Radiotherapy Concerns in TP53 Mutant Breast Cancer

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LFS: **Li-Fraumeni syndrome**

- Whom
  - to be concerned about LFS in breast cancer patients?
- What
  - is the characteristics of breast cancer in LFS?
- How
  - to manage breast cancer in LFS?
    - **Should RT be avoided?**
    - What happens if RT being done in LFS?
      - RAS

Soft-Tissue Sarcomas, Breast Cancer, and Other Neoplasms

A Familial Syndrome?

FREDERICK P. LI, M.D., and JOSEPH F. FRAUMENI, JR., M.D., F.A.C.P.
Bethesda, Maryland

SUMMARY **Four families were identified in which a pair of children had soft-tissue sarcomas: three sets of sibs and one set of cousins. One parent of each affected child developed cancer; carcinoma of the breast occurred in three mothers under 30 years of age. Other young adults in these families had a high frequency of cancer, with no evidence of underlying genetic disorders known to carry a high risk of neoplasia. The increased familial susceptibility to cancer was manifested not only by the large number of members affected but by a seeming excess of multiple primary neoplasms. These findings suggest a new "familial" syndrome of neoplastic diseases in which heredity or oncogenic agents, or both, may have a causal role.**

Family D was identified from the childhood cancer mortality registry described by Miller (8). When the records of the 418 children who died of rhabdomyosarcoma in the United States from 1960 through 1964 were matched by the child's last name and mother's maiden name, 1 sib pair was found. This family was not contacted, and further data were derived solely from hospital charts.

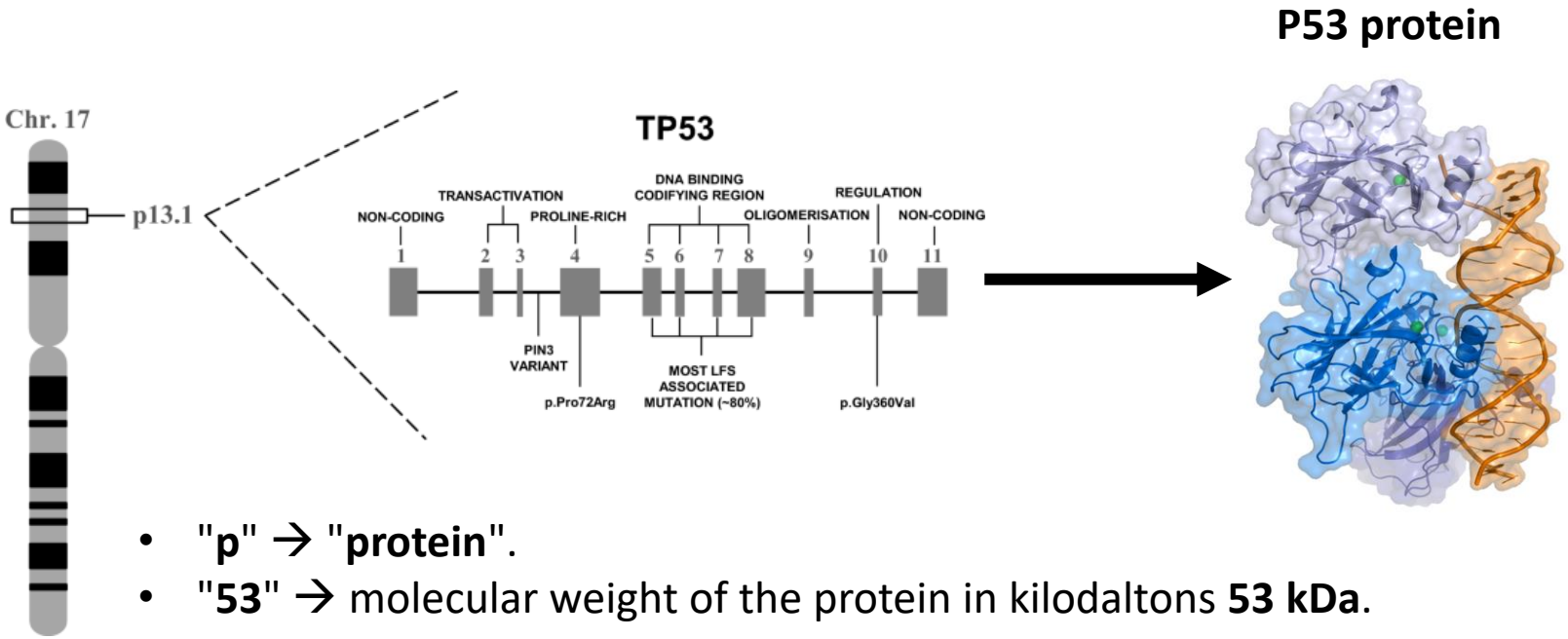
Efforts were made to confirm all reports of cancer by obtaining medical and mortality records and, whenever possible, by review of pathology specimens.

FINDINGS

Frederick Li and Joseph Fraumeni, 1991

The first observations were described **by Li and Fraumeni** in **1969**

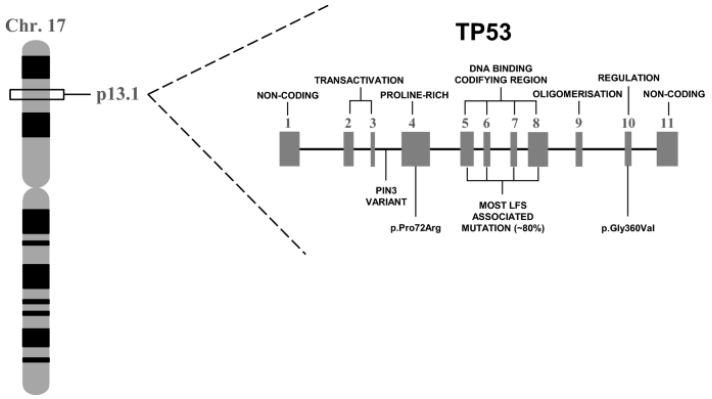
TP53



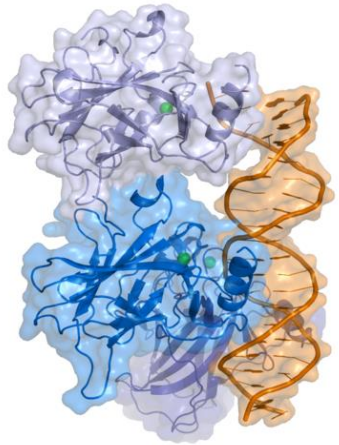
P53 protein

- "**p**" → "**protein**".
- "**53**" → molecular weight of the protein in kilodaltons **53 kDa**.

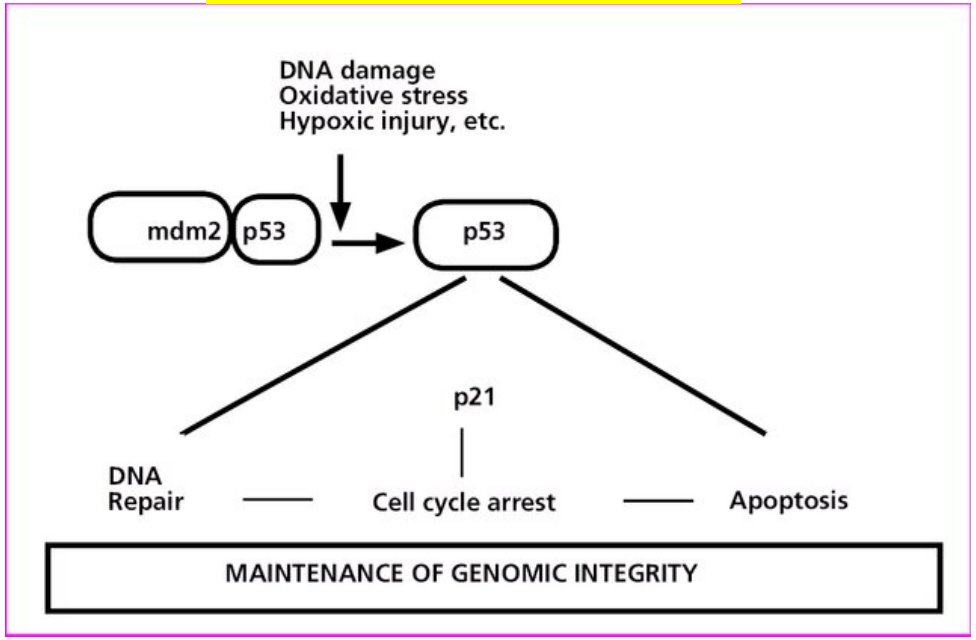
TP53



P53 protein



Guardian of the genome



Li-Fraumeni syndrome

- **Autosomal dominant disorder**
  - Mutation in p53 gene lead to
    - Mutant protein (90%)
    - The absence of protein expression (10%)

- **In the absence of the normal activated p53 protein**
  - Cells containing damaged DNA
    - Survive
    - Proliferate
    - Malignant transformation.

