Cancéropôle Île-de-France

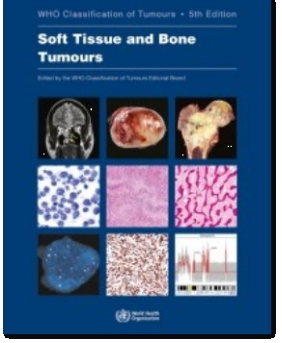
RÉPUBLIQUE FRANÇAISE
INSTITUT NATIONAL DU CANCER

Sarcomes en territoire irradié dans un contexte héréditaire

Pr Camille Tlemsani, Hôpital Cochin, AP-HP

AP-HP. Centre Université Paris Cité

Université Paris Cité



Sarcomes = Tumeurs rares et hétérogènes

WHO Classification 2020

Sarcomes des tissus mous (STM) et viscéraux
1% des cancers

≈100 sous-types histologiques:
- Liposarcomes (25%)
- Leiomyosarcomes (20%)
- Inclassé (20%)
- Synovialosarcomes
- Angiosarcomes
- Rhabdomyosarcomes
- …

= groupe très hétérogène

GIST
(tumeurs stromales gastro-intestinales)

Sarcomes osseux
<0,2% des cancers

Ostéosarcome

Sarcome d'Ewing

Chondrosarcome

Autres:
- Sarcomes osseux rares
- Tumeurs à cellules géantes
- …

- **Sarcomes très hétérogènes: histologie, âge, présentation clinique …**
  - **> 50 sous types de tumeurs et sarcomes osseux**
  - **Difficultés diagnostiques et de prise en charge**

Sarcomes = Facteurs de risque

❑ La plupart du temps:

✓ Inconnus

❑ Rarement:

✓ **Exposition aux rayonnements ionisants**

✓ **Prédisposition génétique :** rétinoblastome, Li Fraumeni, Neurofibromatose de type 1 …

✓ Agents chimiques: Chlorure de vinyle (interdite depuis 1976), Arsenic

✓ Situations particulières: lymphœdème chronique, virale (sarcome de Kaposi)

Sarcomes en territoire irradié

❑ Définition = trépied

- Antécédent de radiothérapie
- Localisation: dans le champ d'irradiation
- Histo: sarcome, de morphologie différente que le cancer initial

- +/- Délais? :

Variable, svt > 5 ans, médiane: 10-15 ans, cas rapportés > 30 ans

Cahan *et al.*, Cancer, 1948

Sarcomes en territoire irradié

❑ Données *Surveillance, Epidemiology, and End Results* (SEER) program:

- ✓ Incidence 3,2/1000 à 15ans vs 2,3/1000 sarcomes
- ✓ Augmentation de l'incidence:
  - -Amélioration survies
  - -Augmentation des indications
  - -Technique: modulation d'intensité ?
- ✓ Pronostic très sombre

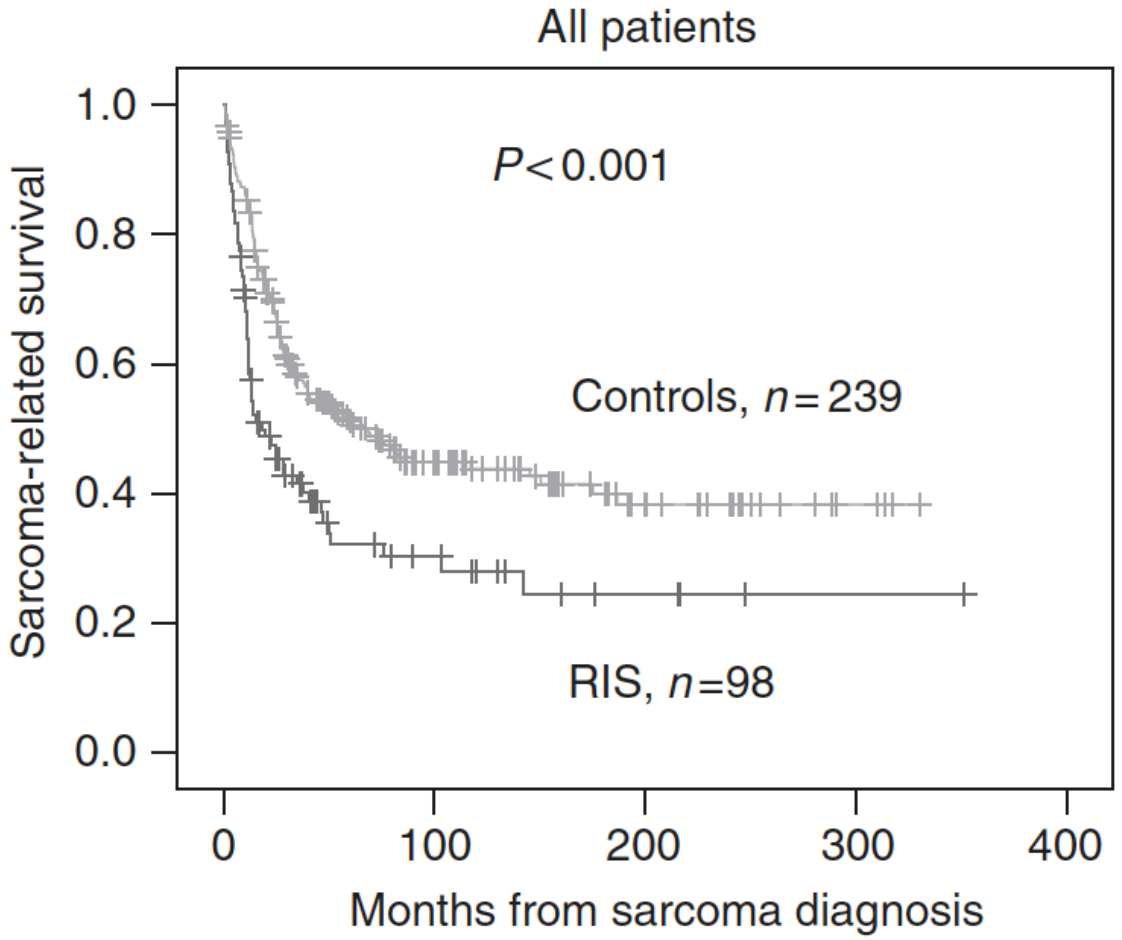
Descriptive statistics of study population stratified by primary cancer site (n = 1,884,469).

1st cancer site	Total n	Secondary sarcoma	RT		RIS	Follow-up time, *yr*	Age at diagnosis, *yr*	Female Gender	Race			Stage	
			Yes	No					White	Black	Other [a]	Local	Regional
Abdomen	1403	4 (0.29%)	23.1%	76.9%	1 (0.07%)	8.1	53.1	52.7%	78.2%	13.0%	8.8%	68.4%	31.6%
Anal	10,606	3 (0.03%)	75.1%	24.9%	3 (0.03%)	8.3	58.7	62.1%	86.8%	9.8%	3.4%	63.8%	36.2%
Brain	17,617	2 (0.01%)	64.4%	35.6%	2 (0.01%)	7.8	42.6	43.5%	88.2%	5.6%	6.2%	100.0%	0
Breast	693,701	161 (0.02%)	47.3%	52.8%	126 (0.02%)	10.2	58.6	99.4%	83.8%	8.8%	7.4%	66.2%	33.8%
Cervical	48,824	17 (0.03%)	46.5%	53.5%	15 (0.03%)	12.3	47.1	100.0%	77.4%	12.8%	9.8%	67.3%	32.7%
Eye	6852	0	45.0%	55.0%	–	9.6	58.6	44.9%	96.7%	1.4%	1.9%	91.8%	8.2%
Head	1469	8 (0.54%)	33.4%	66.6%	3 (0.20%)	10.3	55.7	31.9%	85.9%	7.5%	6.6%	72.4%	27.6%
Larynx	22,125	3 (0.01%)	76.0%	24.0%	3 (0.01%)	11.3	61.7	18.3%	84.5%	11.9%	3.6%	64.9%	35.1%
Lung	109,858	9 (0.01%)	30.4%	69.6%	3 (0.003%)	6.3	65.3	51.0%	84.3%	9.6%	6.1%	53.2%	46.8%
Pelvis	2109	10 (0.47%)	40.5%	59.5%	6 (0.28%)	9.1	53.3	46.0%	82.1%	12.0%	5.9%	73.2%	26.8%
Pharynx	9085	4 (0.04%)	88.3%	11.7%	4 (0.04%)	8.6	57.5	26.3%	69.6%	10.5%	19.9%	19.8%	80.2%
Prostate [b]	594,271	75 (0.01%)	39.3%	60.7%	44 (0.007%)	7.9	65.7	0	80.8%	14.1%	5.0%	–	100.0%
Rectal	77,296	22 (0.03%)	42.3%	57.7%	14 (0.02%)	8.8	61.8	42.5%	82.1%	8.4%	9.5%	62.8%	37.2%
Salivary	9353	6 (0.06%)	52.5%	47.5%	4 (0.04%)	10.6	55.4	48.4%	82.1%	9.1%	8.8%	65.1%	34.9%
Testicular	33,387	5 (0.01%)	40.4%	59.6%	2 (0.006%)	13.1	34.8	0	93.5%	2.4%	4.1%	78.6%	21.4%
Thorax	1484	2 (0.13%)	41.9%	58.1%	1 (0.07%)	10.2	52.4	39.2%	82.6%	10.2%	7.3%	69.3%	30.7%
Thyroid	106,381	6 (0.01%)	47.8%	52.2%	1 (0.0009%)	10.4	46.5	77.9%	83.0%	6.2%	10.9%	65.1%	34.9%
Uterine	138,648	22 (0.02%)	29.7%	70.3%	10 (0.007%)	11.6	60.5	100.0%	87.3%	5.8%	6.9%	85.3%	14.7%
Total	**1,884,469**	**359 (0.02%)**	43.0%	57.0%	**242 (0.01%)**	**9.4**	**60.0**	57.3%	**83.1%**	**10.1%**	**6.8%**	46.2%	53.8%

Snow *et al.*, Cancer Epidelmyology, 2021

Sarcomes en territoire irradié

- ✓ Pronostic très sombre
- ✓ Etude cas témoin norvégienne
- ✓ Survie à 5 ans: 32% vs 51%



Bjerkehagen *et al.*,British Journal of Cancer, 2012

Table 2 Cox regression analysis of sarcoma-related survival in patients with radiation-induced sarcoma (cases) and sporadic sarcomas (controls)

		Univariate analysis	Multivariate weighted Cox regression[a]		
Prognostic factor	***N* = 337**	***P*-value**	***P*-value**	**HR**	**95% CI for HR**
Radiation-induced sarcoma		0.001		0.84	0.58–1.22
Yes	98 (29%)		0.362		
No	239 (71%) ref				
Gender		0.540			
Female	189 (56%)				
Male	148 (44%)				
Age at sarcoma diagnosis (years)		0.02		1.30	0.94–1.79
<60	175 (52%) ref		0.109		
⩾60	162 (48%)				
Time period of diagnosis					
Before 1990	84 (25%) ref				
1990–1999	117 (35%)	0.941			
From 2000	136 (40%)	0.224			
Histological subtype					
Malignant fibrous histiocytoma	138 (41%) ref				
Osteosarcoma	102 (30%)	0.333			
Others	97 (29%)	0.132			
Tumour size				1.57	0.97–2.55
<5 cm	66 (20%) ref	0.002			
⩾5 cm	265 (80%)		0.067		
Unknown	6				
Microscopic tumour necrosis				1.88	1.27–2.78
Yes	213 (67%)		**0.002**		
No	103 (33%) ref	<0.001			
Unknown	21				
Bone or soft-tissue tumour					
Bone	110 (33%) ref				
Soft tissue/viscera	223 (67%)	0.821			
Unknown	4				
Site				1.71	1.18–2.47
Extremity/trunk wall	232 (69%) ref	<0.001	**0.004**		
Head/abdomen/axial/thoracic	106 (31%)				
Metastases at diagnosis				2.93	1.95–4.41
Yes	59 (18%)	<0.001	**<0.001**		
No	278 (82%) ref				
Complete surgical remission				4.48	3.08–6.52
Yes	210 (62%) ref	<0.001	**<0.001**		
No	126 (38%)				
Unknown	1				

Abbreviations: CI = confidence interval; HR = hazard ratio; ref = reference; RIS = radiation-induced sarcoma. Significant values are given in bold. [a]In the multivariate analysis 307 patients are included.

