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REVIEW ARTICLE

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

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ABSTRACT

Li-Fraumeni syndrome (LFS) is a rare disorder that increases the risk of many cancers, including breast cancer (BC), leukemia, soft-tissue sarcomas, central nervous system tumors, and adrenocortical carcinomas. Several previous clinical observations have shown that families with LFS are at higher risk of secondary radiotherapy-induced malignancies. This review article summarizes the available information about secondary malignancies in LFS patients who were treated with radiation therapy. A total of two electronic databases (PubMed and Web of Science) were searched using key words that included 'Li- Fraumeni Syndrome', 'breast cancer', and 'radiotherapy' from their inception to February 2022. Studies reporting radiosensitivity, cancer, and radiotherapy-induced secondary neoplasms were summarized. The majority of the data that were found concerned radiotherapy in patients with BC with LFS, including radiotherapy-induced malignancy. According to recommendations, radiotherapy should be used with caution and adapted to minimize the risk of secondary malignant neoplasms. The potential risk of loco-regional recurrence without radiotherapy or the long-term risk of radiation-induced malignancies must be taken into account when considering adjuvant radiotherapy for LFS and BC patients.

Keywords: breast cancer, Li-Fraumeni syndrome, radiotherapy, radiation-induced malignancies

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Introduction

Li-Fraumeni syndrome (LFS) was first described in 1969 by Li and Fraumeni, who reported a high incidence of soft tissue sarcomas and breast cancer (BC) in young women from four families [1]. Li-Fraumeni syndrome is a rare (1 case per 5 000–20 000 people), autosomal-dominant, and inherited syndrome that is characterized by germline *TP53* mutations [2].

TP53 is frequently referred to as 'the guardian of the genome' and is typically induced in response to cellular stress signals that cause damage to DNA. *TP53* is part of the signaling pathways, including DNA repair, growth arrest, senescence, and apoptosis. Therefore, cells with invalid *TP53*, which can be caused by either weakened or completely abrogated *TP53* function, are more at risk of developing aberrantly activated pathways, in turn inducing carcinogenesis [3, 4]. *TP53* is a tumor suppressor gene that encodes the p53 protein, which has a major role in apoptosis, DNA repair, and cell cycle regulation. The presence of missense mutations in the section of the *TP53* gene encoding the DNA-binding domain obstructs binding of the p53 protein to its target DNA sequences. This leads to the loss of *TP53* tumor suppressor function [5]. 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 [6].

Inherited *TP53* gene mutations, also known as germline mutations, have been reported to increase

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the risk of many cancers, such as breast cancer, leukemia, soft-tissue sarcomas, central nervous system tumors, and adrenocortical carcinomas, which form part of Li-Fraumeni syndrome [7]. *TP53* mutation carriers have about 50% risk of being diagnosed with cancer by the age of 30 years, with a cumulative lifetime risk of ≤ 70% in men and 100% in women [8]. Furthermore, 5–8% of BC patients with *TP53* mutations were diagnosed aged < 30 years [9]. Therefore, the National Comprehensive Cancer Network Guidelines recommend using the Chompret criteria [10] to test for *TP53* mutations in any patient with breast cancer aged < 30 years who tested negative for *breast cancer susceptibility protein* (*BRCA)1* and *BRCA2* mutations [11].

The classic Li-Fraumeni Syndrome is characterized by sarcoma diagnosis at the age of < 45 years old; a first-degree relative (a parent, sibling, or child) with diagnosis of cancer at the age of < 45 years old; and an additional first- or second-degree relative (a grandparent, aunt/uncle, niece/nephew, or grandchild) with cancer diagnosed at the age under 45 years, or a sarcoma diagnosed at any age [12]. The Chompret criteria are presented in Table 1. They facilitate identification of families with LFS who do not meet the classic criteria. The Chompret criteria for clinical diagnosis of LFS include one of the following conditions:

— presence of adrenal cortical carcinoma or a tumor in the choroid plexus, regardless of family history, or presence of multiple tumors (BC excluded);
— presence of two tumors that belong to the LFS tumor spectrum and the occurrence of the first tumor in the LFS tumor spectrum at the age of < 46 years;
— presence of a tumor belonging to the LFS tumor spectrum (< 46 years old) and ≥ 1 first- or second-degree family member with a tumor in the LFS tumor spectrum (< 56 years old) or with multiple tumors [10].

Li-Fraumeni syndrome patients have an 80–90% risk of developing cancer over their lifetimes, which frequently occurs in childhood [13].