Li-Fraumeni syndrome (LFS)

- **Early age at onset** → 50% risk < 30 years in TP53 mutation carriers

- **Multiple cancers**
  - Sarcoma
  - **Breast**
  - Brain tumors
  - Adrenocortical carcinomas
  - Other cancers

→

The most common malignancy in LFS
The lifetime risk is estimated to be 90%.
~~Male breast cancer~~

- **Lifetime risk of cancer** → 80–90%

DIFFERENTIAL DIAGNOSIS

- **BRCA1 and BRCA2 pathogenic variants**
  - Premenopausal breast and ovarian cancer
  - Pancreatic cancer, melanoma, and prostate cancer
- **Mismatch repair cancer (Lynch) syndrome**
  - Leukemia, brain tumors, and intestinal cancer

The risk of contralateral breast cancer in TP53 carriers diagnosed at less than 35 years of age is approximately 4 to 7 percent annually, around twice that in BRCA carriers

TABLE 59.2 GENES ASSOCIATED WITH HEREDITARY BREAST CANCER

Gene/Syndrome	Approximate Relative Breast Cancer Risk
BRCA1/BRCA2	10–20 times relative risk
P53-Li-Fraumeni	2–6 times relative risk
PTEN Cowden	2–4 times risk
STK11 Peutz-Jeghers	10–15 times risk
ATM (ataxia–telangiectasia)	3–4 times risk
CHEK2	2 times risk
BRIP1–Fanconi anemia	2 times risk
PALB2	2–3 times risk

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    - What happens if RT being done in LFS?
      - RAS

DIAGNOSTIC CRITERIA

- **Classical Li-Fraumeni syndrome**
- Chompret criteria
- Li-Fraumeni-like syndrome

Classic Li-Fraumeni syndrome[1] - Diagnostic criteria

All of the following:
• A proband with sarcoma diagnosed before age 45 years
• A first-degree relative with any cancer before age 45 years
• A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age

Patients at high risk for Li-Fraumeni syndrome

Table 1. Chompret criteria for germline *TP53* mutation screening

Chompret Criteria
Family cancer history
A proband with tumor belonging to the LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) under the age of 46 years AND at least one first- or second-degree relative with an LFS tumor (except breast cancer if proband has breast cancer) under the age of 56 years or with multiple tumors
OR
Multiple tumors
A proband with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum and the first of which occurred under the age of 46 years
OR
Rare cancers
Patients with adrenocortical cancer, choroid plexus cancer, and anaplastic rhabdomyosarcoma, irrespective of family history
OR
Juvenile breast cancer
Breast cancer patients aged ≤ 31 years

LFS — Li-Fraumeni syndrome

Whom to test for TP53 pathogenic variants?

- Females with early onset breast cancer
  1. **< 31 years**
  2. **Without BRCA1/2 mutation**
     - Possibly those with HER2+ breast cancer up to age 35 years
     - The index of suspicion for Li-Fraumeni syndrome is increased if there is a family history of sarcoma, brain tumor, or adrenocortical carcinoma

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Patients with a TP53 variant identified on **tumor-only genomic** testing: If they were diagnosed with cancer <30 years of age or have a clinical scenario concerning for a germline mutation.

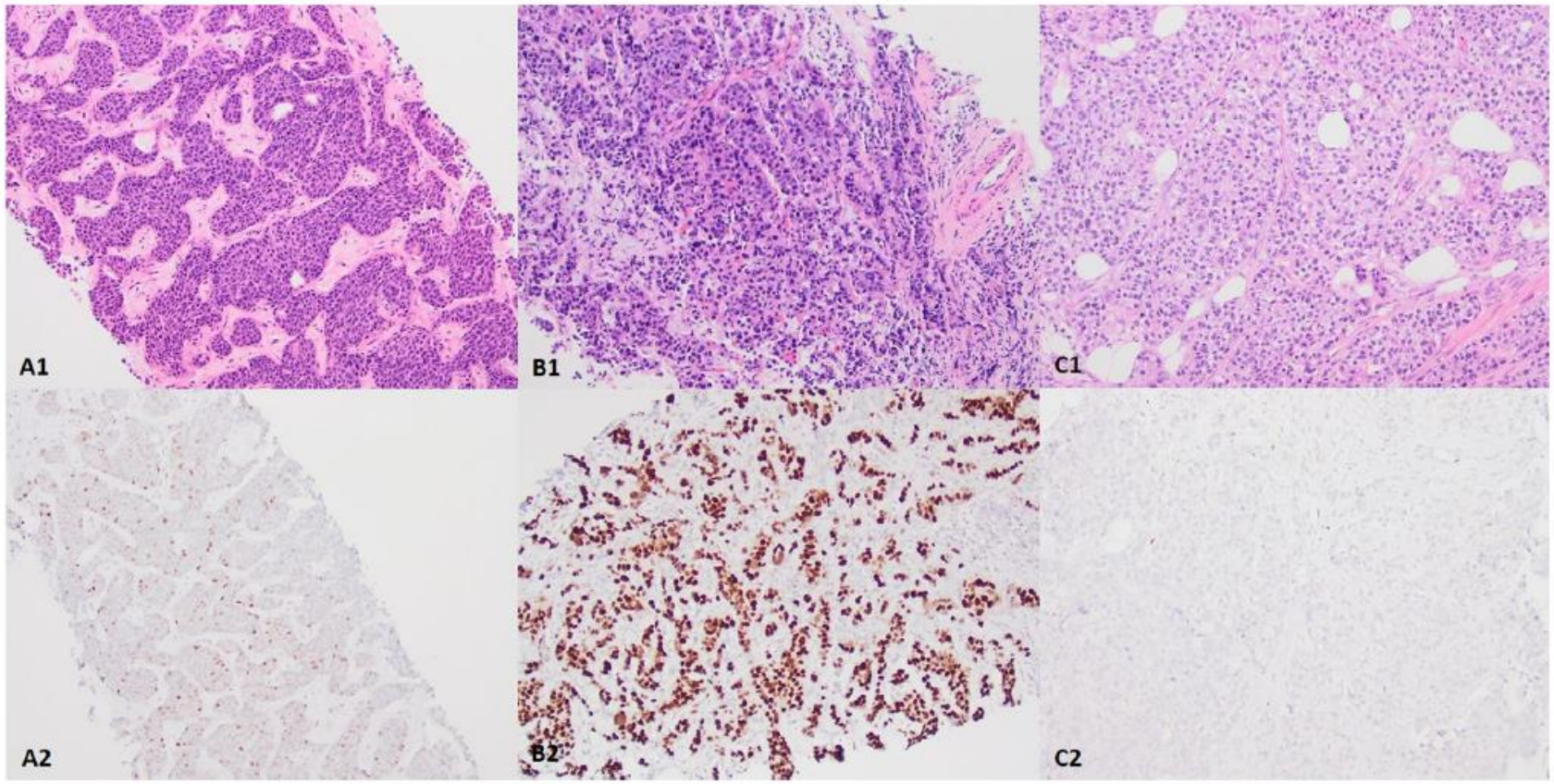

Fig. 2 Representative cases showing patterns of p53 immunohistochemical staining. **A** wild-type pattern. **B** overexpression pattern. **C** null pattern. A1-C1, H&E staining (×100). A2-C2, p53 IHC staining (×100)

p53 protein expression patterns associated with *TP53* mutations in breast carcinoma

Sarah A. Anderson[1] · Brooke B. Bartow[1] · Shuko Harada[1] · Gene P. Siegal[1] · Shi Wei[1] · Valeria L. Dal Zotto[1] · Xiao Huang[1]

Received: 13 March 2024 / Accepted: 24 April 2024 / Published online: 20 June 2024

Conclusion

This study suggests that a p53 IHC assay, with appropriate interpretation, can predict *TP53* mutation status in a large subset of breast carcinomas. Further, a p53 null pattern is associated with a truncating mutation in the *TP53* gene and signals worse pathologic features, compared to cases with an overexpression pattern. For the cases with an equivocal p53 IHC expression, further validation studies are required.

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Li-Fraumeni associated breast cancer

- Premenopausal breast cancer.
  - Median age: 34 year
  - In a population-based series of breast cancer in those <31 years of age, 6 of 115 patients **(5 percent)** had TP53 pathogenic variants [31].

- More likely to have amplification of HER2
  - In a series of 12 cancers in nine young females, 10 were positive for HER2 **(83 percent)**, whereas only 16 percent of a control group of 231 breast cancers in young females without the TP53 pathogenic variant were positive for HER2.

- There was no difference in the frequency of ER and PR positivity (?)

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    - **Should RT be avoided?**
    - What happens if RT being done in LFS?
      - **RAS**

MANAGEMENT

- Cancer surveillance strategy
- Cancer management

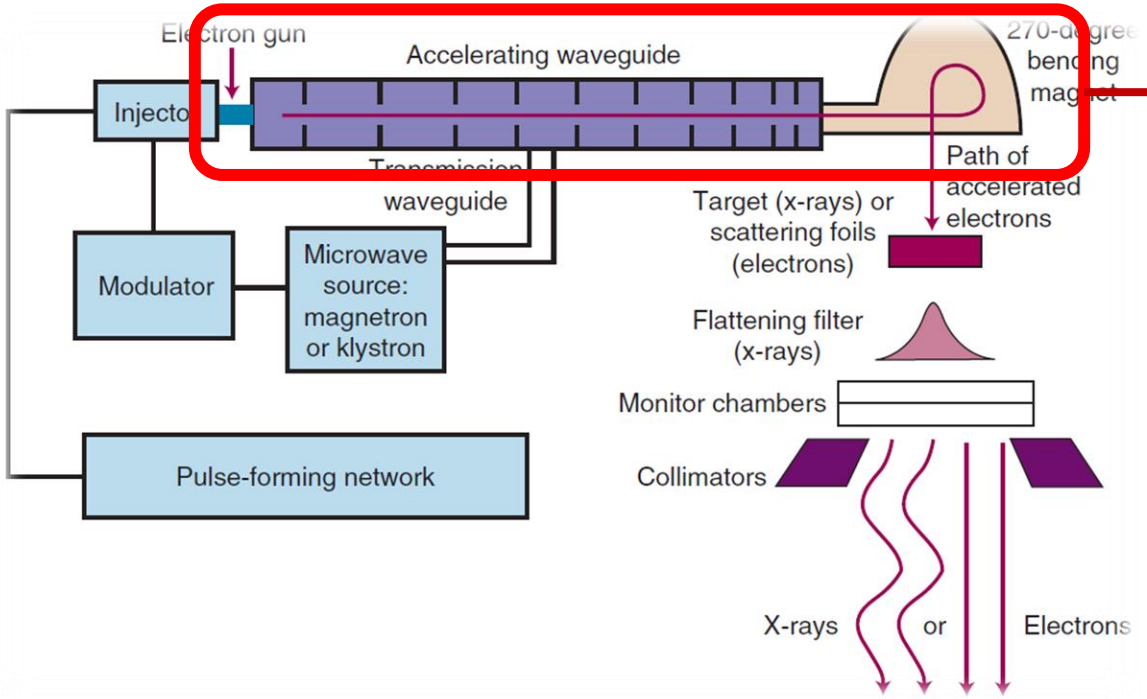
Exam	Periodicity	Age to start	Age to end	Select clinical indications
Whole-body MRI without gadolinium enhancement	Annual	Birth	Indefinite	High cancer risk *TP53* variant* or patient previously treated by chemotherapy or radiotherapy
		18 years	Indefinite	
Breast MRI	Annual	20 years	65 years	
Brain MRI¶	Annual	Birth	18 years	High cancer risk *TP53* variant
		18 years	50 years	
Abdominal ultrasound	Every 6 months	Birth	18 years	
Urine steroids	Every 6 months	Birth	18 years	When abdominal ultrasound does not allow a proper imaging of the adrenal glands
Colonoscopy¶	Every 5 years	18 years	Indefinite	Only if the carrier received abdominal

