	61.5	mOS = 64.2 m	no
Rombouts	2019	NA	NA	NA	9.1	1.4	5y-OS = 40.5%	no
Gutkin	2020	0	27 MA, 4 WLE	12 R0, 6 R1	8.8	44.1	mOS = 16.9 y	chemotherapy

Kokkali et al., IJMS 2022

Radiation therapy in the early disease ?

AGAINST

- Natural history (**radiation**-induced)
- maximum tolerated dose of radiation probably already delivered

BUT

- Aggressiveness (especially RIBA)
- High local recurrence rate

DATA

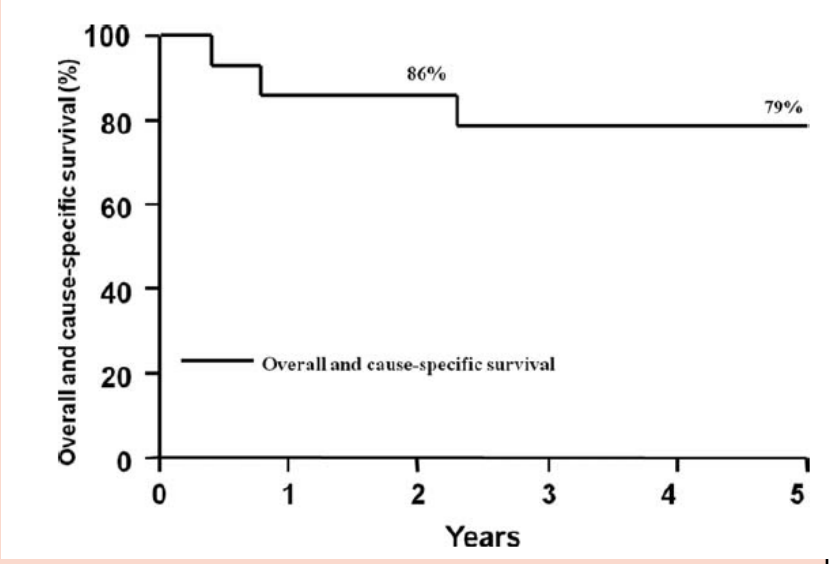
- Heterogeneous use of RT in the different studies, depending on local practice
- A benefit from adj RT mainly in LRFS in some studies (mainly AS)

Depla et al., Eur. J. Cancer. 2014; McGowan et al., Int. J. Radiat. Oncol. Biol. Phys. 2000; Ghareeb et al. Am. J. Clin. Oncol. 2016

Alternative Radiation techniques

Hyperfractionated accelerated RT (HART)

- small fractional doses, moderate total dose, large field margins over a short period with good tolerance
- Tested in RIBA (3 RT therapies 1 Gy/day), Florida University: 7/7 pCR at surgery



RT in combination with hyperthermia

- 2 small studies from the Netherlands
- RIS of the chest wall
- Short OS

Palta et al., Cancer. 2010; Smith et al., Acta Oncol 2014; Linthorst et al., Strahlenther. Onkol. 2013

Chemotherapy in the early disease ?

Author	Year of Publication	Nodal Involvem.	Type of Surgery (N)	Margin Status (N)	Adjuvant RT (%)	(neo)Adjuvant Chemo (%)	OS/DFS (Years)	Prognostic Association
Karlsson	1998	NA	NA	NA	NA	NA	NA	no
Lagrange	2000	NA	2 MA, 8 WLE	2 R2	28.6	35.7	NA	surgery
Blanchard	2002	NA	30/34 surgery	NA	30	43	NA	size
Billings	2004	NA	10 MA, 10 WLE	NA	10	20	NA	no
Kirova	2005	NA	11 MA, 5 WLE	NA	5.6	5.6	mOS = 22 m	no
Sher	2007	NE	12 MA, 1 WLE	NA	0	NA	NA	size
Hodgson	2007	NA	25 MA, 1 WLE	NA	0	NA	NA	no
Palta	2010	2/14	14 MA	NA	100 (HART)	0	5y-OS = 86%, 5y-PFS = 64%	benefit of HART in addition to surgery
Pencavel	2011	0/3	12 MA, 6 WLE	NA	NA	NA	mDFS = 30 m. 5y-DFS = 26%	surgery at experienced center
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Rombouts	2019	NA	NA	NA	9.1	1.4	5y-OS = 40.5%	no
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Kokkali et al., IJMS 2022