Bjerkehagen *et al.*,British Journal of Cancer, 2012

Sarcomes en territoire irradié

❑ **Métanalyse:** Inchaustegui *et al*., 2023

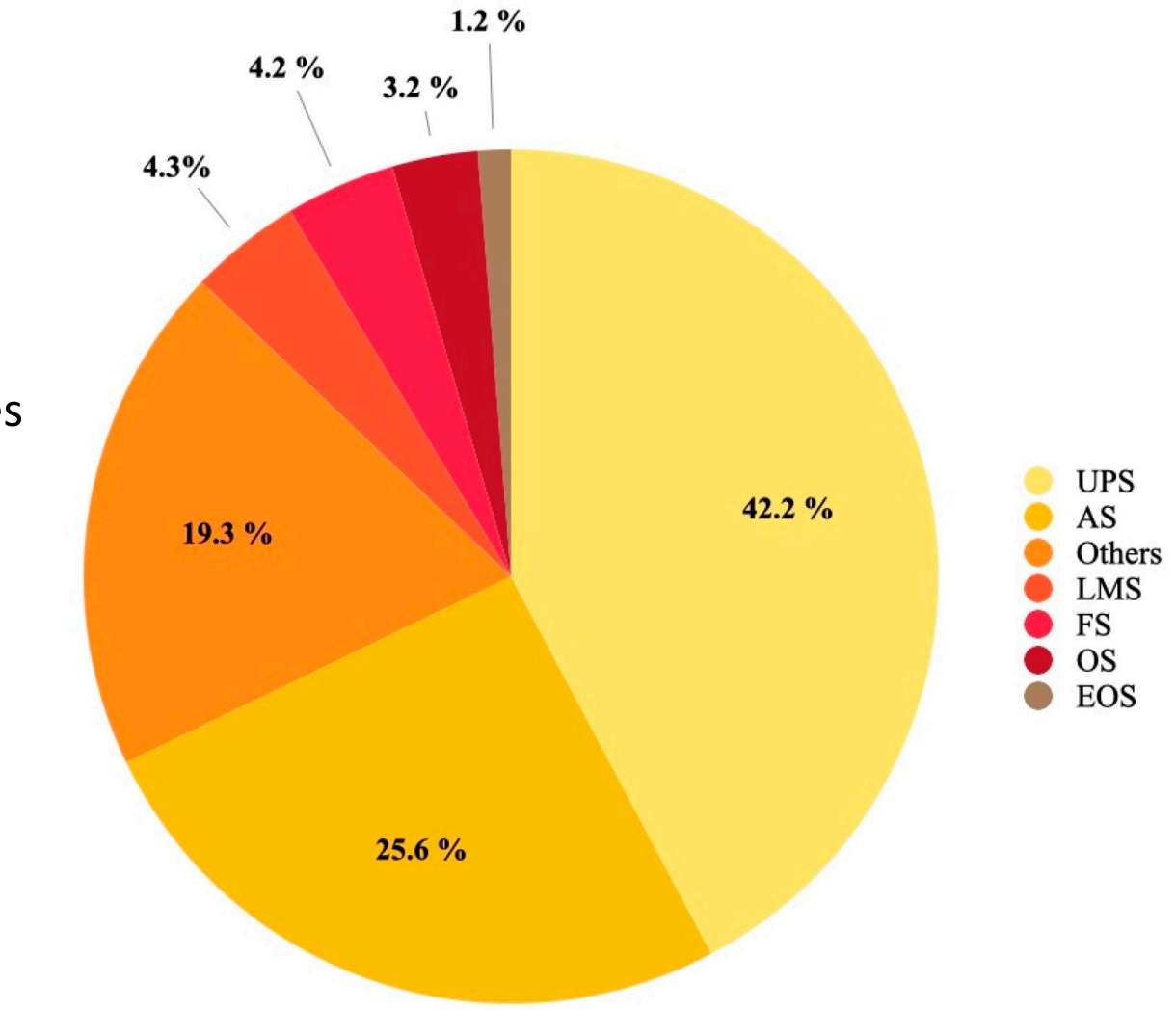
21 études 1371 patients

Sous-types les plus représentés:

- UPS, angiosarcomes, léïomyosarcomes, fibrosarcomes
- Ostéosarcome

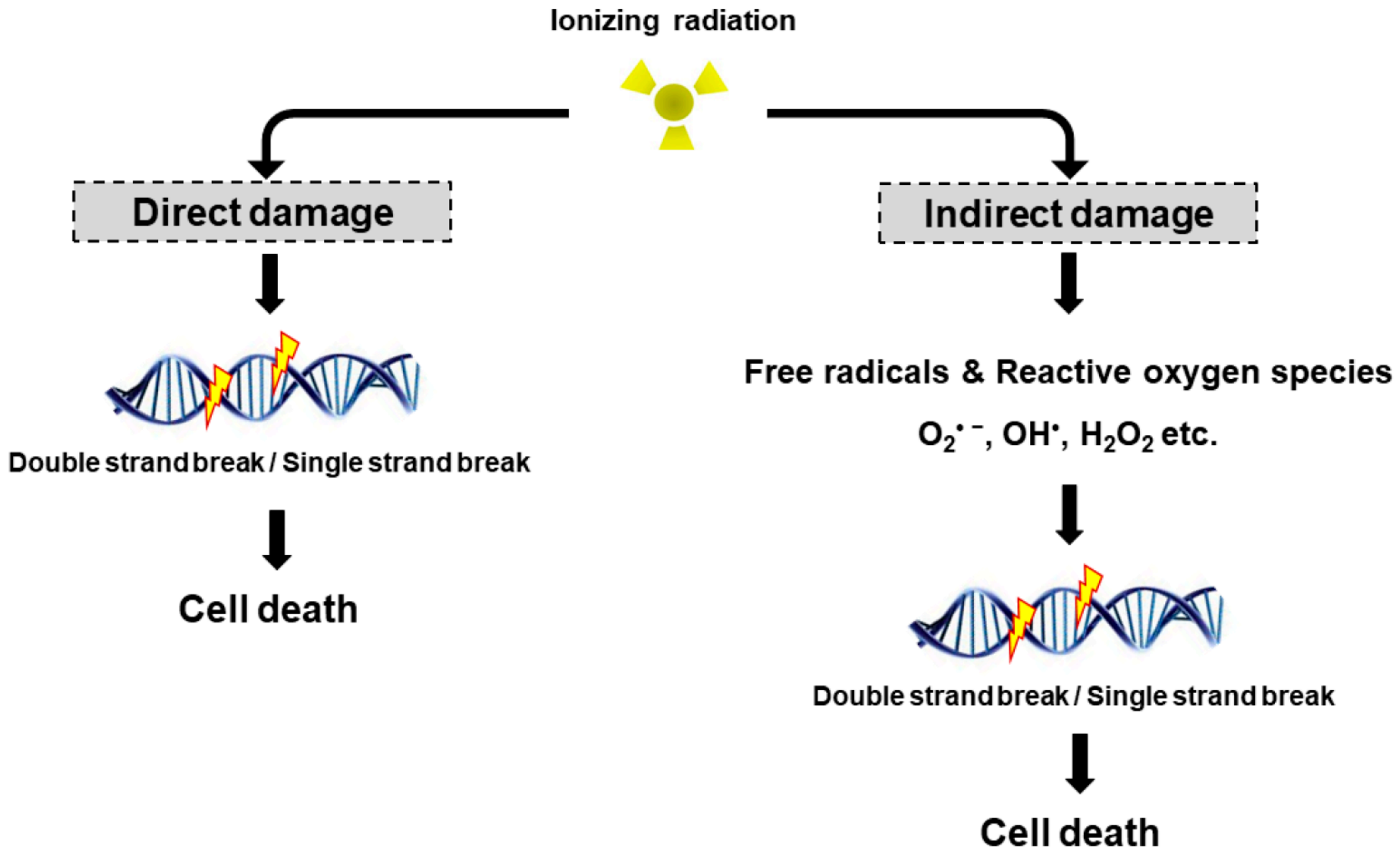
Doses de radiothérapie:

- Médiane: 29.2 Gys (10-54.4)
- Volume irradié?