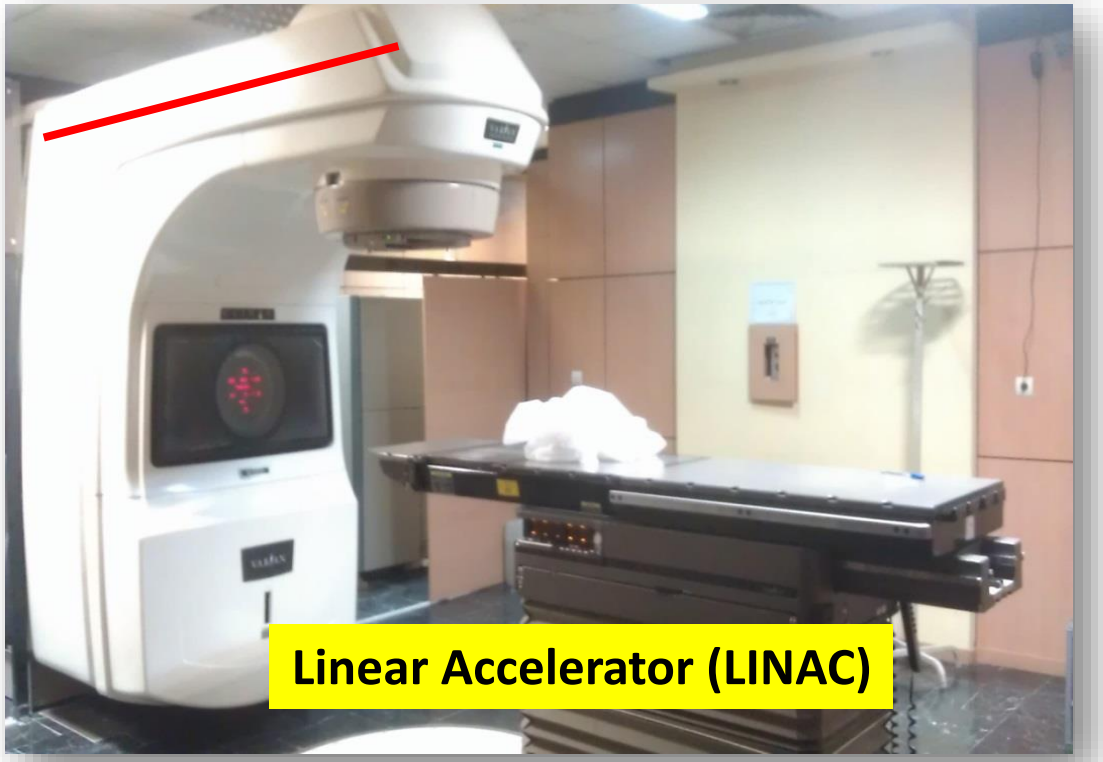
Cancer management

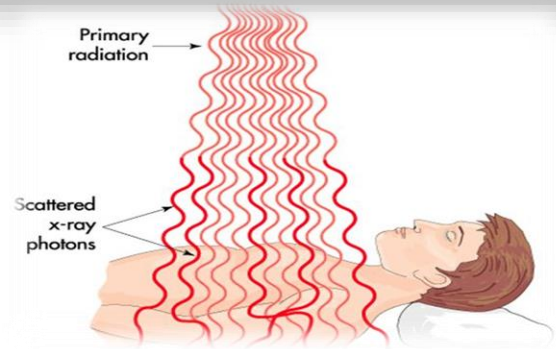
- The management of the various cancers is generally the same
  - as that in patients without Li-Fraumeni syndrome.

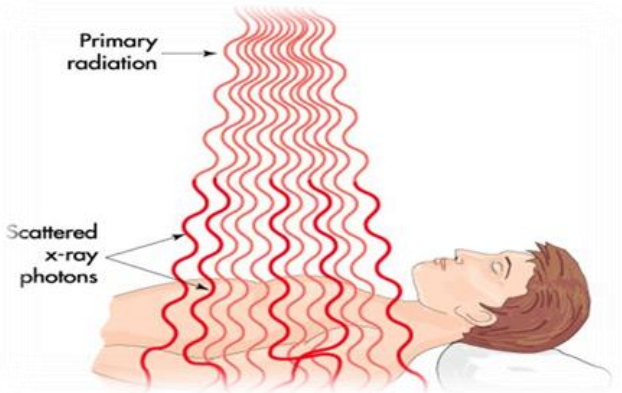
- However, for females with breast cancer
  - **Mastectomy, rather than lumpectomy → RT**, is generally preferred

  - Because of the risks of second breast cancers or radiation induced neoplasms


Electron gun
Accelerating waveguide
Injecto
Transmission waveguide
Path of accelerated electrons
Target (x-rays) or scattering foils (electrons)
Modulator
Microwave source: magnetron or klystron
Flattening filter (x-rays)
Monitor chambers
Collimators
Pulse-forming network
X-rays
or
Electrons


Linear Accelerator (LINAC)


Primary radiation
Scattered x-ray photons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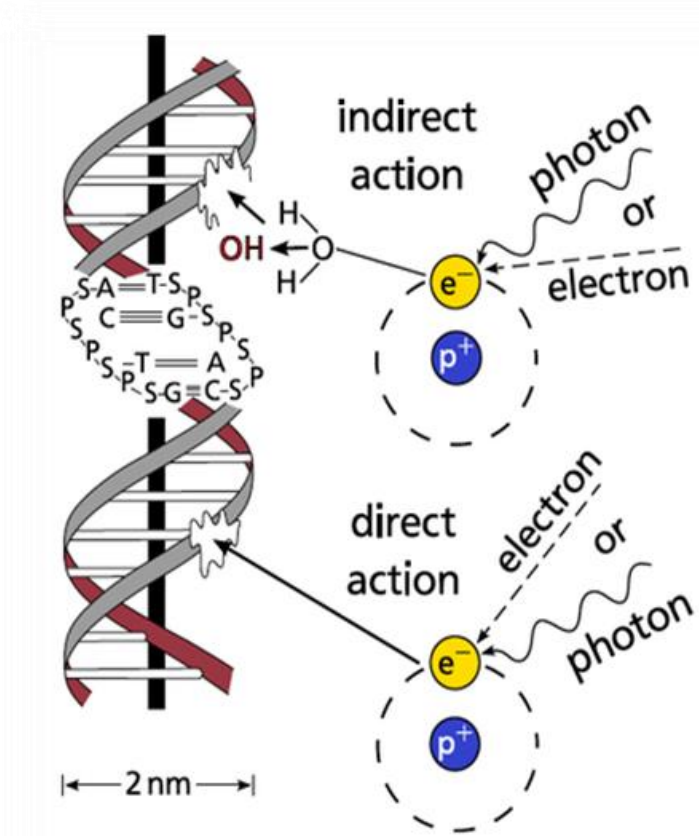
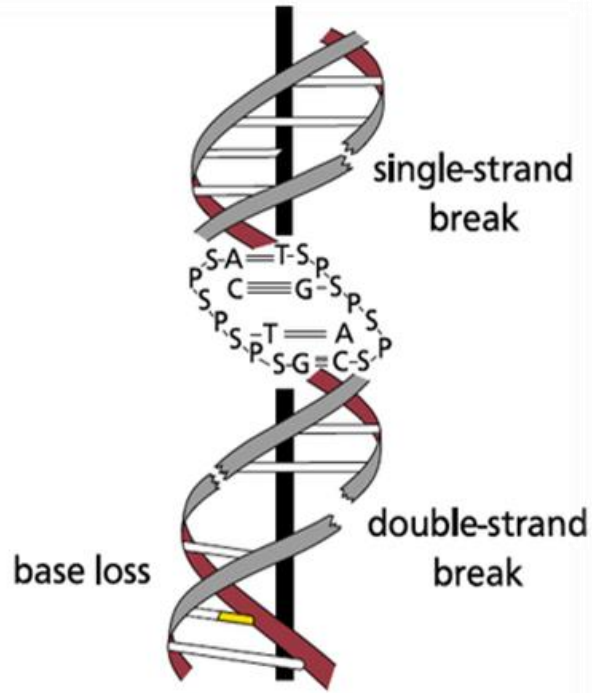

indirect action
photon
or
electron
H
OH
O
H
e⁻
p⁺
direct action
electron
or
photon
e⁻
p⁺
2 nm

(a)


single-strand break
base loss
double-strand break

(b)

TABLE 1-1 Stages in the Radiobiology Continuum

Time Scale of Events (Stage)	Initial Event	Final Event	Response Modifiers/ Possible Interventions
10^{-16} to 10^{-12} second (Physical)	Ionization of atoms	Free radicals formed in biomolecules	Type of ionizing radiation; shielding
10^{-12} to 10^{-2} second (Physico-chemical)	Free radicals formed in biomolecules	DNA damage	Presence or absence of free radical scavengers, molecular oxygen, or oxygen-mimetic radiosensitizers
1.0 second to several hours (Biochemical)	DNA damage	Unrepaired or mis-rejoined DNA damage	Presence or absence of functioning DNA damage recognition and repair systems; repair-inhibiting drugs; altering the time required to complete repair processes
Hours to years (Biological)	Unrepaired or mis-rejoined DNA damage	Clonogenic cell death; apoptosis; mutagenesis; transformation; carcinogenesis; early and late effects normal tissues; whole-body radiation syndromes; tumor control, etc.	Cell-cell interactions; biological response modifiers; adaptive mechanisms; structural and functional organization of tissues; cell kinetics; etc.