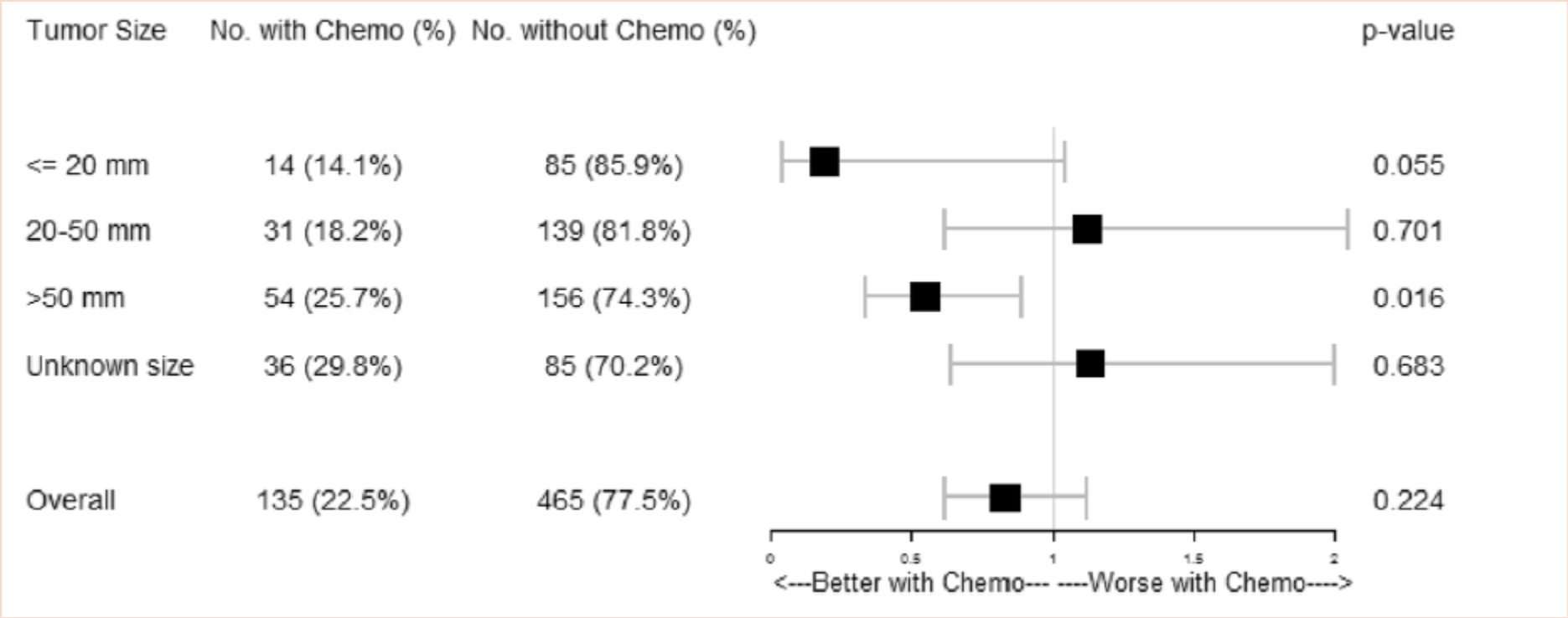
Systemic therapy in the early disease ?

- Similarly to other STS, uncertain role
- Chemotherapy administered only in a small percentage of RIBS in the different retrospective series, inconsistent criteria
- Data mainly in the adjuvant and not neoadjuvant setting
- Different studies of RIS without analysis of RIBS
- No documented impact on OS

BUT there is some evidence to consider its use in AS

- Stanford study (N=58): OS benefit from adh chemo in SBAS and not in PBAS
- USA analysis of BAS: OS benefit from chemo in T>5 cm

Gutkin et al., Am. J. Clin. Oncol. 2020; Abdou et al., Breast Cancer Res. Treat. 2019; McClelland et al, Breast Cancer Res. Treat. 2019



USA analysis of approx 800 BAS

McClelland et al, Breast Cancer Res. Treat. 2019

5. Management of metastatic disease

Chemotherapy

- very limited evidence on the activity of the different drugs
- Data mainly on RIBA (ORR 48% L1)
- Extrapolation from STS trials

  - Doxo (if max dose not administered) +/- Ifo
  - Taxane (ANGIOTAX study: 4 month-PFS=45%)
  - Gemcitabine +/- Taxane

Sher et al., Cancer 2007;
Penel et al., J. Clin. Oncol. 2008;
Stacchiotti et al., Ann. Oncol. 2012