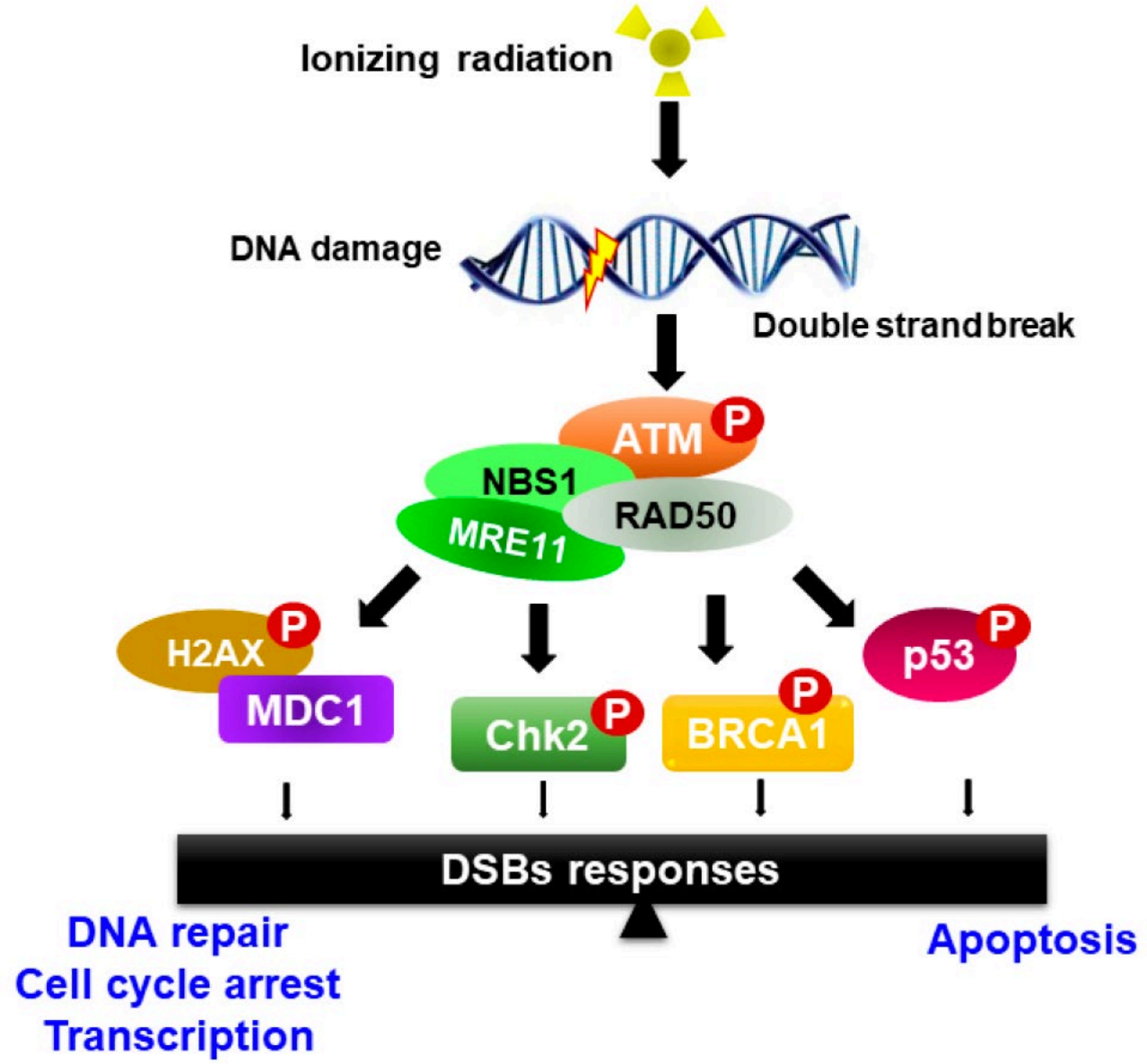
Inchaustegui et al., Cancers, 2023

Sarcomes en territoire irradié: physiopathologie



Hur *et al.*, International Journal of Molecular Sciences, 2017

Sarcomes en territoire irradié: physiopathologie



Hur *et al.*, International Journal of Molecular Sciences, 2017

Syndromes de prédisposition aux sarcomes

Inherited syndrome	Inheritance	Genes	Chief clinical features	Associated sarcomas
FAP	AD	*APC* at 5q21-22	Thousands of colonic adenomatous polyps with colon cancer at age <40 years, osteomas, hepatoblastomas	Desmoid tumors
Beckwith-Wiedemann	Sporadic/AD	*CDKAIC*, *KCNQ1OT1*, *LIT1*, *IGF2*, and *H19*	Overgrowth syndrome: macroglossia, omphalocele, hemihypertrophy, gigantism	Embryonal RMS
Bloom	AR	*RECQL3* on 15q26.1	Progeroid syndrome: growth retardation, sun sensitivity, telangiectasias, and other skin changes	Osteosarcoma, embryonal RMS
Carney-Stratakis	AD	*SDHB* at 1p36, *SDHC* at 1q21, *SDD* at 11q23	Dyad of paraganglioma and GIST	GIST
Constitutional mismatch repair syndrome	AR	*PSM2* at 7p/q22.1	Predisposition to hematologic malignancies, CNS tumors, gastrointestinal tumors and polyps, and other embryonic tumors	Embryonal RMS
Costello	AD	*HRAS* at 11q15 / 12p12.1	RASopathy: coarse facies, short stature, cardiac anomalies, developmental delay, and congenital myopathy	Embryonal RMS
Familial GIST	AD	*KIT*, *PDGFRA* at 4q12	Multifocal GISTs in setting of interstitial cells of Cajal hyperplasia	GIST
Familial pleuropulmonary blastoma (DICER 1 syndrome)	AD	*DICER1* at 14q23.13	Predisposition to pleuropulmonary blastomas and other dysplastic/malignant lesions	Embryonal RMS
Familial rhabdoid predisposition syndrome	AD	*SMARCB1/INI1* at 22q11.33	Renal or extrarenal malignant rhabdoid tumors, CNS tumors	Malignant rhabdoid tumor
Gorlin syndrome/nevoid basal cell carcinoma syndrome	AD	*PTCH* at Xp11.23 / 9q22	Multiple basal cell carcinomas, odontogenic keratocysts, palmar/plantar pits, calcification of the falx cerebri, rib abnormalities	Embryonal RMS
Hereditary retinoblastoma	AD	*RB1* at 13q14.2	Retinoblastoma, often bilateral and in early childhood (<5 years age)	Osteosarcomas, STS
HLRCC	AD	*FH* at 1q42	Cutaneous and uterine leiomyomas, type 2 papillary RCC	Uterine leiomyosarcoma
LFS	AD	*TP53* at 17p13.1, *CHEK2* at 22q12	Predisposition to early onset of multiple cancers, most commonly premenopausal breast cancer, STS, CNS tumors, osteosarcomas, adrenocortical carcinomas, and leukemias	Osteosarcomas, RMS, STS
Mosaic variegated aneuploidy	AR	*BUB1B* at15q15	Intrauterine growth restriction, microcephaly, predisposition to cancer (Wilms tumor, hematologic malignancies).	Embryonal RMS
Multiple osteochondromas	AD	*EXT1* at 8q24, *EXT2* at 11p11.	Multiple osteochondromas	Chonodrosarcomas
NF1	AD	*NF1* at 17q11.2	Café-au-lait spots, neurofibromas, iris harmartomas (Lisch nodules), optic gliomas, skeletal abnormalities	MPNST, GIST, RMS
Nijmegen breakage syndrome	AR	*NBS1* at 8q21.3	Chromosomal instability syndrome associated with microcephaly, growth retardation, immunodeficiency, and tumor predisposition	Embryonal RMS
Noonan syndrome	AD	*PTPN11* at 12q24, *SOS1* at 2-22	RASopathy associated with dysmorphic facies, short stature, neck webbing, cardiac anomalies, deafness, and bleeding diathesis	Embryonal RMS, giant cell tumor of bone, granular cell tumor, PVNS
Rothmund-Thomson syndrome II	AR	*REQL4* at 8q24.3	Characterized by poikiloderma, as musculoskeletal (short stature, radial defects, and hypoplastic patellae) and organ abnormalities (esophageal atresia, cataracts, and myelodysplasia)	Osteosarcoma
Rubinstein-Taybi	AD	*CREBBP* at 16p13.1	Multiple congenital anomalies, developmental delay, microcephaly, and dysmorphic features	Embryonal RMS, LMS
Tuberous sclerosis	AD	*TSC1* at 9q34, *TSC2* at 16p13.3, *TSC3* at 12q22-24.1	Hamartomas of multiple organs, angiomyolipomas, other renal tumors (cysts and RCCs), lymphangiomyomatosis, and angiofibromas	PEComa tumor (Pacoima), chordomas
Werner	AR	*WRN* at 8p11.2-12	Progeroid syndrome with tight atrophic skin and bird-like facies, early onset atherosclerosis, diabetes, and osteoporosis	Osteosarcoma, embryonal RMS

Abbreviations: AD, autosomal dominant; APC, adenomatous polyposis coli; AR, autosomal recessive; CNS, central nervous system; FAP, familial adenomatous polyposis; FH, fumarate hydratase; GIST, gastrointestinal stromal tumor; HLRCC, hereditary leiomyomatosis and renal cancer; LFS, Li-Fraumeni syndrome; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; NF1, neurofibromatosis type 1; PDGFRA, platelet-derived growth factor receptor A; PEComa, perivascular epithelioid cell tumor; PVNS, pigmented villonodular synovitis; RCC, renal cell carcinoma; RMS, rhabdomyosarcoma; STS, soft-tissue sarcoma; TSC1, tuberous sclerosis complex 1.

Farid M, Ngeow J. Sarcomas Associated With Genetic Cancer Predisposition Syndromes: A Review. Oncologist. 2016 Aug;21(8):1002-13.

Syndromes de prédisposition aux sarcomes

Dans le cadre de « syndromes »:

Rothmund-Thomson
Beckwith-Wiedmann
Maladies des RECQ hélicases
Osteochondromatose multiple
NF1
DICER1
…

Prédispositions génétiques aux sarcomes

Spécifiques à certains sous-types histologiques:

Syndrome de Carney
Syndrome de Gorlin
GIST familiale
Tumeurs rhabdoides
Sclérose tubéreuse de Tourneville
...

Syndrome de prédisposition aux cancers:

Syndrome de Li Fraumeni
Mutation de RB1
Autres: MMR, BRCA…

Syndromes de prédisposition aux sarcomes

Dans le cadre de « syndromes »:

Rothmund-Thomson
Beckwith-Wiedmann
Maladies des RECQ hélicases
Osteochondromatose multiple
NF1
DICER1
…

Prédispositions génétiques aux sarcomes

Spécifiques à certains sous-types histologiques:

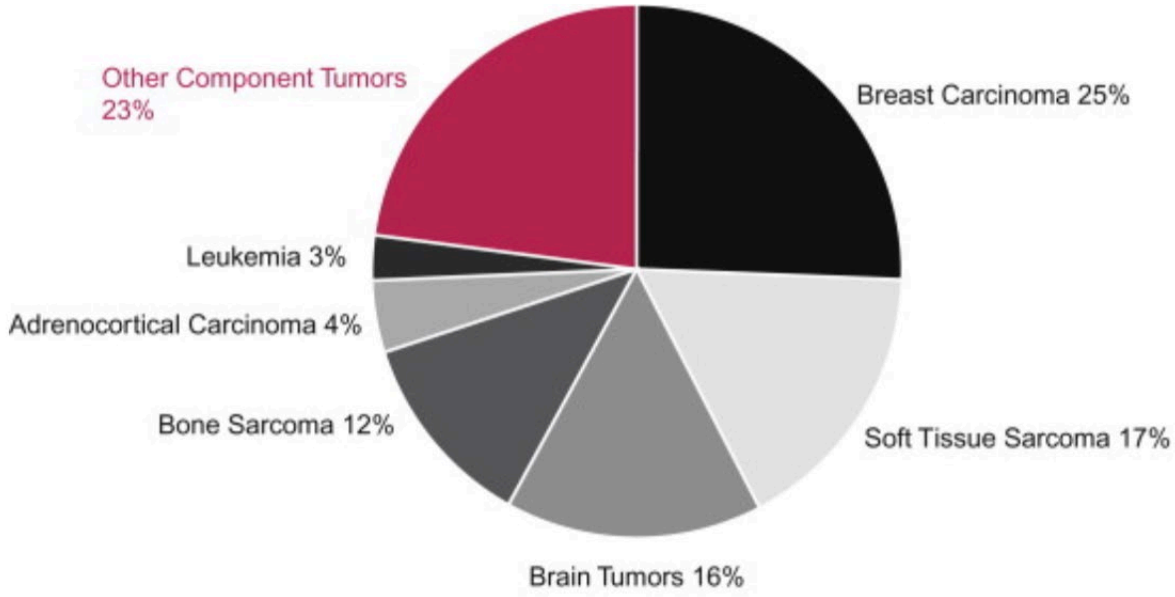
Syndrome de Carney
Syndrome de Gorlin
GIST familiale
Tumeurs rhabdoides
Sclérose tubéreuse de Tourneville
...

Syndrome de prédisposition aux cancers:

Syndrome de Li Fraumeni
Mutation de RB1
Autres: MMR, BRCA…

Syndrome de Li Fraumeni

- ❑ Mutation constitutionnelle de *TP53*
- ❑ Rare: prévalence estimée à 1/ 20 000
- ❑ Transmission autosomique dominante, 10% de mutation de novo
- ❑ Spectre tumoral large
  - Sarcomes
  - Leucémies
  - Tumeurs cérébrales,
  - Cancer du sein (souvent triple positif)
  - Corticosurrénalomes
  - Lymphomes
  - Cancer du poumon (souvent *EGFR* muté)
  - …



➔ Corrélation phénotype génotype partielle

- ❑ Critères cliniques d'indication de test

Syndrome de Li Fraumeni et sarcomes

Guidelines for the Li–Fraumeni and heritable *TP53*-related cancer syndromes

European Journal of Human Genetics

2020

Thierry Frebourg[1] · Svetlana Bajalica Lagercrantz[2] · Carla Oliveira[3] · Rita Magenheim[4] · D. Gareth Evans[5] · The European Reference Network GENTURIS

- ❑ **Sarcomes des tissus mous:** critères familiaux
- ❑ **Rhabdomyosarcomes embryonnaires +++**
- ❑ **Ostéosarcomes:**
  - Critères familiaux
  - ORL
- ❑ **En territoire irradié <46 ans**

All patients who meet the modified 'Chompret Criteria' should be tested for germline *TP53* variants:

- *Familial presentation*: proband with a *TP53* core tumour (breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumour, adrenocortical carcinoma) before 46 years AND at least one first- or second-degree relative with a core tumour before 56 years; *or*
- *Multiple primitive tumours*: proband with multiple tumours, including 2 *TP53* core tumours, the first of which occurred before 46 years, irrespective of family history; *or*
- *Rare tumours*: patient with adrenocortical carcinoma, choroid plexus carcinoma, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history; *or*
- *Very early-onset breast cancer*: Breast cancer before 31 years, irrespective of family history