Radiation-induced secondary malignancies (RISM)→ like sarcomas

Radiation-associated sarcomas (RAS)

- The most common in **breast cancer**, lymphoma, head and neck, and gynecologic cancers
- **Soft tissue** > bone sarcoma
  - MPNST, UPS, Angiosarcoma, Fibrosarcoma, LMS (RB survivors)
- Avg Latency period **7-17 year**

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- The most common in breast cancer, lymphoma, head and neck, and gynecologic cancers
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  - MPNST, UPS, Angiosarcoma, Fibrosarcoma, LMS (RB survivors)
- Avg Latency period 7-17 year

In BC survivors

- Avg Latency period 10-11 year
- The most common RAS for breast cancer is **angiosarcoma**
  - Avg Latency period **4-8 year**

Secondary sarcomas and angiosarcomas after breast cancer radiotherapy

First author, year	Trial design	Follow-up, years	Cumulative total, percent	
			No RT	RT
Sarcoma				
Taghian A; 1991	Cohort*	10	–	0.2
		20		0.4
		30		0.8
Obedian E; 2000	Nonrandomized, cohort*	15	0.2	0.4
Galper S; 2002	Cohort*	11	–	0.4
Yap J; 2002	Case-control¶	15	0.2	0.3
Huang J; 2001	Cohort	–	0.07	0.13
Kirova Y; 2005	Retrospective	5		0.07
		10		0.27
		15		0.48
Angiosarcoma				
Marchal C; 1999	Retrospective		–	0.05
Strobbe L; 1998	Retrospective		–	0.2
Huang J; 2001	Cohort	–	0.005	0.08

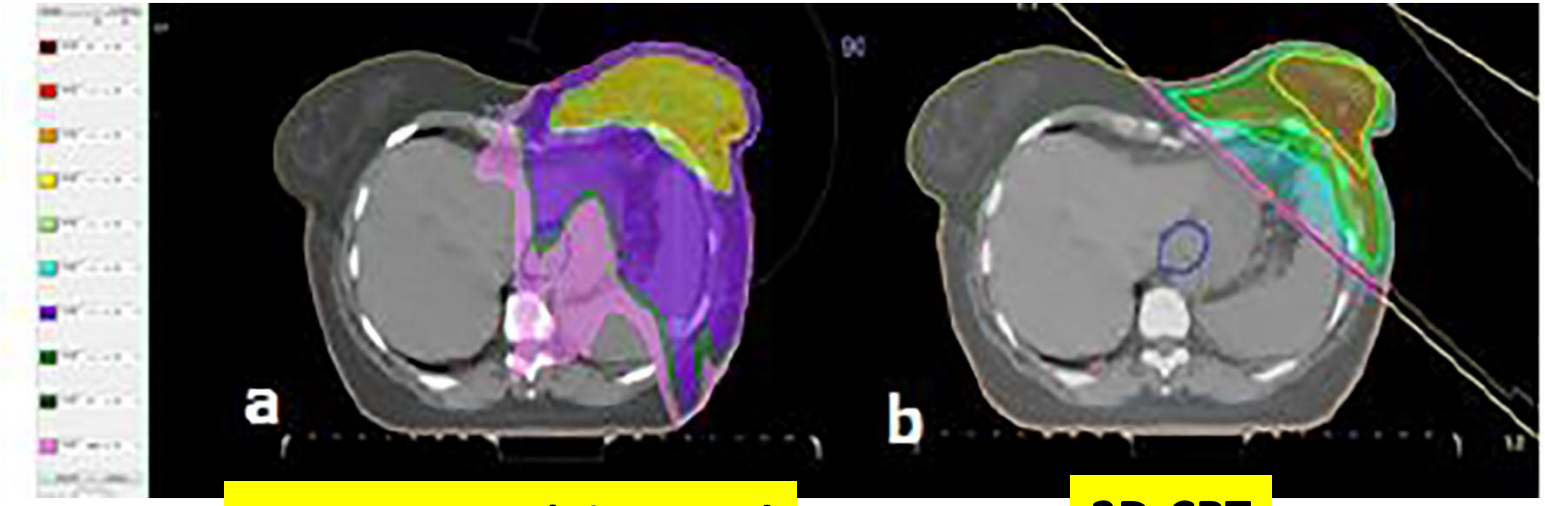
Radiation-associated sarcomas

- Dose
- Age
- Potential effect modifiers
  - Chemotherapy agents
  - Chronic edema
  - **Genetic predisposition**

Dose

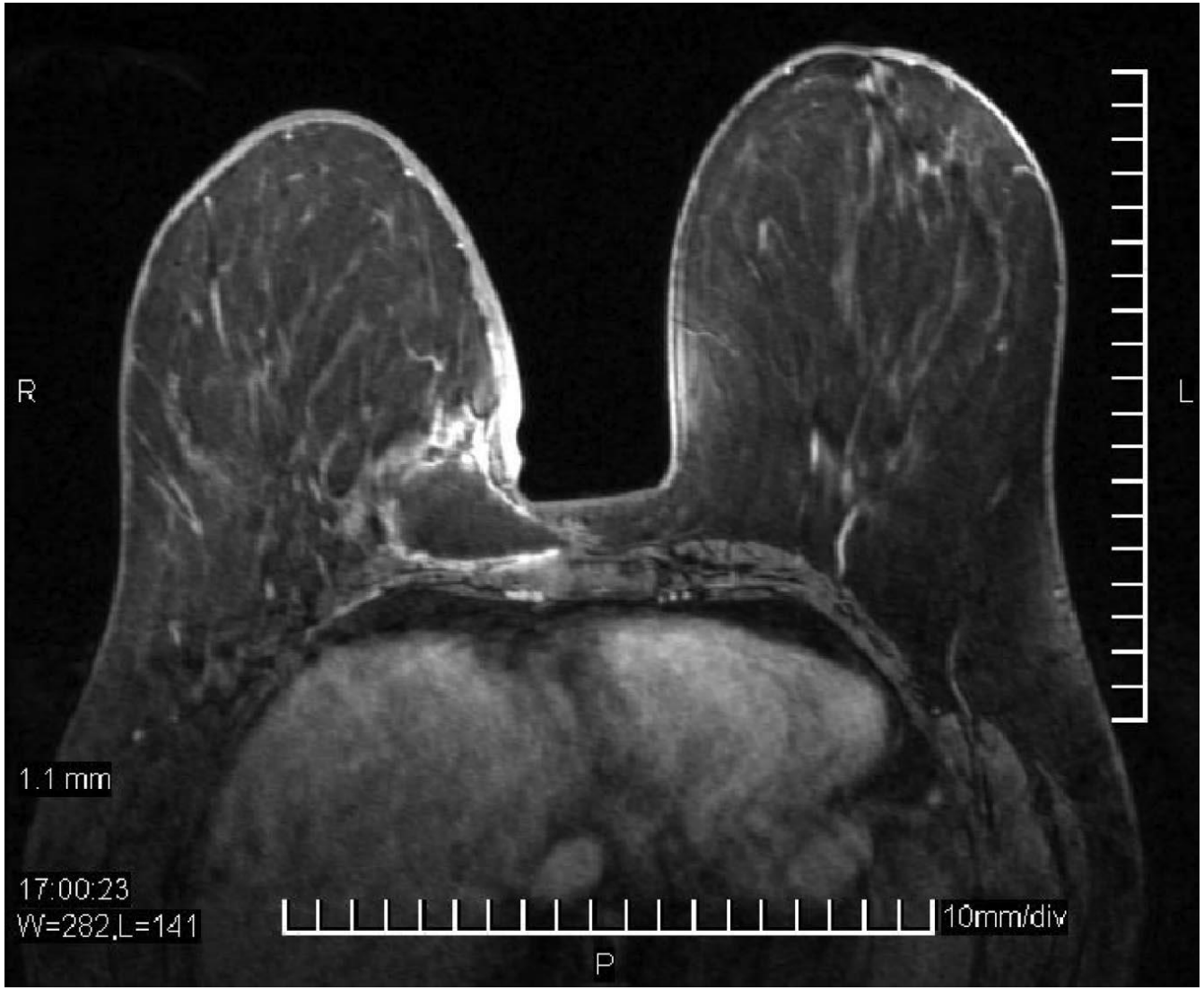
- To induce a tumor → radiation dose must be great enough to cause genetic damage but not so great that it kills the cell

- This often happens to tissues → near the edge of the radiation field.