Table 3. Response Rates

Disease Status	No. of Patients		
	At 2 Months	At 4 Months	At 6 Months
Assessable patients	27*	22	21
Progressive disease	7	12	16
Complete response	0	1	3†
Partial response	5	3	1
Stable disease	15	6	1
Overall response rate			
%	18	18	19
95% CI	4 to 33	2 to 34	3 to 35
Nonprogression rate			
%	74	45	24
95% CI	57 to 90	25 to 66	6 to 42

- ANGIOTAX study: small French phase II study of 30 angiosarcoma patients (33% BAS)
- Retrospective series from MSKCC, N=79 RIBA
- Retrospective data on paclitaxel efficacy in cutaneous AS and RIAS

Table 6. Median treatment time on first-line chemotherapy in patients with unresectable or metastatic disease

Chemotherapy regimen	Administrations, *N*	Median treatment time, months
Brivanib	2	3.34
Doxorubicin	2	2.07
Doxorubicin/Paclitaxel	1	5.16
Gemcitabine	0	—
Gemcitabine/Docetaxel	1	2.57
Ifosfamide	1	1.32
Liposomal Doxorubicin	7	4.67
Paclitaxel	3	3.45
Sirolimus	1	14.93
Sorafenib	3	25.1

Penel et al., J. Clin. Oncol. 2008;
D'Angelo et al., Br. J. Cancer. 2013;
Italiano et al., Cancer. 2012

5. Management of metastatic disease

Bevacizumab

- Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) in AS and breast AS
- Activity of BEV monotherapy in a small study of epithelioid hemangioendothelioma and angiosarcoma (4 breast AS)

All patients, $N = 30$	n (%)
PR	4 (13)
SD	15 (50)
PD	11 (37)
Angiosarcoma, $N = 23$	n (%)
PR	2 (9)
SD	11 (48)
PD	10 (43)

Agulnik et al., Ann. Oncol. 2013;
Ray-Coquard et al., J. Clin. Oncol. 2015

5. Management of metastatic disease

TKIs

- **Pazopanib**: retrospective EORTC study in advanced vascular sarcomas (ORR of 20% in 40 AS pts, similar in RI and non-RI)
- **Sorafenib (**MYC and FLT4 co-amplifications harbored by some RIBA): .
  - Ph.2 STS trial: activity only in AS (5/37 PR, 3/5 RIBA)
  - Not confirmed in a subsequent phase 2 study
  - MSKCC retrospective study of RIBA: longest median treatment time of 25.1 months

Kollár, Acta Oncol. 2017;
Maki et al., J. Clin. Oncol. 2009
D'Angelo et al., Br. J. Cancer. 2013;

5. Management of metastatic disease

IO

- in a small study of 20 RIS (3 AS): high mutational rate, 45% PDL1/PD1 (+) and TILs (+),
- Some isolated responses to ICI in AS
- Case series of 7 AS pts: At 12 weeks, 5/7 patients (71%) had PR (5 cutaneous AS, 1 RIBA,

Malone et al., J. Clin. Oncol. 2019
Martin-Broto et al., J. Immunother. Cancer. 2020;
Florou et al, Cancer. 2019

Prognosis

- Approximately 1/2 patients will present local recurrence, despite an initial wide surgical treatment
- ……

Table 2 Univariate and multivariate Cox regressional analyses for prognostic factors of distant metastases-free survival in patients with localised resectable RIAS

Variable	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)				
<70	Reference	–	*	*
≥70	1.06 (0.98–1.15)	0.146	*	*
Positive margins				
No	Reference	–	*	*
Yes	4.20 (1.12–15.67)	0.033	*	*
Tumour size (cm)				
<5	Reference	–	Reference	–
≥5	5.70 (1.18–27.50)	0.030	5.70 (1.18–27.50)	0.030
Treatment				
Surgery	Reference	–	*	*
Surgery + chemotherapy	2.08 (0.46–9.51)	0.344	*	*

Cohen-Hallaleh et al., Clin. Sarcoma Res. 2017
Seinen et al., Ann. Surg. Oncol. 2012

Conclusions

- iatrogenic disease with distinct characteristics, such as a shorter latency period compared to other RIS
- their incidence is so low that the benefits of RT for BC outweigh the risk for SBS……
- Very limited retrospective data
- Specific trials are needed on the role of adjuvant treatment and metastatic diease treatment

Thank you very much
for your attention