Children and adolescents should be tested for germline *TP53* variants if presenting with:

- Hypodiploid acute lymphoblastic leukaemia (ALL); *or*
- Otherwise unexplained *sonic hedgehog*-driven medulloblastoma; *or*
- Jaw osteosarcoma

Patients who develop a second primary tumour, within the radiotherapy field of a first core *TP53* tumour which occurred before 46 years, should be tested for germline *TP53* variants

Syndrome de Li Fraumeni et sarcomes

❑ Pronostic des sarcomes avec un syndrome de Li Fraumeni

= identique que dans contexte sporadique

❑ Cohorte française:

✓ Ostéosarcomes de 1980 à 2019 avec un syndrome de Li Fraumeni. Saucier *et al*., Pediatr Blood Cancer, 2024

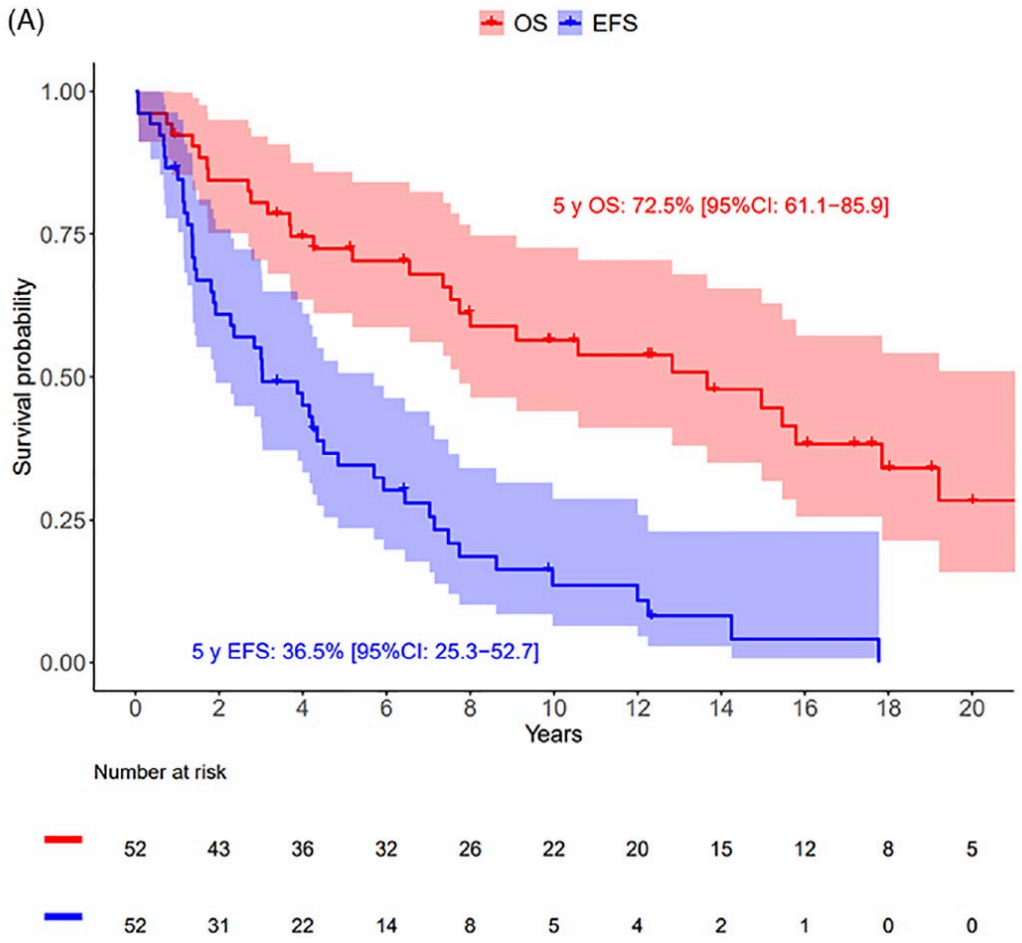
✓ 52 patients

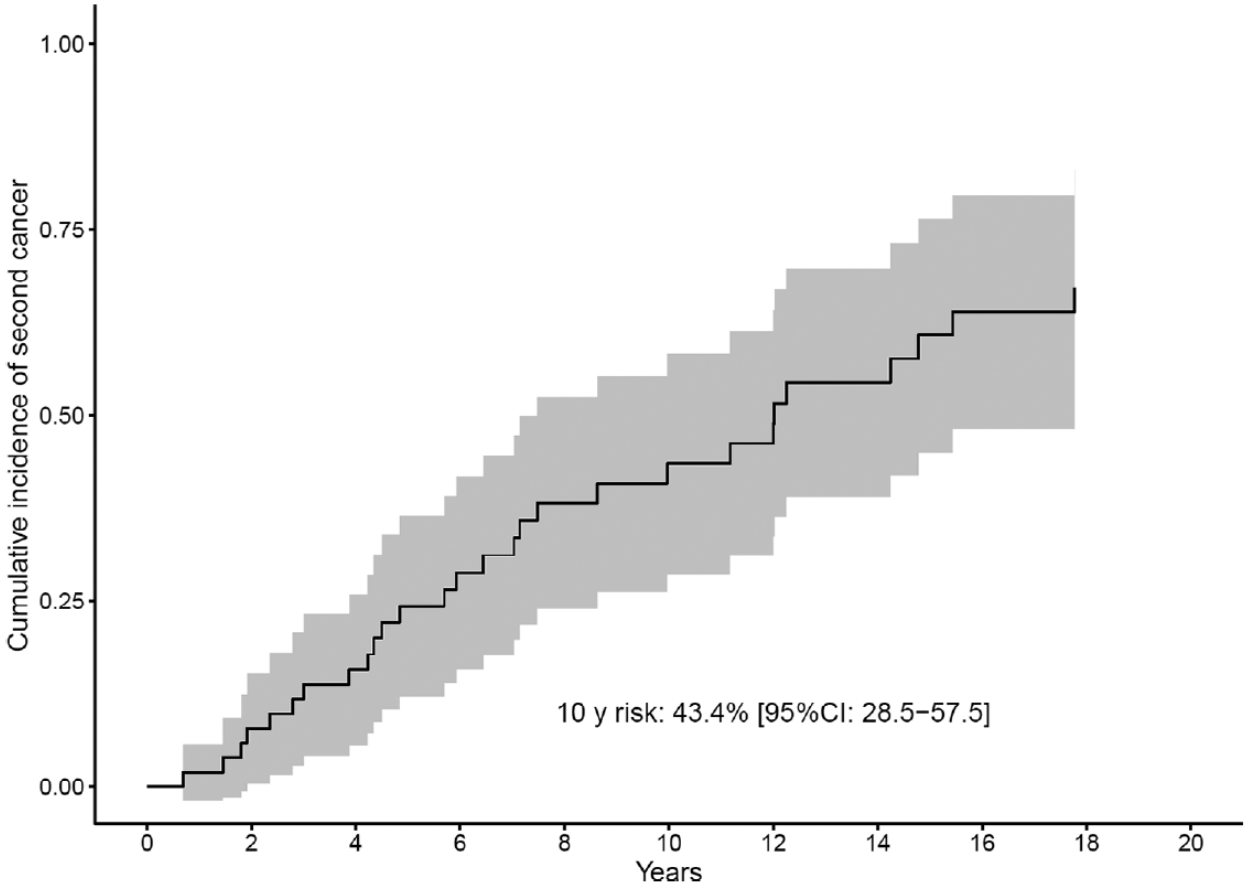
Saucier et al., Pediatr Blood Cancer, 2024

Syndrome de Li Fraumeni et sarcomes

	Present series		SEER data		
	Number of cases	%	Number of cases	%	
Age at diagnosis of the 1st osteosarcoma (years)					
<10	12	23	353	9	<.001
10–24	39	75	1973	47	
≥25	1	2	1855	44	
Histologic subtype[a]					
Conventional high-grade central osteoblastic or NOS	30	48	1757	69	<.001
Conventional high-grade chondroblastic	12	19	388	15	
High-grade surface	3	5	0		
Periosteal	11	18	27	1	
Secondary	6	10	NA	NA	
Tumor site[a]					
Limb	41	66	2243	87	<.001
Jaw	9	15	82[b]	3	
Axial	10	16	263	10	
Multifocal	2	3	NA	NA	
Presence of distant metastases					
Yes	15	25	489	21	.538
No	46		1805		

Saucier et al., Pediatr Blood Cancer, 2024





- ✓ Pronostic identique aux ostéosarcomes survenus dans un cadre sporadique
- ✓ Pronostic conditionné par la survenue de seconds cancers

Saucier et al., Pediatr Blood Cancer, 2024

Bone sarcomas and cancer predisposition syndromes

Camille Tlemsani [1,2], Gaëlle Bougeard [3], Marion Gauthier-Villars [4], Philippe Denizeau [5], Sarah Winter [6], Caroline Michot [7], Geneviève Baujat [7], Brigitte Bressac [8], Tiphaine Adam de Beaumais [9], Aymeric Rouchaud [10], Fadila Mihoubi-Bouvier [11], Franck Bourdeaut [6], Laurence Brugières [12], Thierry Leblanc [13], Edwige Kasper [3], Nadège Corradini [14], on behalf of GroupOs SFCE oncogenetic's groups

Recommandations françaises 2025:

✓ Groupe Sarcome Français

✓ SFCE

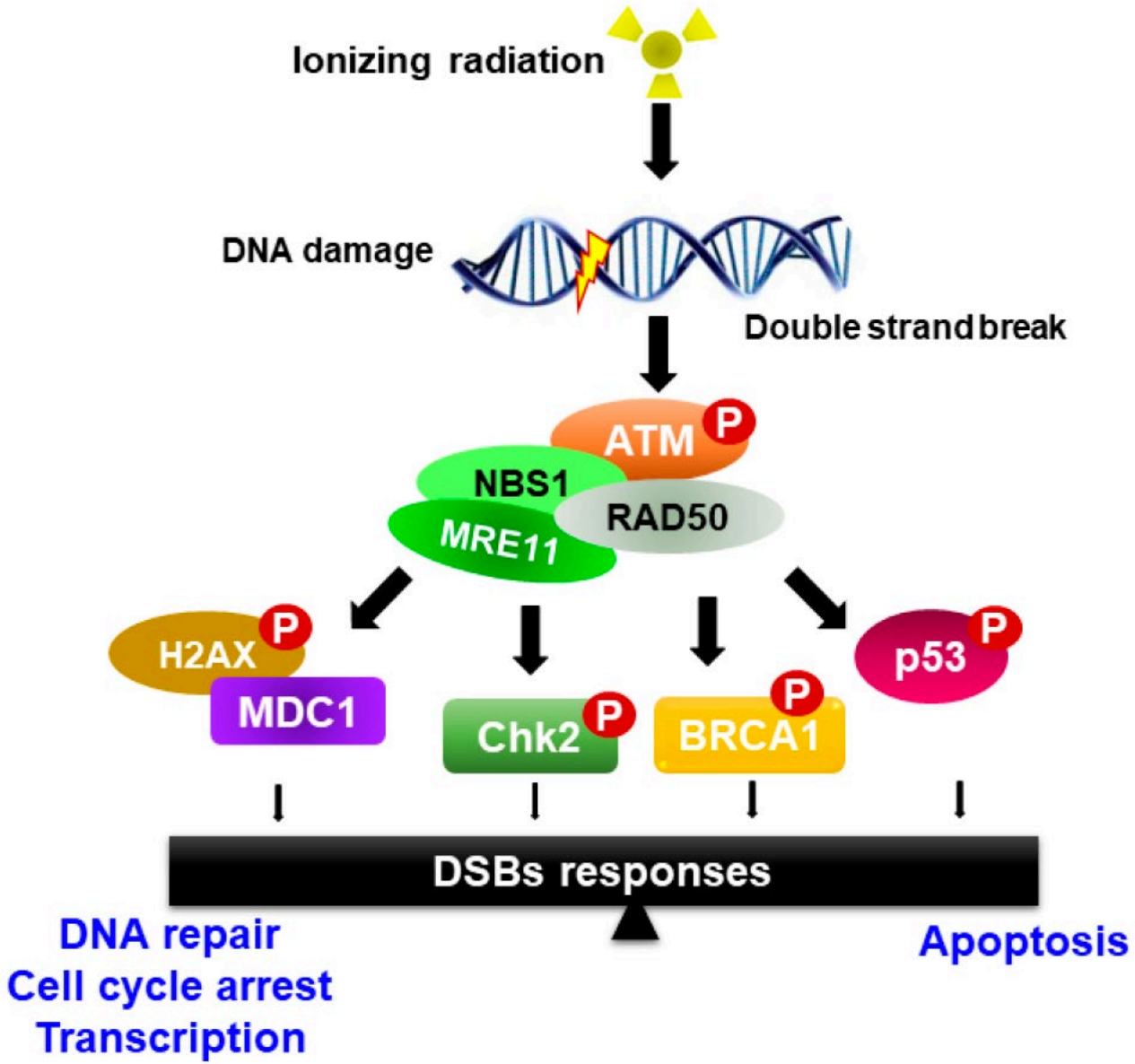
Bone sarcomas adapted updated Chompret criteria for Li-Fraumeni syndrome