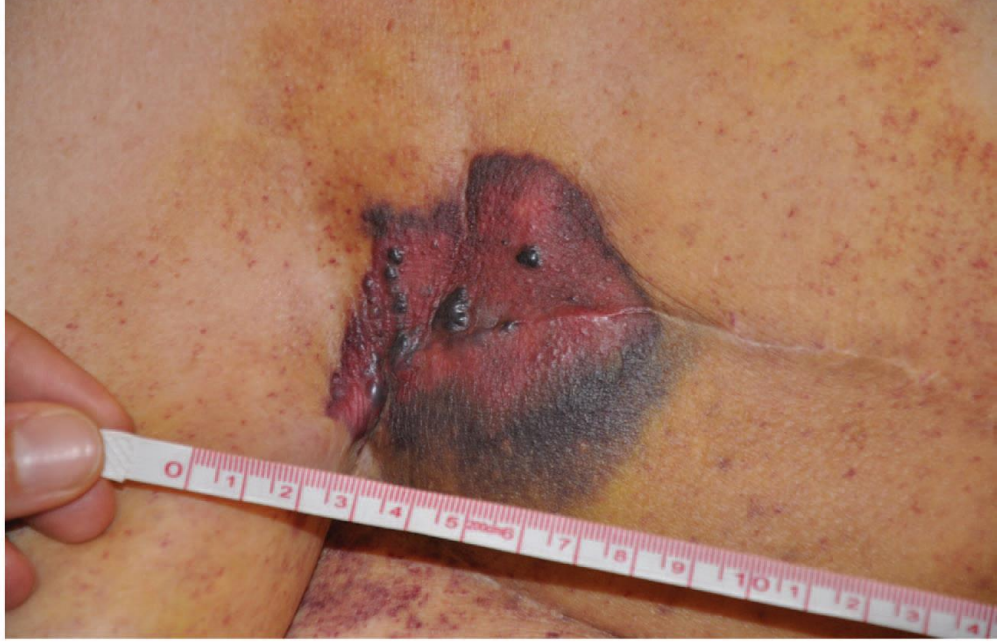


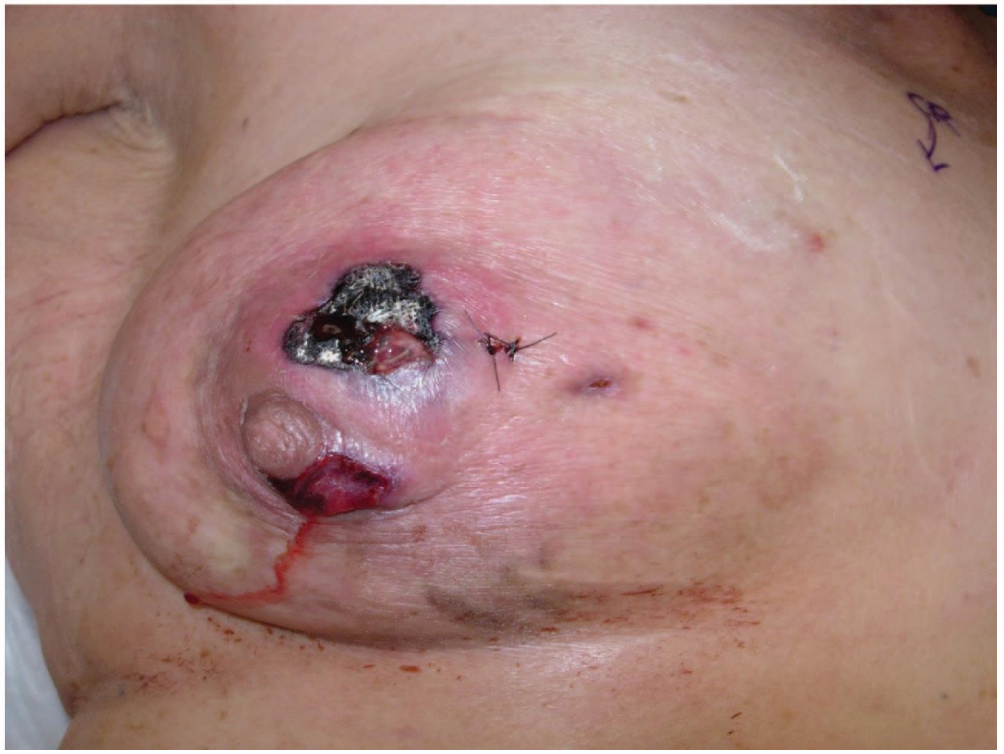
Low Dose Bath in IMRT!

3D-CRT



Magnetic resonance imaging (MRI) scan of a radiation-induced sarcoma (RIS) of the breast. A breast MRI scan shows gadolinium in a patient with RIS.





Radiation-induced angiosarcoma.
(A): Radiation-induced angiosarcoma occurring in a patient previously radiated after mastectomy.

(B): Radiation-induced angiosarcoma occurring in a patient previously radiated after lumpectomy. Photos courtesy of Dr. Chan Raut, M.D., Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts

Reirradiation in RAS

- Few Data
  - RT+ hyperthermia
  - Hyper ration

ANGIOSARCOMA AFTER BREAST-CONSERVING THERAPY: EXPERIENCE WITH HYPERFRACTIONATED RADIOTHERAPY

Steven J. Feigenberg, M.D.,* Nancy Price Mendenhall, M.D.,* John D. Reith, M.D.,† Jon R. Ward, M.D.,* and Edward M. Copeland III, M.D.‡

Departments of *Radiation Oncology, †Pathology, and ‡Surgery, University of Florida College of Medicine, Gainesville, FL

Purpose: To report our promising results of hyperfractionated radiotherapy (RT) in conjunction with surgery for angiosarcoma occurring after breast-conserving therapy for early-stage breast cancer.
Methods and Materials: Since 1997, 3 cases of angiosarcoma after breast-conserving therapy have been managed at the University of Florida. The histologic specimens in each case were reviewed and graded by one of us (J.D.R.).
Results: Explosive growth of discolored skin lesions coincident with histologic evidence of angiosarcoma characterized all 3 cases but was preceded by a fairly indolent period (almost 2 years) of atypical vascular hyperplasia in 2 patients. All 3 patients were treated initially with radical surgery for the angiosarcoma, but extensive recurrences were noted within 1 to 2 months of surgery. Because of the extremely rapid growth noted before and after surgery, hyperfractionated RT was used. Two of the patients underwent planned resection after RT, and neither specimen demonstrated any evidence of high-grade angiosarcoma. All 3 patients were alive without any recurrent disease 22, 38, and 39 months after treatment.
Conclusions: Hyperfractionated irradiation appears to be effective treatment for rapidly proliferating angiosarcoma. For previously untreated angiosarcoma, we now recommend hyperfractionated RT followed by surgery to enhance disease control and remove as much reirradiated tissue as possible.

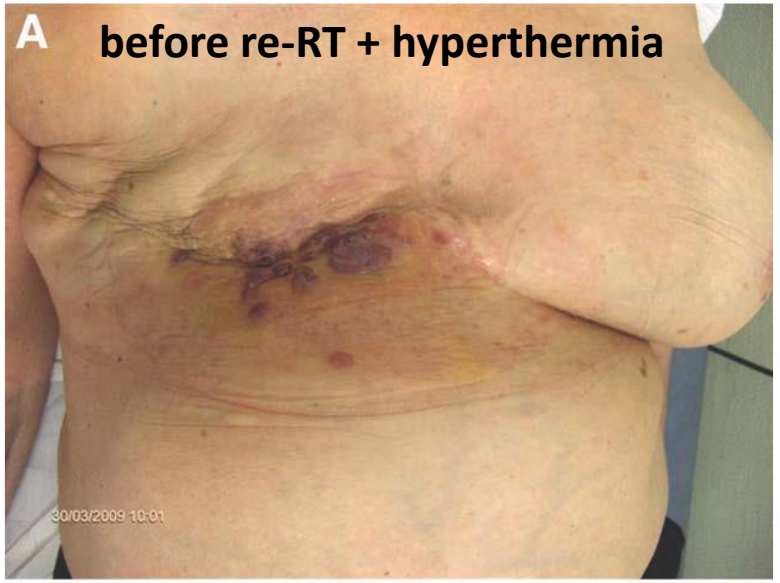
Reirradiation and Hyperthermia for Radiation-Associated Sarcoma

Marianne A. A. de Jong, MD[1]; Sabine Oldenborg, MD[1]; S. Bing Oei, MD[2]; Vanessa Griesdoorn, MD[1,2]; M. Willemijn Kolff, MD[1]; Caro C. E. Koning, MD, PhD[1]; and Geertjan van Tienhoven, MD, PhD[1]

BACKGROUND: The objective of this study was to evaluate the role of reirradiation and hyperthermia in the treatment of radiation-associated sarcoma (RAS) in the thoracic region, which is an increasing, yet extremely rare condition with a poor prognosis. **METHODS:** Between 1979 and 2009, 16 patients with RAS in the thoracic region were treated in the Academic Medical Center and the Institute Verbeeten with reirradiation and hyperthermia. In 13 patients, this treatment was given for unresectable disease and 3 times after resection as adjuvant treatment. The median latency period between the original malignancy diagnosis and the RAS diagnosis was 86 months (range 19-212 months). Histology was angiosarcoma in 11 patients (69%). The literature on reirradiation with or without hyperthermia for RAS was reviewed. **RESULTS:** The median survival was 15.5 months (range, 3-204 months). Four patients were not evaluable for response. The response rate for the remaining 12 patients was 75% (7 complete responses and 2 partial responses). Six patients remained free of local failure until death (5 months and 7 months) or last follow-up (8 months, 11 months, 39 months, and 68 months). **CONCLUSIONS:** The current study indicates that combined reirradiation and hyperthermia for RAS in the thoracic region is feasible. The high response rate and the possibility of durable local control suggest that this treatment is promising. *Cancer* 2012;118:180-7.

KEYWORDS: radiation-associated sarcoma, radiotherapy, hyperthermia.

Figure 1. For hyperthermia, heat was induced electromagnetically by using these microstrip applicators.



Chemotherapy agents

- Exposure to chemotherapy, **particularly alkylating agents**
  - **In children**
    - May potentiate the effect of previous RT in childhood cancer survivors
  - **In adult**
    - Whether chemotherapy potentiates the effects of RT is less clear.

- One systematic review
  - No evidence that prior chemotherapy was a contributing risk factor.

- The overall lower cumulative dose of alkylating agents
  - in breast cancer as compared with sarcoma is one hypothesis for the lack of an association in this context.

Chronic edema

- **Cutaneous lymphangiosarcoma**
    - Is more often found in breasts developing postoperative and post-irradiation edema and fibrosis (Stewart-Treves syndrome).

- It mainly affects women
    - **> 60**
    - Those who underwent axillary lymphadenectomy + RT.

- The very rare nature of Stewart-Treves syndrome suggests that if there is an interaction between radiation and lymphedema, it is very weak.

Genetic predisposition

- To date, however, strong evidence for enhanced radiosensitivity has been observed only for Nijmegen breakage syndrome

- The situation is less clear for Li-Fraumeni syndrome
  - Germline TP53 pathogenic variants
    - May have reduced capacities for eliminating or repairing radiation-induced DNA damage,
    - Therefore, LFS may be a predisposing factor for radiation-induced second primary cancer

- p53-deficient cells are **unable to arrest cell cycle progression** or undergo **apoptosis** after radiotherapy.
- In addition, these cells tend to be **more resistant** to DNA-damaging agents, such as radiation

radiation

MDPI

Review

Exploring the Role of p53 in Radiosensitivity: A Key Player in Cancer Therapy

Tusher- Al-Arafat [1,*], Aihong Mao [2], Takanori Katsube [3] and Bing Wang [3,*]

as cell cycle arrest, DNA repair, apoptosis, and senescence in response to various stress signals, including radiation-induced DNA damage. Activation of p53 triggers the transcription of target genes involved in DNA repair pathways, such as p21, MDM2, and GADD45, facilitating the repair of radiation-induced DNA damage or the elimination of irreparably damaged cells. This, in turn, influences the overall radiosensitivity of tissues. Mutations in the *TP53* gene, which encodes p53, are among the most frequent genetic alterations in human cancers. Loss or dysfunction of p53 can compromise the cellular response to radiation, leading to increased resistance to therapy and poorer clinical outcomes. Conversely, intact p53 function is associated with enhanced radiosensitivity due to its ability to promote cell cycle arrest and apoptosis in response to radiation-induced DNA damage. In conclusion, elucidating the molecular mechanisms by which p53 influences radiosensitivity is essential for advancing our understanding of the radiation response in cancer cells and developing more effective therapeutic approaches to cancer treatment. This review provides a comprehensive overview of the multifaceted role of p53 in modulating cellular responses to radiation, emphasizing its influence on radiosensitivity.

Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome

Steve Heymann[1*], Suzette Delaloge[2], Arslane Rahal[2], Olivier Caron[3], Thierry Frebourg[4], Lise Barreau[5], Corinne Pachet[5], Marie-Christine Mathieu[6], Hugo Marsiglia[1,7], Céline Bourgier[1]

Abstract

Background: There are no specific recommendations for the management of breast cancer patients with germ-line p53 mutations, an exceptional genetic condition, particularly regarding postoperative radiotherapy. Preclinical data suggested that p53 mutations conferred enhanced radiosensitivity *in vitro* and *in vivo* and the few clinical observations showed that Li-Fraumeni families were at a higher risk of secondary radio-induced malignancies.

Methods: We reviewed a cohort of patients with germ-line p53 mutations who had been treated for breast cancer as the first tumor event. We assessed their outcome and the incidence of secondary radio-induced malignancies.

Results: Among 47 documented Li-Fraumeni families treated from 1997 to 2007 at the Institut Gustave Roussy, 8 patients had been diagnosed with breast cancer as the first tumor event. Three patients had undergone conservative breast surgery followed by postoperative radiotherapy and five patients had undergone a mastectomy (3 with postoperative radiotherapy). Thus, 6/8 patients had received postoperative radiotherapy. Median follow-up was 6 years. Median age at the diagnosis of the primary breast cancer was 30 years. The histological characteristics were as follows: intraductal carcinoma *in situ* (n = 3), invasive ductal carcinoma (n = 4) and a phyllodes tumor (n = 1). Among the 6 patients who had received adjuvant radiotherapy, the following events had occurred: 3 ipsilateral breast recurrences, 3 contralateral breast cancers, 2 radio-induced cancers, and 3 new primaries (1 of which was an in-field thyroid cancer with atypical histology). In contrast, only one event had occurred (a contralateral breast cancer) among patients who had not received radiation therapy.

Conclusions: These observations could argue in favor of bilateral mastectomy and the avoidance of radiotherapy.

One chest wall angiosarcoma and one breast histiocytofibrosarcoma

Subsequent Malignancies in Patients With Li-Fraumeni Syndrome Treated With Radiation Therapy

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Results: Of the 23 LFS patients who received RT, 16 (70%) developed a secondary and 5 (22%) developed a tertiary malignancy. Eleven (48%) developed a secondary and 2 (13%) developed a tertiary malignancy in the RT field. The median time to develop a secondary malignancy in the RT field was 9 years (2-22 years). The most common cancers in the RT field included soft tissue sarcomas 7 (54%), lung cancer 2 (15%) and osteosarcoma 2 (15%) while the most common secondary cancers outside the RT field were breast cancer 5 (38%), soft tissue sarcoma 3 (23%), and pancreatic cancer 2 (15%).

Conclusions: In LFS patients who received RT for their primary cancer, 48% developed a secondary malignancy in the RT field. Soft tissue sarcoma was the predominant type of secondary cancer in the RT field, while breast cancer was most common outside of the RT field.

Radiation therapy and secondary malignancy in Li-Fraumeni syndrome: A hereditary cancer registry study

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Abstract

Background: Li-Fraumeni Syndrome (LFS) is a rare cancer-predisposing condition caused by germline mutations in *TP53*. Conventional wisdom and prior work has implied an increased risk of secondary malignancy in LFS patients treated with radiation therapy (RT); however, this risk is not well-characterized. Here we describe the risk of subsequent malignancy and cancer-related death in LFS patients after undergoing RT for a first or second primary cancer.

Methods: We reviewed a multi-institutional hereditary cancer registry of patients with germline *TP53* mutations who were treated from 2004 to 2017. We assessed the rate of subsequent malignancy and death in the patients who received RT (RT group) as part of their cancer treatment compared to those who did not (non-RT group).

Results: Forty patients with LFS were identified and 14 received RT with curative intent as part of their cancer treatment. The median time to follow-up after RT was 4.5 years. Fifty percent (7/14) of patients in the curative-intent group developed a subsequent malignancy (median time 3.5 years) compared to 46% of patients in the non-RT group (median time 5.0 years). Four of seven subsequent malignancies occurred within a prior radiation field and all shared histology with the primary cancer suggesting recurrence rather than new malignancy.

Conclusion: We found that four of14 patients treated with RT developed in-field malignancies. All had the same histology as the primary suggesting local recurrences rather than RT-induced malignancies. We recommend that RT should be considered as part of the treatment algorithm when clinically indicated and after multidisciplinary discussion.

Should Radiation Therapy be Avoided in Breast Cancer Patients with Li-Fraumeni Syndrome?

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Conclusion: Given the rarity of LFS, the literature on patients receiving RT for breast cancer is limited to small case series like our study. One series evaluated 8 breast cancer patients with LFS including 6 undergoing RT and found more cancer events in patients treated with RT, concluding that RT should be avoided. In contrast, we did not find any in-field secondary malignancies among our cohort. Although this study is purely observational, our results differ from prior studies and question whether RT should always be avoided in LFS patients. It is possible that in LFS patients with node-positive breast cancer, the benefits of RT could outweigh the risks of an RT-induced secondary malignancy.

Radiotherapy in patients with breast cancer and Li-Fraumeni syndrome — a narrative review

- **In most studies**
  - Patients with a *TP53* P/LP variant were at increased risk of radiation-induced second malignant neoplasms [31, 32, 34–39, 41, 42].
- **In some studies**
  - The incidence of RISMs after the treatment of localized BC was lower compared with that reported in the previous literature [33, 40, 43].

Radiotherapy in patients with breast cancer and Li-Fraumeni syndrome — a narrative review

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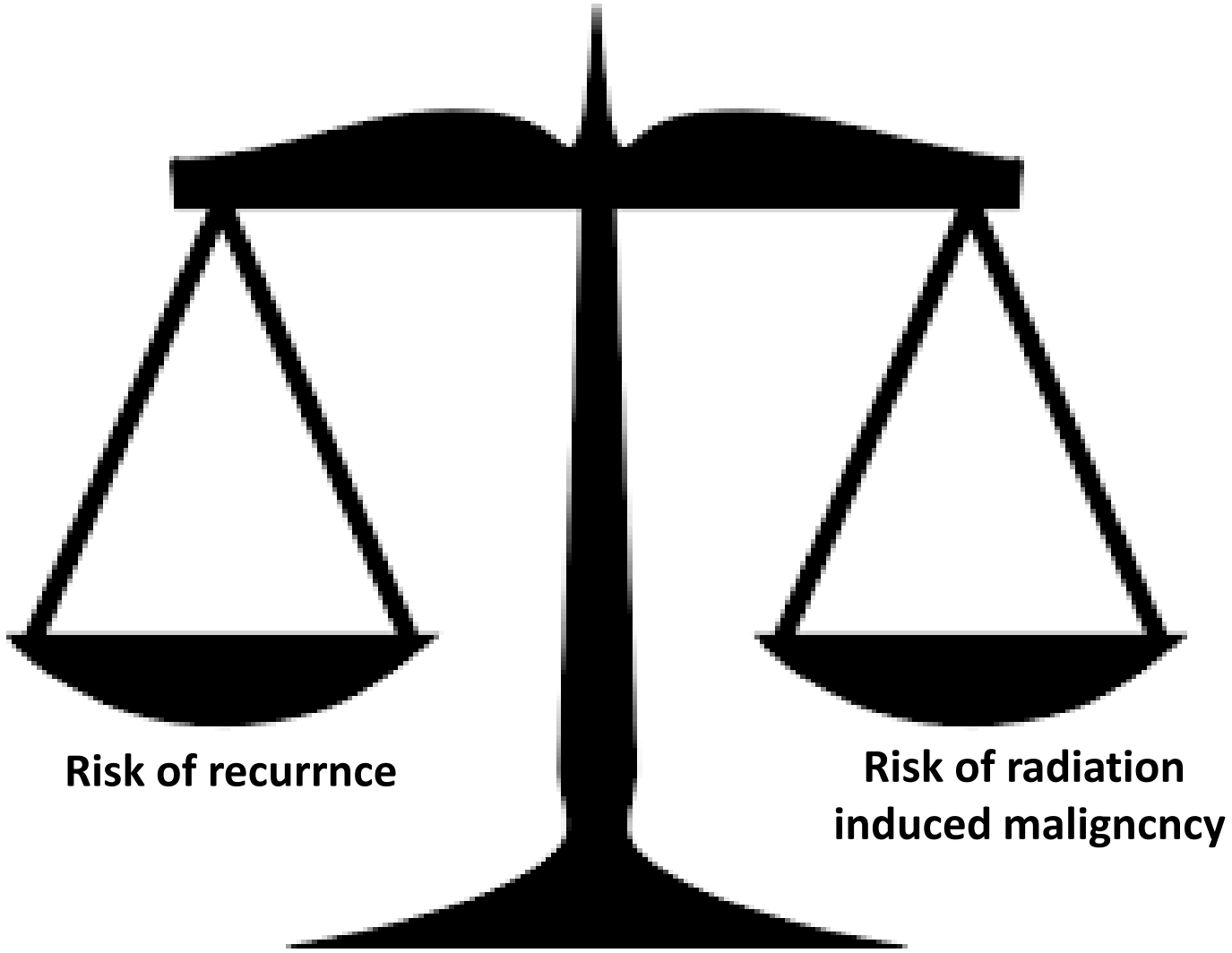
Table 5. Conclusions of the individual studies for adult patients with *TP53-related* breast cancer

Study	Recommendation for radiotherapy	Other recommendation
Heymann et al. [36]	Adjuvant radiation therapy for localized breast cancer should be extensively discussed and prohibited whenever the risk/benefit ratio is doubtful	Both a mastectomy of the cancer-bearing breast and a contralateral prophylactic mastectomy (with immediate reconstruction, as frequently as possible) should be advised
Barbosa et al. [37]	Radiotherapy should be avoided. In cases in which radiotherapy is justified, patients should be followed up intensively	Prioritize breast mastectomy without radiation to minimize the risk of secondary malignancies
Nandikolla et al. [38]	Radiation as adjuvant therapy should be given careful consideration in LFS patients due to the risk of treatment resistance and associated secondary malignancies	N/A
Kumammoto et al. [3]	Imaging and treatments that use radiation should be avoided as much as possible (if there are other options). If there are no other options for routine treatment, irradiation is allowed if the risk-benefit balance indicates its utility	*PET/CT* radiation in individuals with a *TP53* pathogenic variant is not recommended because it could cause secondary cancer
Hendrickson et al. [43]	RT should be considered as part of the treatment algorithm when clinically indicated and after multidisciplinary discussion	N/A

Should RT be avoided in LFS?