Familial presentation	Proband with tumour belonging to LFS tumour spectrum < 46 years (e.g. premenopausal breast cancer, STS, OS, CNS tumour, ACC) AND at least one 1st or 2nd degree relative with LFS tumour (except breast cancer if proband has breast cancer) < 56 years or with multiple tumours
Multiple primitive tumours	Proband with multiple tumours (except multiple breast tumours), two of which belong to LFS tumour spectrum and first of which occurred < 46 years
	Patient who develop a second primary tumour within the radiotherapy field of a previous core LFS tumour which occurred < 46 years
Early-onset breast cancer	Breast cancer < 31 years of age
Rare tumours	Patient with ACC, Choroid Plexus Tumour, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history
Specific tumours in children & AYA	Hypodiploid ALL, unexplained *sonic hedgehog*-driven medulloblastoma
Osteosarcomas	OS < 13 years Jaw or axial OS Periosteal or high-grade chondroblastic OS (children and AYA) OS in context of Multiple Primitive Tumours OS in context of strict LFS criteria

ACC: adrenocortical carcinomas; ALL: acute lymphoblastic leukemia; AYA: adolescent and young adults; CNS: central nervous system; LFS: Li-Fraumeni Syndrome; OS: osteosarcoma; STS: soft-tissue sarcomas.

Tlemsani *et al.*, Bull Cancer, 2025

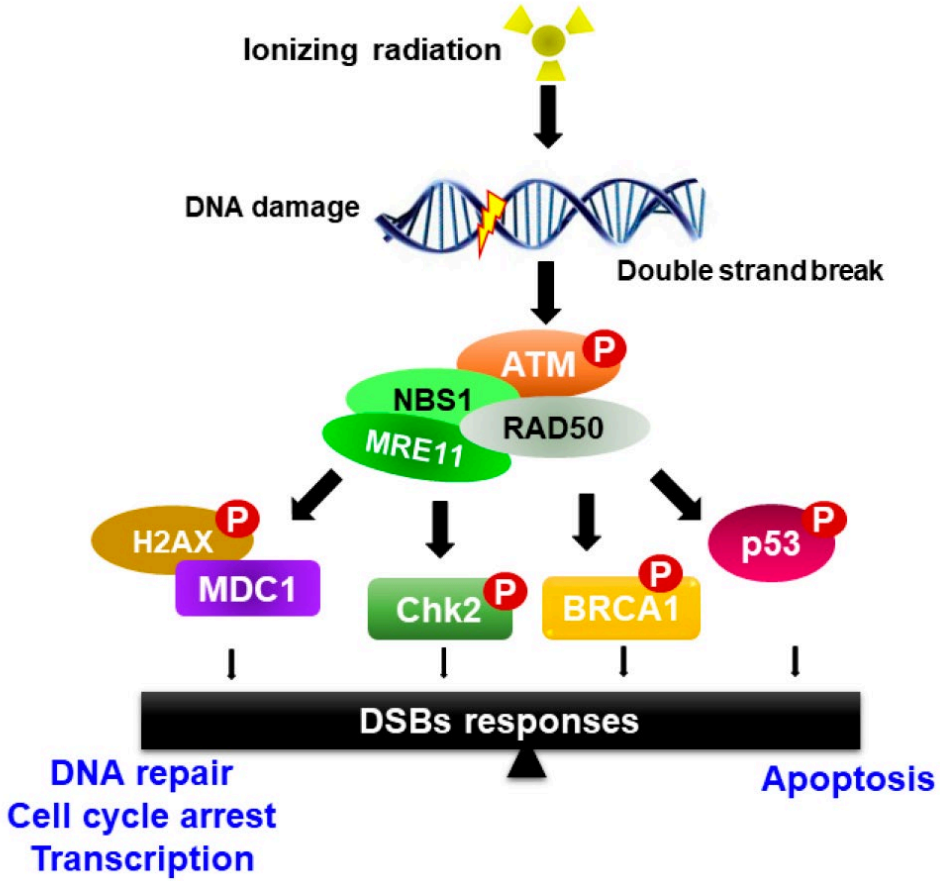
Sarcomes en territoire irradié: physiopathologie

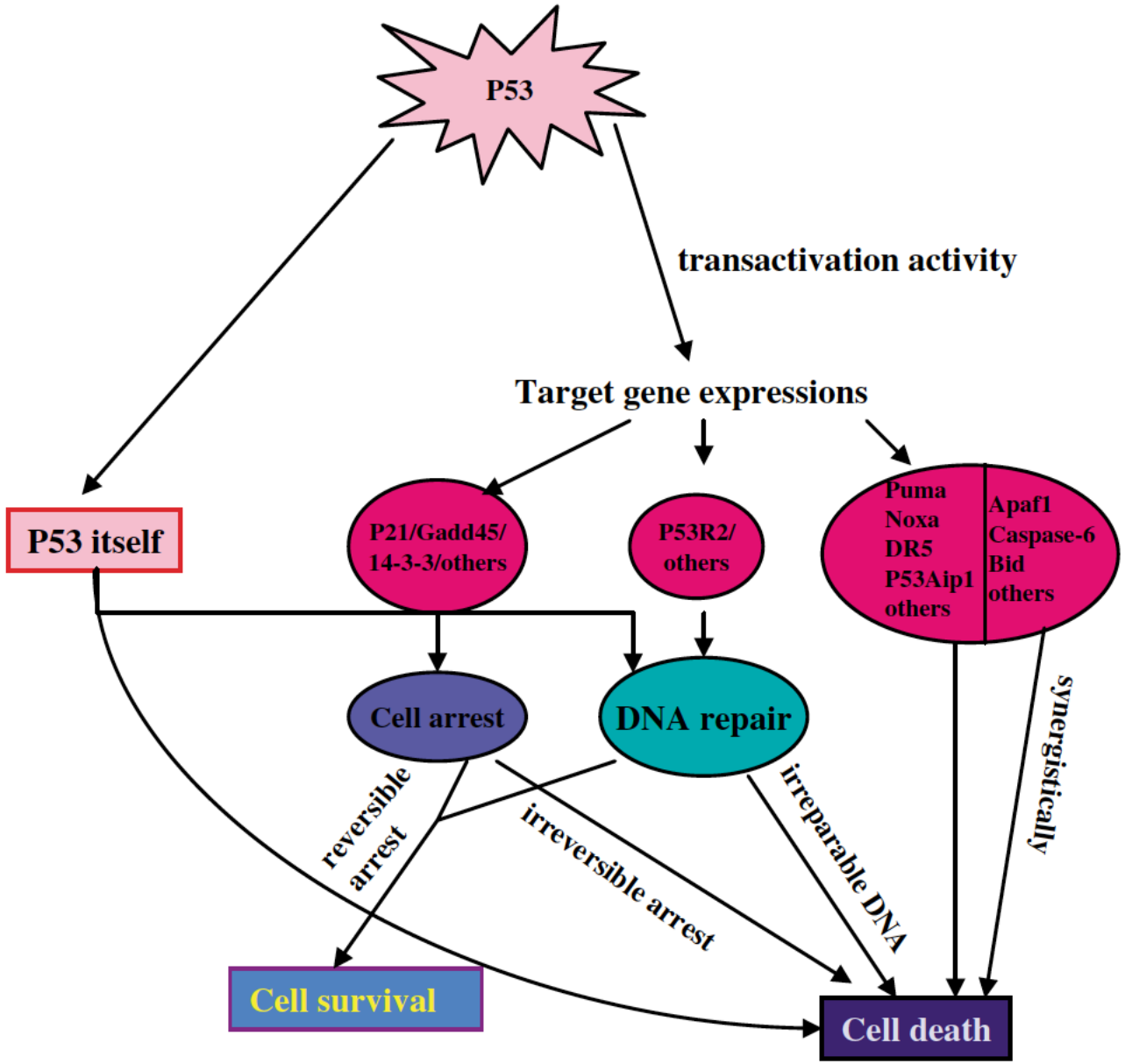


- Susceptibilité génétique aux cancers joue une rôle clé dans la réparation de l'ADN
- Quel est l'impact de la susceptibilité génétique sur le risque de développer un sarcome en territoire irradié?

Hur *et al.*, International Journal of Molecular Sciences, 2017

Rôle de p53





Fei *et al*., Oncogene, 2003
Hur *et al*., International Journal of Molecular Sciences, 2017

Sarcomes en territoire irradié et syndrome de Li Fraumeni

❑ Incidence difficile à évaluer

➔Petites séries: 10 à 70% de cancers en zone irradiée, en majorité des sarcomes

➔Délais plus courts ? < 5 ans

➔Pas de relation avec la dose reçue

➔Impact du type de radiothérapie et du fractionnement ?

❑ Recommandations : Lancet Oncol 2021

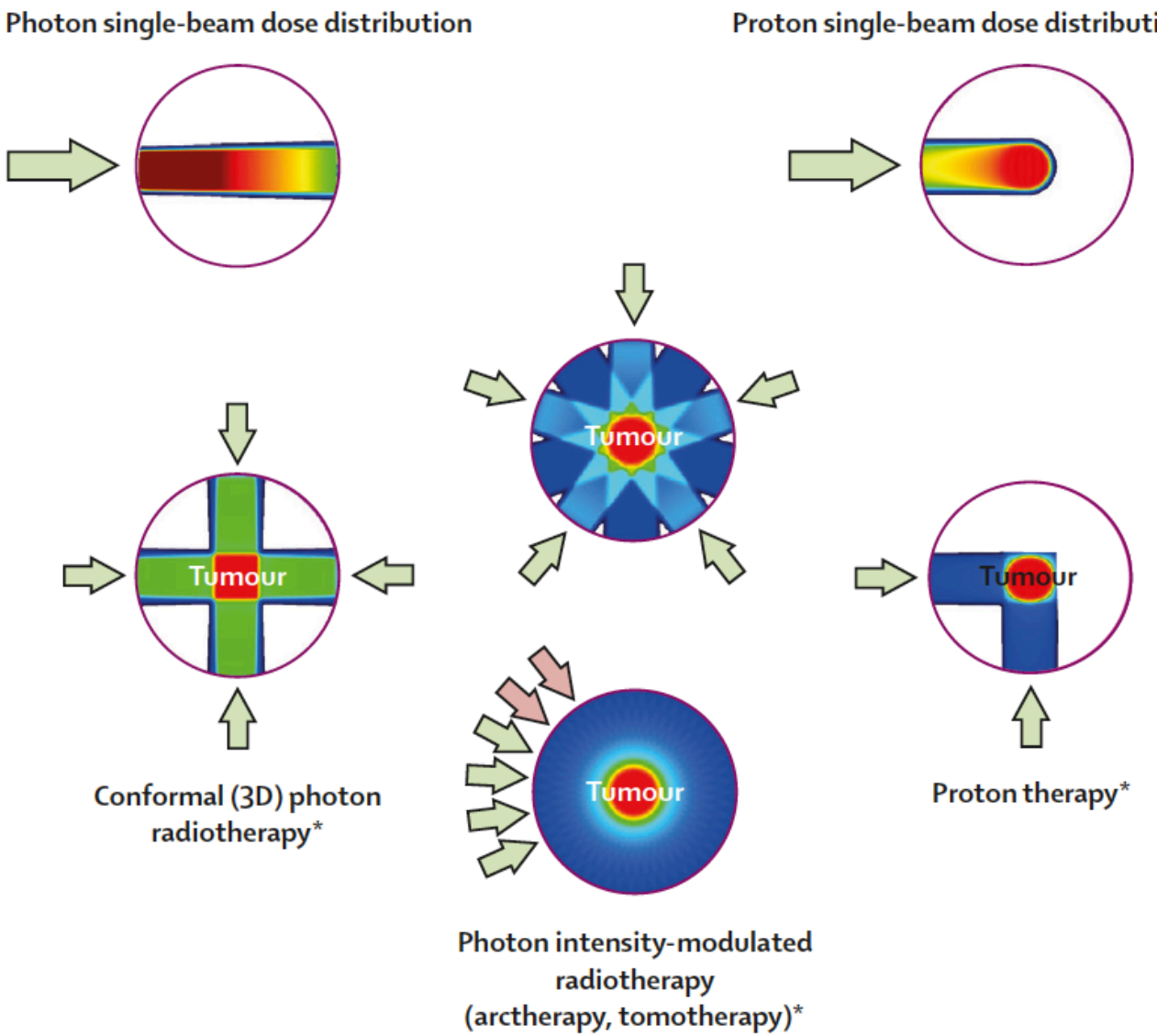
➔Eviter la radiothérapie: balance bénéfice- risque

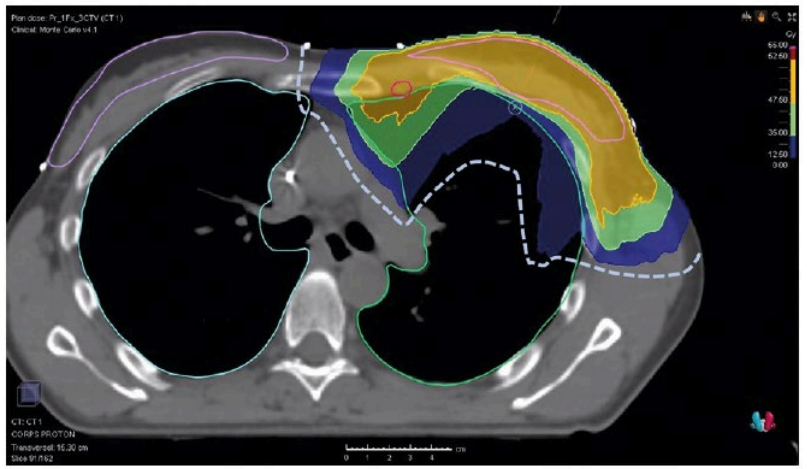
➔Technique de radiothérapie :

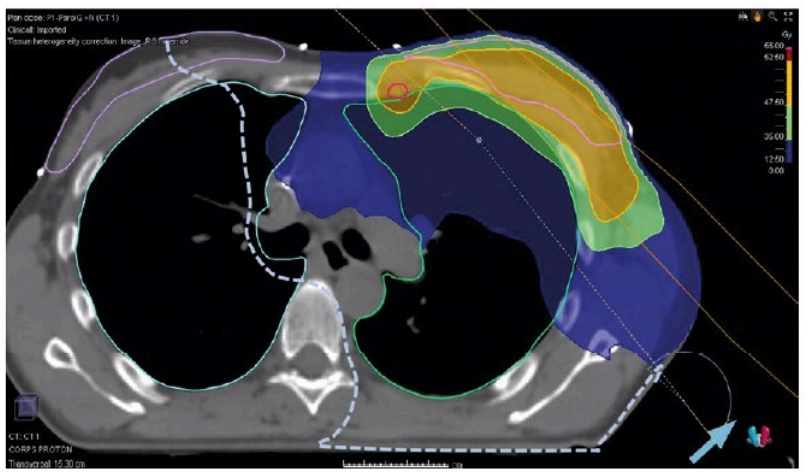
Privilégier protonthérapie

Limiter l'irradiation des tissus sains

Thariat *et al*., Lancet Oncol 2021







Thariat *et al*., Lancet Oncol 2021

Sarcomes en territoire irradié et syndrome de Li Fraumeni

❑ Incidence difficile à évaluer

➔Petites séries: 10 à 70% de cancers en zone irradiée, en majorité des sarcomes

➔Délais plus courts ? < 5 ans

➔Pas de relation avec la dose reçue

➔Impact du type de radiothérapie et du fractionnement ?

❑ Recommandations : Lancet Oncol 2021

➔Eviter la radiothérapie: balance bénéfice- risque

➔Technique de radiothérapie :

Privilégier protonthérapie

Limiter l'irradiation des tissus sains

RCP Nationale Li Fraumeni : 1x/mois

Coordination: Drs Bougeard, Corradini, Tlemsani

SecretariatRCPNLFS@lyon.unicancer.fr

Thariat *et al*., Lancet Oncol 2021

Risk of New Cancers After Radiotherapy in Long-Term Survivors of Retinoblastoma: An Extended Follow-Up

Ruth A. Kleinerman, Margaret A. Tucker, Robert E. Tarone, David H. Abramson, Johanna M. Seddon, Marilyn Stovall, Frederick P. Li, and Joseph F. Fraumeni Jr

VOLUME 23 · NUMBER 10 · APRIL 1 2005

JOURNAL OF CLINICAL ONCOLOGY

1601 pts

Table 4. Risk of New Cancers in 1-Year Survivors of Hereditary Rb by Radiation for Rb

Cancer Site (ICD-O classification)	Radiation (n = 849; person-years at risk, 21,706)* O	E	SIR*	95% CI	No Radiation (n = 114; person-years at risk, 3,602) O	E	SIR	95% CI
All sites†	241	11.2	22	19 to 24	19	2.77	6.9	4.1 to 11
Heavily irradiated sites (≥ 1 Gy)								
Bone (170)	73	0.18	406	318 to 511	2	0.03	69	8.4 to 250
Soft tissue (171, 192.4, 192.5)	33	0.23	140	96 to 196	1	0.04	23	0.6 to 131
Nasal cavities (160)	32	0.02	1,364	933 to 1925	0	0.01	0.0	0.0 to 688
Eye and orbit (190)	17	0.05	312	181 to 499	0	0.01	0.0	0.0 to 392
Brain, CNS (191, 192.0-192.3, 192.9)	10	0.62	16	7.7 to 29	0	0.11	0.0	0.0 to 33
Pineoblastoma (194.4)	5	0.05	104	34 to 244	0	0.01	0.0	0.0 to 509
Buccal cavity (140-149)‡	7	0.27	26	10 to 53	0	0.07	0.0	0.0 to 54
Thyroid (193)	2	0.50	4.0	0.5 to 15	0	0.11	0.0	0.0 to 35
Moderately irradiated sites (0.4-1.0 Gy)								
Female breast (174)	8	1.91	4.2	1.8 to 8.2	2	0.61	3.3	0.4 to 12
Cutaneous melanoma (173 and M872-878)	26	0.85	30	20 to 45	3	0.20	15	3.1 to 44
Lung (162)	2	0.63	3.2	0.4 to 11	3	0.21	14	3.0 to 42
Leukemia (204-207)	1	0.76	1.3	0.03 to 7.3	1	0.13	7.8	0.2 to 43
Hodgkin's lymphoma (M9650-67)	1	0.75	1.3	0.03 to 7.4	2	0.13	16	1.9 to 56
Lightly irradiated sites (< 0.4 Gy)								
Corpus uteri (182)	5	0.25	20	6.4 to 46	2	0.10	20	2.5 to 74
Colon (153)	3	0.37	8.1	1.7 to 24	0	0.11	0.0	0.0 to 34
Bladder (188, 189.9)	2	0.25	7.9	0.9 to 28	0	0.07	0.0	0.0 to 52
Excess absolute risk per 10,000 person-years			105.9				45.1	

Kleinerman *et al.*, JCO, 2005

original reports

Pathogenic Germline Mutations in DNA Repair Genes in Combination With Cancer Treatment Exposures and Risk of Subsequent Neoplasms Among Long-Term Survivors of Childhood Cancer

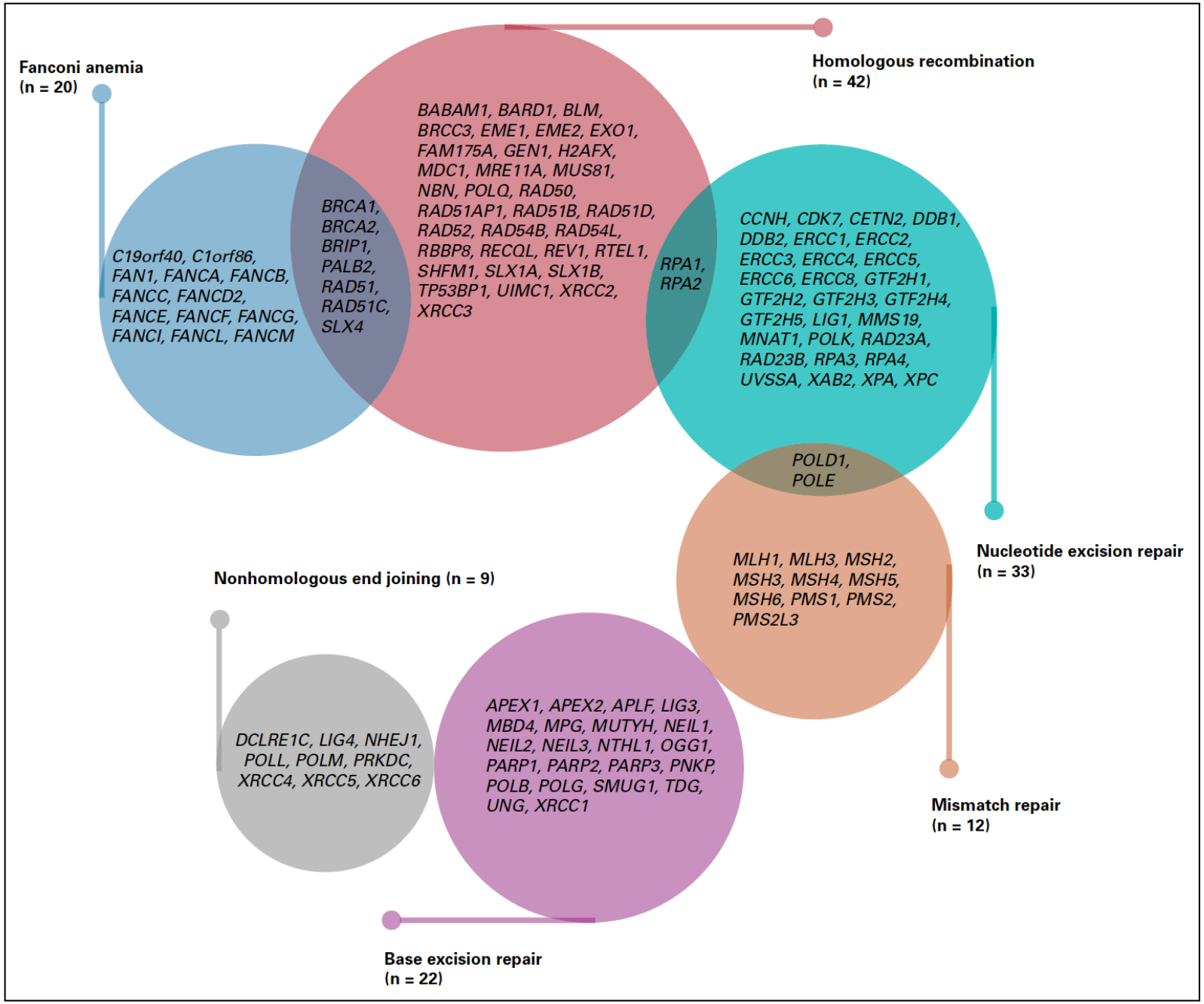
Na Qin, PhD, MD[1]; Zhaoming Wang, PhD[1,2]; Qi Liu, MSc[3]; Nan Song, PhD[1]; Carmen L. Wilson, PhD[1]; Matthew J. Ehrhardt, MD, MS[1,4]; Kyla Shelton, MPH[1]; John Easton, PhD[2]; Heather Mulder, BSc[2]; Dennis Kennetz, MSc[2]; Michael N. Edmonson, BA[2]; Michael C. Rusch, BA[2]; James R. Downing, MD[5]; Melissa M. Hudson, MD[1,4]; Kim E. Nichols, MD[4]; Jinghui Zhang, PhD[2]; Leslie L. Robison, PhD[1]; and Yutaka Yasui, PhD[1]