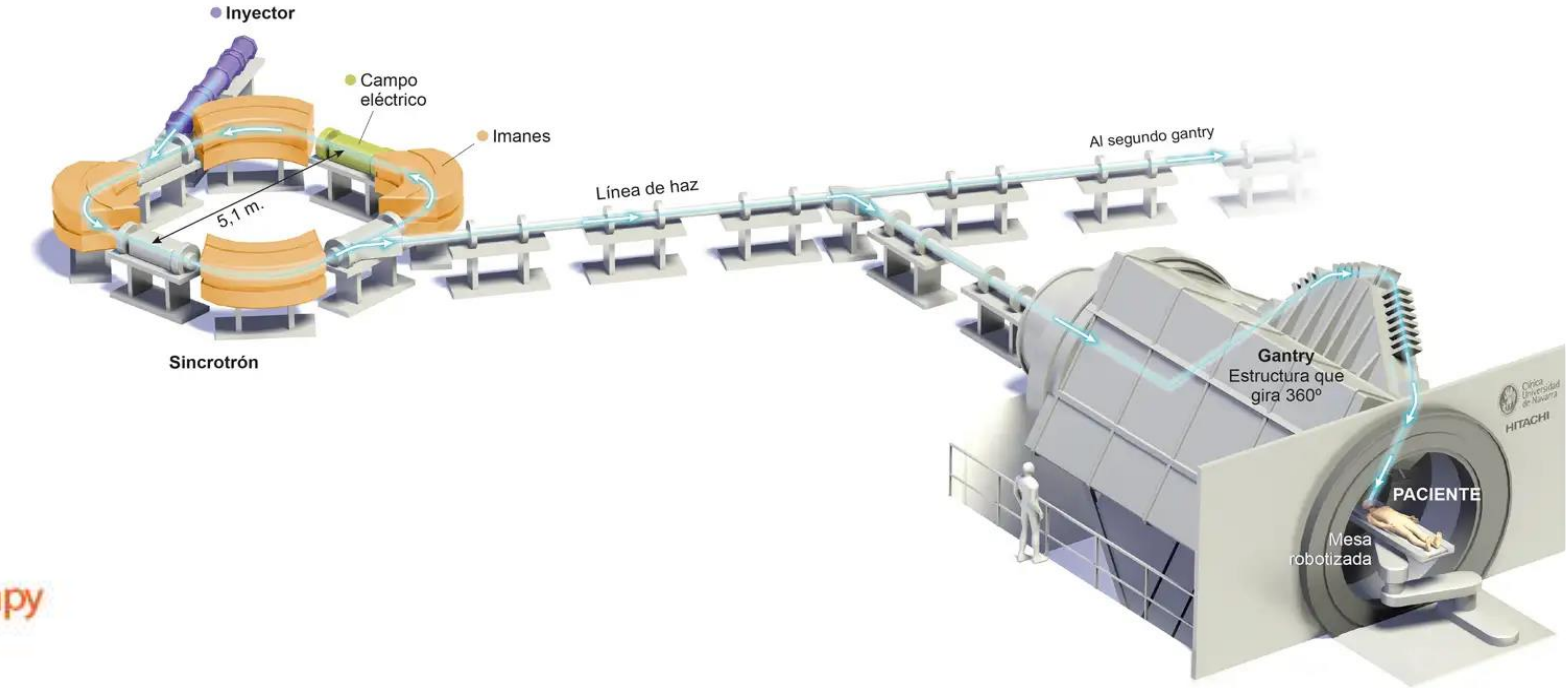
Radiotherapy in patients with breast cancer and Li-Fraumeni syndrome — a narrative review

Avoidance or adaptation of radiotherapy in patients with cancer with Li-Fraumeni and heritable *TP53*-related cancer syndromes

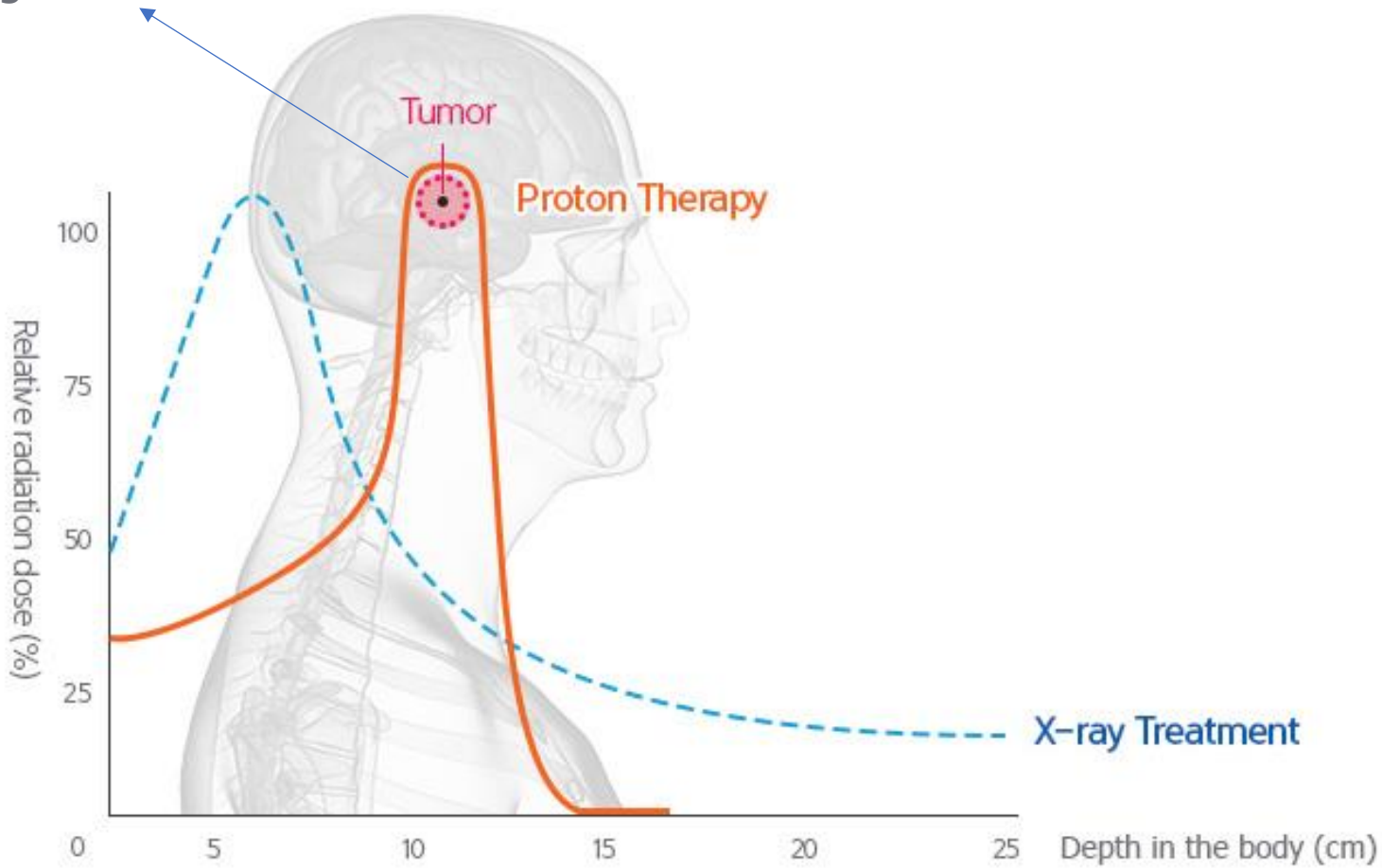
Juliette Thariat, Francois Chevalier, Daniel Orbach, Luc Ollivier, Pierre-Yves Marcy, Nadege Corradini, Arnaud Beddok, Nicolas Foray, Gaelle Bougeard

	Standard treatment for the adult general population	Recommendation for adult patients with heritable *TP53*-related cancer syndromes
Breast cancer	In-situ breast cancer: tumourectomy plus external-beam radiotherapy. Invasive breast cancer: tumourectomy plus external-beam radiotherapy, including to lymph nodes in case of nodal invasion	In-situ breast cancer: mastectomy plus immediate reconstruction. Invasive breast cancer: no strong evidence-based alternative. Intraoperative external-beam radiotherapy might be discussed for early primary node-negative tumours; hadrontherapy (mostly by proton therapy) might be preferred to limit irradiated volumes; intensity-modulated radiotherapy (due to low-dose bath) might not be better than three-dimensional external-beam radiotherapy if proton therapy is not available; comparative dosimetry studies might be useful
Prostate cancer	Low-risk prostate cancer: active surveillance, surgery, brachytherapy, external-beam radiotherapy, or stereotactic body radiotherapy. Favourable intermediate-risk prostate cancer: same as for low-risk prostate cancer except no active surveillance. Unfavourable intermediate-risk prostate cancer: same as for intermediate-risk prostate cancer with or without short-term hormonal therapy or dose escalation. High-risk prostate cancer: high-dose external-beam radiotherapy or external-beam radiotherapy plus brachytherapy boost plus long-term hormonal therapy, or surgery with or without adjuvant external-beam radiotherapy plus long-term hormonal therapy	Low-risk prostate cancer: active surveillance using prostate specific-antigen blood tests and non-ionising imaging, or surgery. Intermediate-risk prostate cancer: surgery. High-risk prostate cancer: surgery (if operable) plus long-term hormonal therapy