Journal of Clinical Oncology®

4,402 survivors:

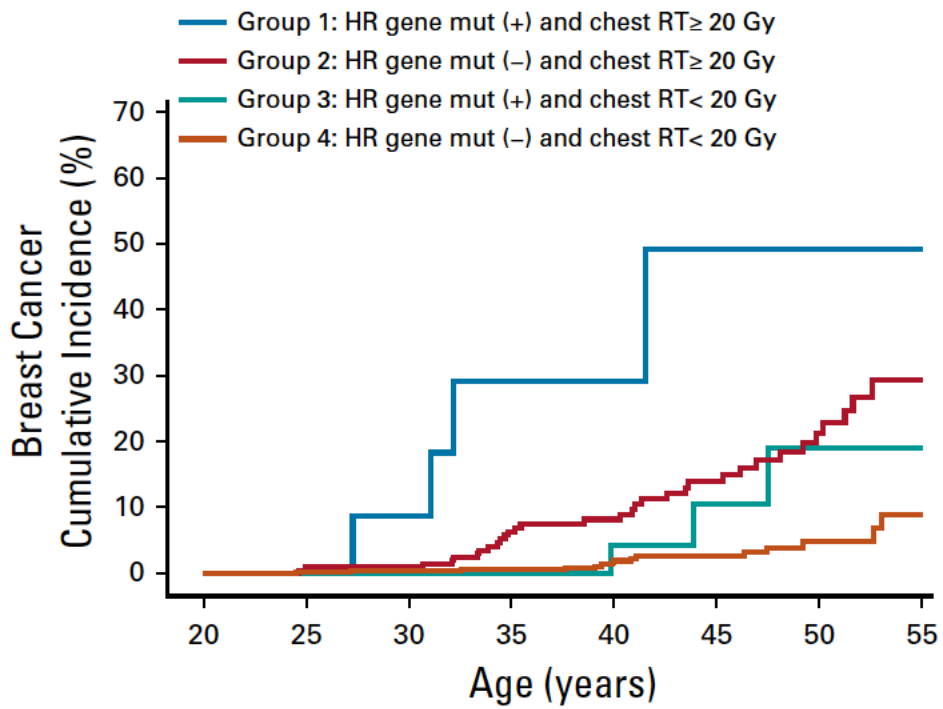
- ✓ 495 (11.2%) developed 1,269 subsequent neoplasms
- ✓ 508 (11.5%) survivors had germline mutations in DNA repair

Quin *et al*., Journal of Clinicla Oncology, 2020



Quin *et al*., Journal of Clinicla Oncology, 2020

A

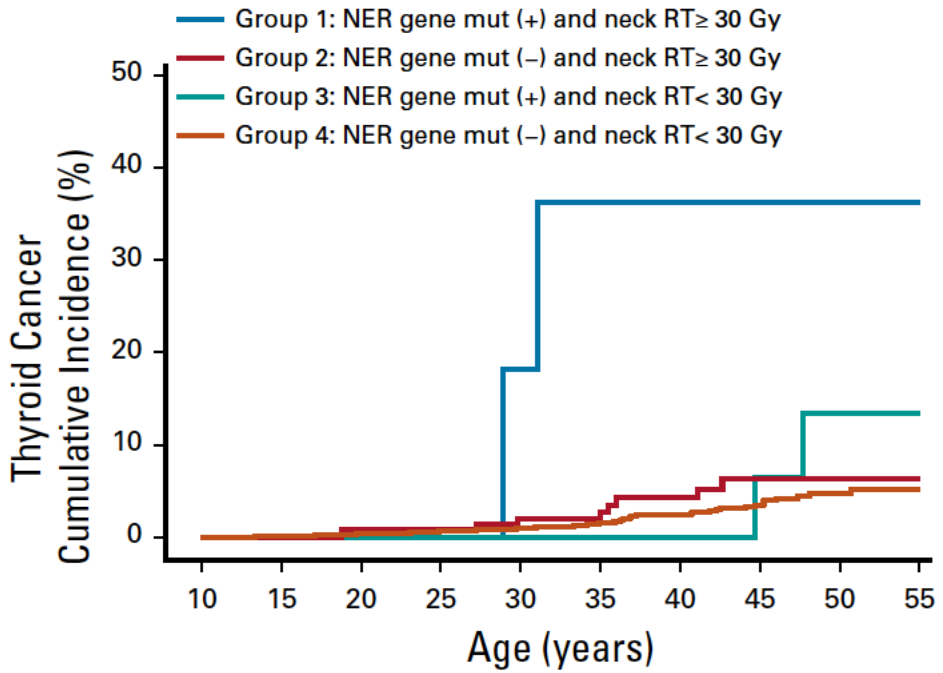


No. at risk:

Group 1	11	11	10	6	4	2	1	0
Group 2	133	218	206	165	127	86	52	17
Group 3	54	52	41	32	22	12	4	3
Group 4	1,139	1,064	811	559	333	181	78	30

Cancer du sein et radiothérapie

D

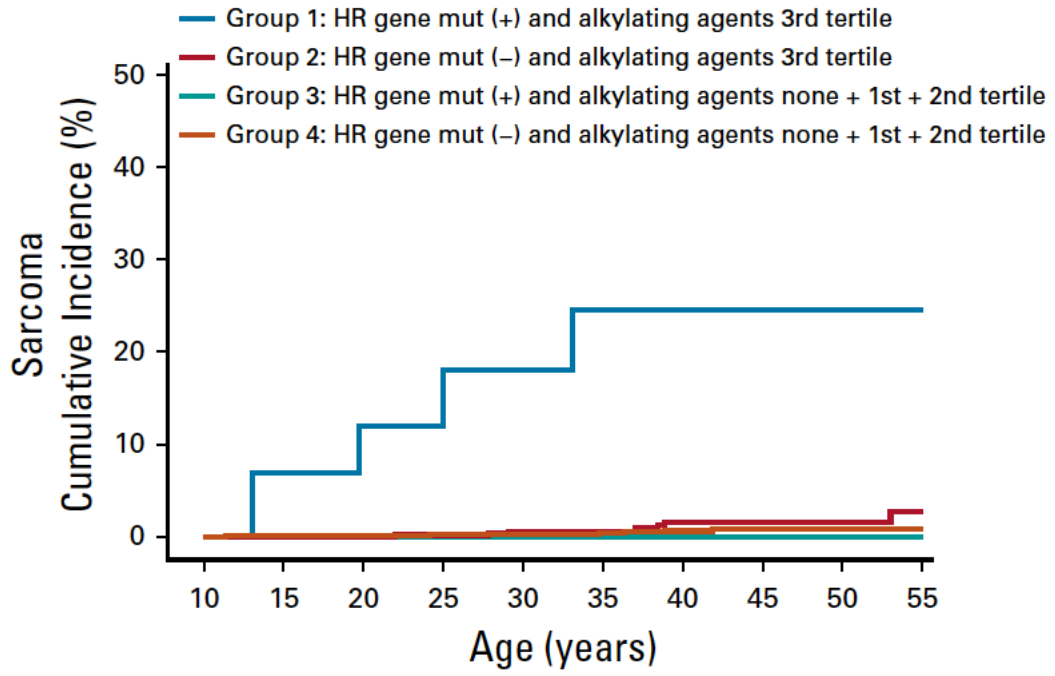


No. at risk:

Group 1	0	2	4	6	5	4	3	2	2	2
Group 2	26	82	158	204	182	145	120	85	60	30
Group 3	42	53	49	54	48	35	20	13	8	4
Group 4	1,593	2,112	2,505	2,543	2,003	1,412	889	510	245	85

Cancer de la thyroide et radiothérapie

Quin *et al*., Journal of Clinicla Oncology, 2020

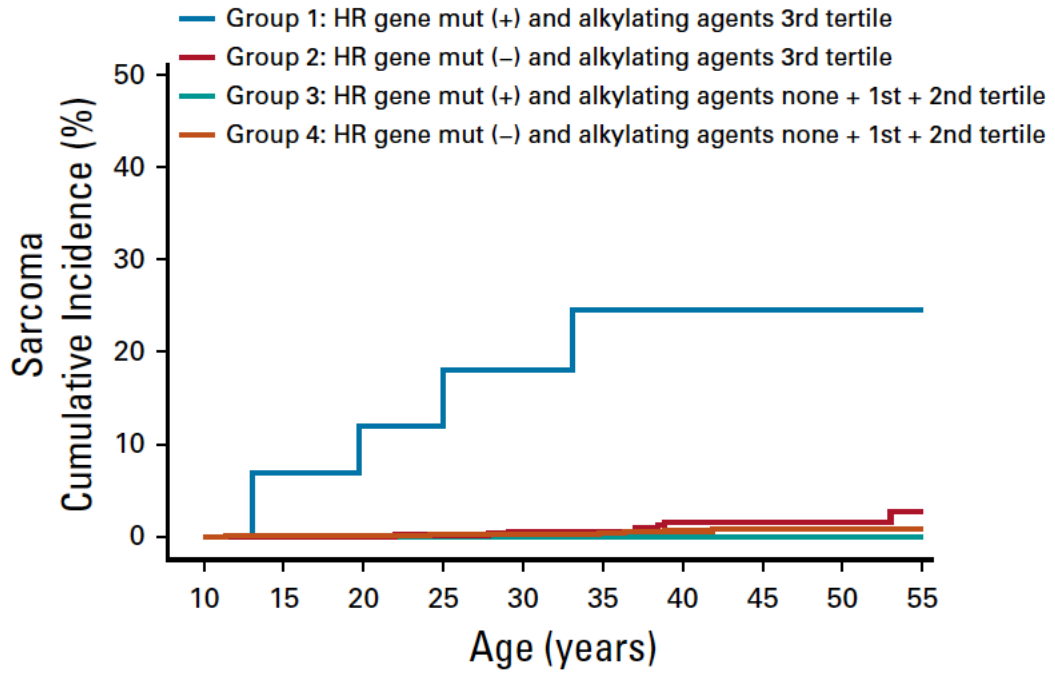


No. at risk:

Group 1	13	18	21	17	17	13	13	7	5	2
Group 2	285	420	524	560	450	351	272	202	124	4
Group 3	57	74	108	102	80	66	47	24	9	47
Group 4	1,420	1,893	2,200	2,246	1,740	1,191	728	395	188	77

Sarcomes et alkylant

Quin *et al*., Journal of Clinicla Oncology, 2020



No. at risk:

Group 1	13	18	21	17	17	13	13	7	5	2
Group 2	285	420	524	560	450	351	272	202	124	4
Group 3	57	74	108	102	80	66	47	24	9	47
Group 4	1,420	1,893	2,200	2,246	1,740	1,191	728	395	188	77

Sarcomes et alkylant

Peu de données dans la littérature et pas d'association claire entre sarcomes en territoire irradiée et prédispositions aux cancers impliquant gènes de la RH

Quin *et al*., Journal of Clinicla Oncology, 2020

Conclusions et perspectives

❑ Facteurs de risque de sarcomes:

- Prédispositions génétiques, en particulier syndrome de Li Fraumeni
- Exposition aux radiations ionisantes -> rare mais de mauvais pronostic

❑ Facteurs combinés?

Données dans le syndrome de Li Fraumeni

❑ Importance de la prévention, du dépistage et d'adapter la prise en charge des populations à risque

- Identifier les populations à risque
- Éviter les radiations: balance bénéfice risque
- Développement/Adaptation de nouvelles techniques d'irradiation
- Surveillance des patients

❑ Perspectives?

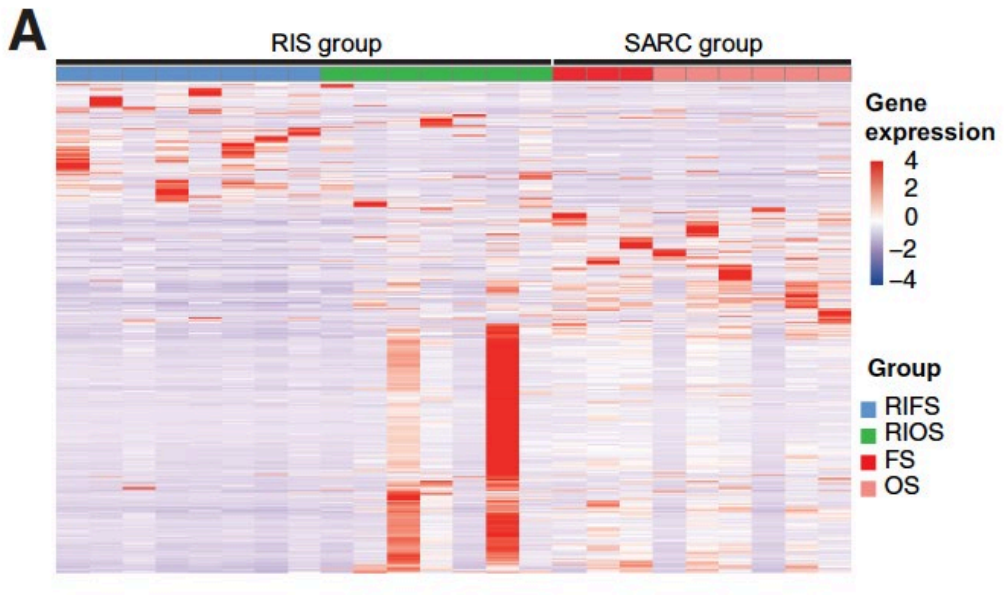
Connaitre les mécanismes physiopathologiques sous-jacents -> peu de données sur la biologie de ces tumeurs -> perspectives thérapeutiques

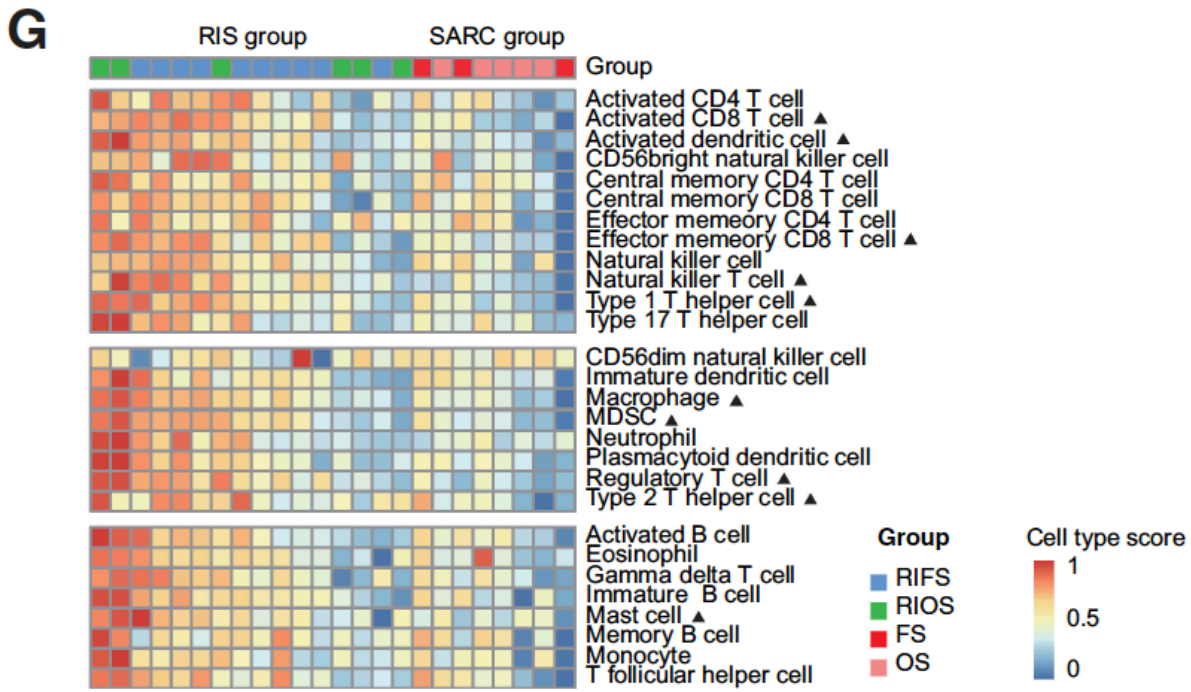
Genomic Profiling of Radiation-Induced Sarcomas Reveals the Immunologic Characteristics and Its Response to Immune Checkpoint Blockade

CLINICAL CANCER RESEARCH

2023

Dong-Chun Hong[1], Jing Yang[1], Cong Sun[2], Yuan-Tao Liu[2], Lu-Jun Shen[3], Bu-Shu Xu[1], Yi Que[4], Xiaojun Xia[5], and Xing Zhang[1]





Hong *et al*., Clinical Cancer Research, 2023

Efficacy and Safety of Immune Checkpoint Blockade in Patients With Li-Fraumeni Syndrome

JCO® Precision Oncology

2023

Michele Bottosso, MD[1,2]; Benjamin Verret, MD[1,3]; Olivier Caron, MD[4]; Nadim Hamzaoui, MD[5,6]; Eric Pasmant, PhD, PharmD[5,6]; Francois-Xavier Danlos, MD, PhD[7,8,9]; Pascaline Boudou-Rouquette, MD[5,10]; Arunya Srikaran, MD[10]; Hélène Blons, PhD, PharmD[11]; Valentina Guarneri, MD, PhD[2,12]; Sherene Loi, MD, PhD[13,14]; Fabrice André, MD, PhD[1,3]; and Camille Tlemsani, MD, PhD[5,10]

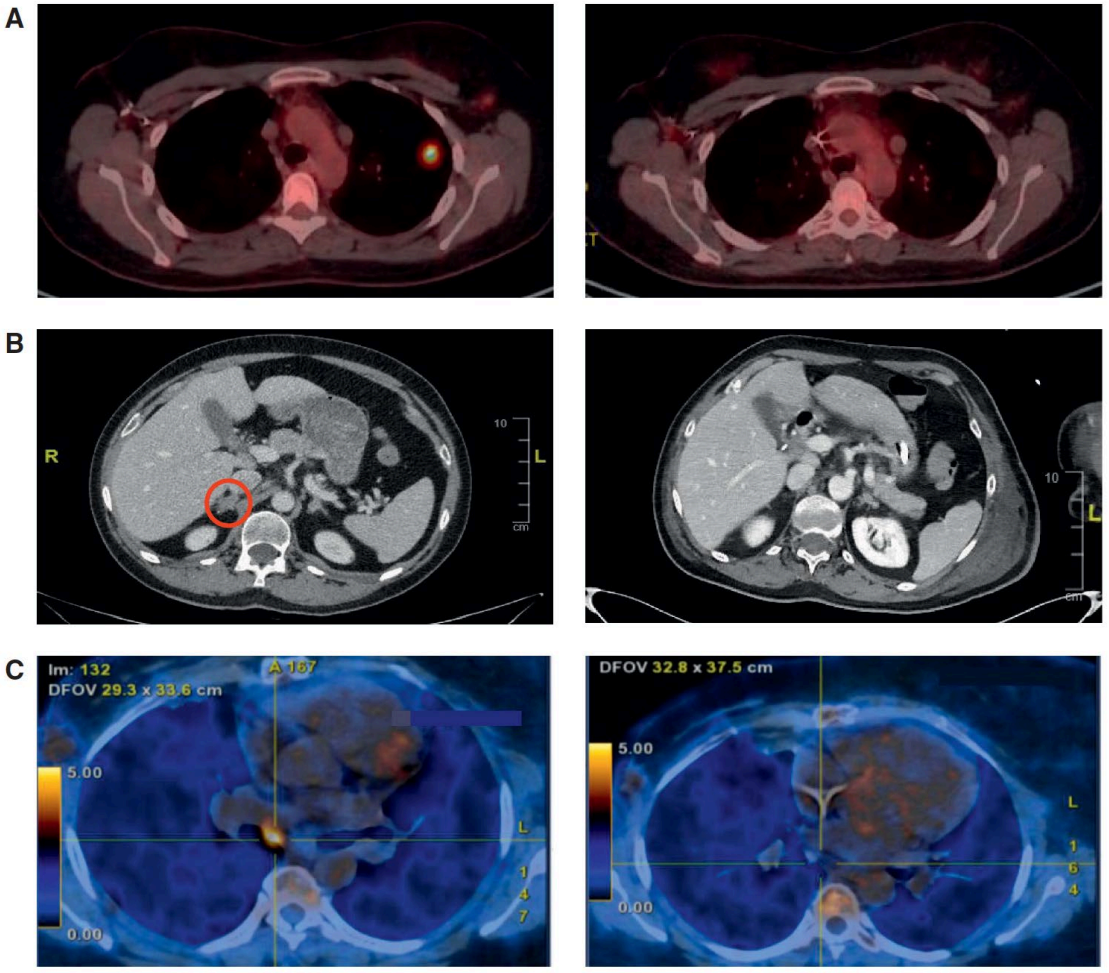


TABLE 1. Clinicopathologic and Molecular Features of Patients With Li-Fraumeni Syndrome–Related Cancer Treated With the Immune Checkpoint Blockade

Characteristics	Case 1	Case 2	Case 3
Tumor type	Triple-negative breast cancer	HER2+ breast cancer	*STK11* mutated NSCLC
Age at diagnosis, years	28	33	44
Type of *TP53* pathogenic variant	NM_000546.6 c.836G>A p.(Gly279Glu)	NM_000546.6 c.733G>A p.(Gly245Ser)	NM_000546.6 c.996C>G p.(Ile332Met)
Genomic alterations	*AKT2* amplification	NA	*STK11*, *SMARCA4*, *FANCD2*, *DAXX* mutations
TMB	2.5 mut/Mb	NA	7.8 mut/Mb
Line of treatment with ICB	First	Fifth	First
Metastatic sites	Lung	Adrenal gland and contralateral breast	Lymph nodes
Type of treatment	Paclitaxel + pembrolizumab	Trastuzumab + pembrolizumab	Pemetrexed + carboplatin + pembrolizumab
Immunotherapy duration	5 months	1 month	1 month
Toxicities	G3 rash G1 hypothyroidism	G5 Lambert-Eaton syndrome	G3 transaminase elevation G4 lichen planus pemphigoides
Best response	CR	CR on adrenal gland, PD on breast	CR
Duration of response	18 months	4 months (fatal toxic event)	10 months

Botosso *et al.*, JCO precision oncology, 2024

Des questions?

camille.tlemsani@aphp.fr