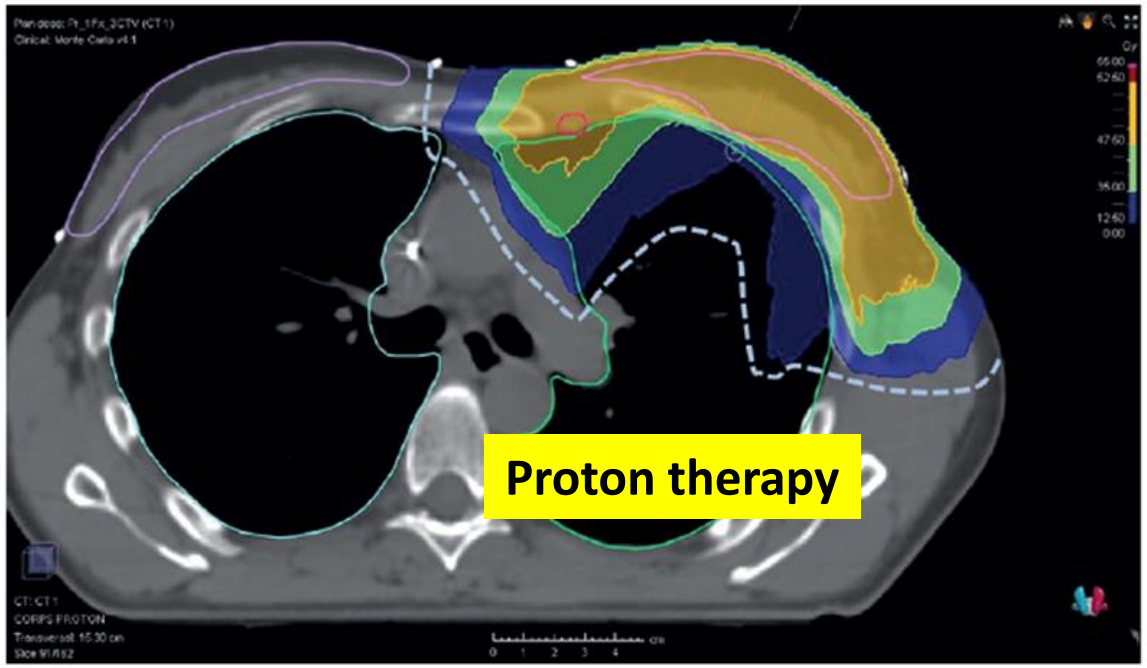
Proton therapy **IORT**

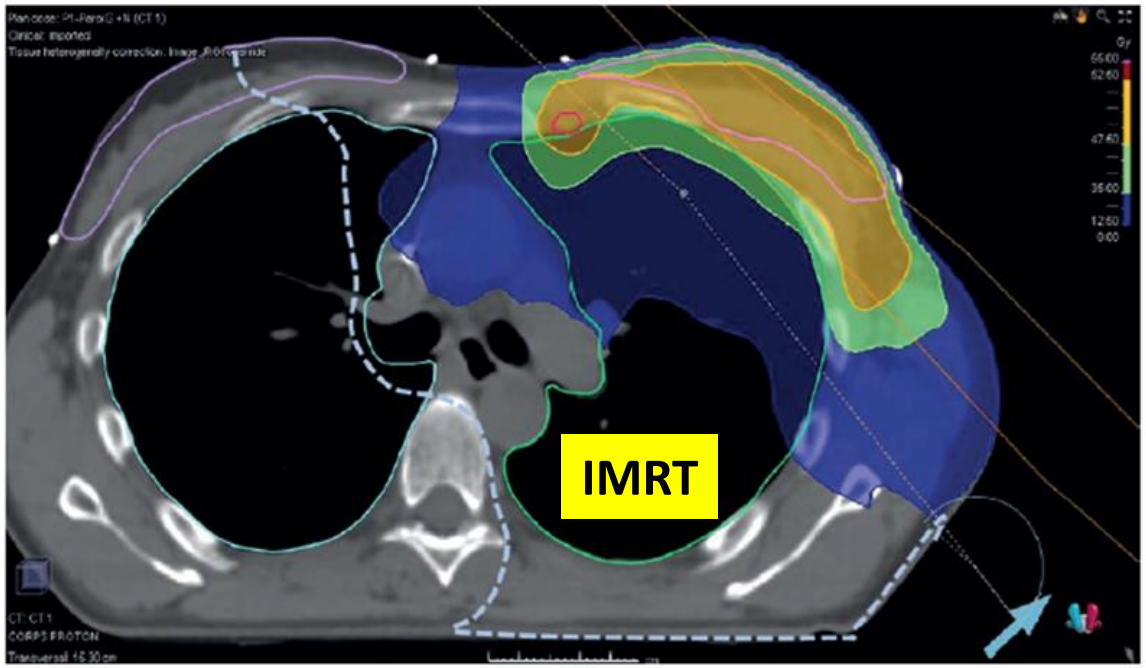


Bragg Peak



http://www.samsunghospital.com/home/proton/en/whatIsProtonTherapy/principle.do





- DNA damage induced by hadron therapy may be more difficult to repair.
- Irradiated volumes : proton radiation are **two-fold smaller** compared with those from a photon
- The risk of secondary malignant neoplasm was **2–10-fold lower** with proton therapy

Frequency of Radiation Therapy-Induced Malignancies in Patients With Li-Fraumeni Syndrome and Early-Stage Breast Cancer and the Influence of Radiation Therapy Technique

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We analyzed 48 patients with a median age of 39 years (range, 21-62). The majority (71%) had the *TP53* R337H variant, and 87% were unaware of their LFS diagnosis at the time of BC treatment. Treatment modalities included mastectomy (62%), (neo)adjuvant chemotherapy (66%), and RT (62%), with RT being more common after breast-conserving surgery (87% vs 46% with mastectomy, *P* = .010). Among the 30 patients treated with RT, 10% developed RIM in the irradiated field, consisting of 3 soft tissue malignancies. RT dose (≤40.8 or >40.8 Gy) did not influence RIM occurrence, but the type of RT did. RIM was observed in 100% of cases with 2D RT (2/2), 50% with IMRT (1/2), and 0% with 3D RT (0/16) (*P* = .004).

2D-RT: 100%
3D-RT: 0
IMRT: 50%
Small sample size!

Conclusions

Our study underscores a concerning rate of RIM after adjuvant RT, emphasizing the importance of a thorough risk-benefit evaluation before recommending RT, with preference for its avoidance if possible. Although subgroup sizes were limited, the risk of RIM appeared to be influenced by the RT technique, with higher rates observed with 2D RT and IMRT compared with 3D RT. Early *TP53* testing is essential to guide the BC treatment plan.

Table 6. Recommendations, guidelines and expert opinions statements of the scientific societies for adult patients with *TP53-related* breast cancer

NCCN [11]	• ***TP53*** mutation carriers are advised to minimize radiation exposure due to the potential association with increased risk of a cancer diagnosis • The use of radiotherapy should generally be avoided in individuals with a TP53 P/LP variant, clinical decision-making should take into account the availability of other curative treatment options
Medical guidelines for Li–Fraumeni syndrome 2019, version 1.1 [3]	• Radiation exposure from imaging tests, such as CT and PET-CT, and for treatment should be avoided as much as possible • Radiation exposure, irradiation, and alkylating agents should be avoided as much as possible, to avoid increasing the risk of secondary cancer onset • As there may be no other options for routine treatment, irradiation is allowed if the risk-benefit balance indicates its utility
ASCO/ASTRO [52, 53]	• For women with breast cancer who are carriers of a germline ***TP53*** mutation, irradiation of the intact breast is contraindicated • Mastectomy is the recommended therapeutic option • Postmastectomy RT should only be considered in patients with significant risk of locoregional recurrence (type: formal consensus; evidence quality: low; strength of recommendation: moderate) • Outcomes reported in published case reports support the recommendation against RT in women with breast cancer who are carriers of a ***TP53*** mutation
European Reference Network for Rare, Low Prevalence and Complex Disease [44]	• The identification of a disease-causing ***TP53*** variant in a cancer patient is important before initiating the treatment • Priority should be given to surgical or ablative treatments, avoiding radiotherapy when possible and preferably using non-genotoxic chemotherapies • When there is no alternative to conventional treatments, adaptation of drug or radiotherapy doses, and the use of proton therapy that ensures a more focused delivery of radiation than photonic therapy might constitute therapeutic options in germline disease-causing ***TP53*** variant carriers

CT — computed tomography; P/LP — pathogenic/likely pathogenic; PET/CT — positron emission tomography-computed tomography; RT — radiotherapy

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ESO–ESMO fifth international consensus guidelines for breast cancer in young women (BCY5)

Indications for post-operative RT are independent of *BRCA* status.	Expert opinion
Limited and inconclusive evidence is available in presence of pathogenic gene variants in other predisposing genes (e.g. CHEK2, ATM): in these patients the risk–benefit ratio needs to be individually discussed.	
For patients with a germline TP53 mutation, post-operative RT is relatively contraindicated and mastectomy is preferred.	
In these patients, post-mastectomy RT should be discussed only in cases of significant risk of locoregional recurrence. This underscores the importance of early genetic testing at the time of diagnosis to aid optimal treatment planning.	

LFS: **Li-Fraumeni syndrome**

- Whom
  - to be concerned about LFS in breast cancer patients?
- What
  - is the characteristics of breast cancer in LFS?
- How
  - to manage breast cancer in LFS?
    - **Should RT be avoided?**
    - What happens if RT being done in LFS?
      - RAS