Therefore, the present study aimed to summarize the available information about secondary malignancies in LFS patients treated with radiotherapy. Additionally, it presents recommendations according to the findings following radiotherapy in BC patients with LFS.

Methods

This systematic review aimed to describe the risk of developing radiation-induced secondary malignancies in BC patients with LFS. In addition, another aim was to present more up-to-date recommendations according to observations following radiotherapy in BC patients with LFS. The review was performed according to PRISMA guidelines [14].

We conducted a literature search in the Web of Science (https://www.webofscience.com) and PubMed databases (https://pubmed.ncbi.nlm.nih.gov). The results were supplemented with searches on Google Scholar (https://scholar.google.com). The search terms used were as follows: "Li-Fraumeni Syndrome and radiotherapy in breast cancer patients", "Li-Fraumeni Syndrome and radiotherapy side effects in breast cancer patients", or "Li-Fraumeni Syndrome and radiation-induced second malignancies in breast cancer patients". As a result, we found seven publications in PubMed and 16 publications in the Web of Science database that met the criteria (BC patients with Li-Fraumeni Syndrome who received radiotherapy). The search results are summarized in Table 1. The study selection scheme is presented in Figure 1.

Results

We conducted literature searches using PubMed and Web of Science databases in September 2022. The initial search yielded 27 results in PubMed and 59 in Web of Science. After excluding duplicates, 16 articles remained. Furthermore, we screened the titles and abstracts of the articles. The list of article types is presented in Table 2.

Breast cancer patients with LFS

Women with germline mutations in the *TP53* gene have a very high risk (≤ 85%) of being diagnosed with

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
Juvenile breast cancer
Breast cancer patients aged ≤ 31 years

LFS — Li-Fraumeni syndrome

BC by the age of 60 years. The median age at diagnosis of these types of BC is 34 years [15]. In addition, 5–8% of patients with BC at ages < 30 years old were found to harbor germline *TP53* gene mutations [9]. In particular, 15–35% of LFS patients will develop multiple primary tumors [16, 17].

Characteristics of BC in LFS patients were presented in several previous studies. Masciari et al. [18] reported that BC in women with LFS (*TP53* pathogenic germline variants) is more likely to be hormone receptor (HR)-positive and/or receptor tyrosine-protein kinase erbB-2 (HER2)-positive. Similar results were obtained by Melhem-Bertrandt et al. [19]. The authors also reported that this group of women is more likely to exhibit HER2 amplifications and/or overexpression (present in 67% of cases, compared with 25% in the control group in this study) [19]. Correlation analysis previously conducted by Li et al. [20] on Chinese patients with BC showed a significant association of *TP53* pathogenic variants with HR- and HER2+ expression, higher Ki-67 expression, and histological grade. In the analyzed group, LFS patients who were *TP53* mutation carriers were significantly more likely to be identified with pathological grade 3, estrogen receptor-negative (ER–), progesterone receptor-negative (PR–), HER2+ and Ki-67≥ 25% expression ($p < 0.01$) [20]. In other previous studies, a higher rate of *TP53* pathogenic germline variants was identified in patients with BC at more advanced stages or with more aggressive characteristics, including the triple-negative subtype and the HER2--amplified cases [21, 22]. *TP53* variants have also been associated with various indicators of cell proliferation, such as a high mitotic rate, increased Ki-67, and cyclin E expression [23, 24]. The immunophenotypical profile of BC in LFS patients has been previously described and is associated with HER2 amplification and overexpression (53–83%) [18, 25]. In particular, ~50% of cases were found to co-express both ER and HER2 [25].

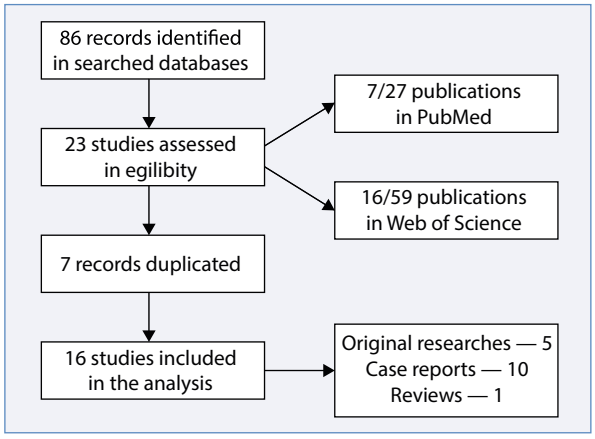

Figure 1. Study selection scheme for systematic reviews

Radiotherapy-induced malignancies after breast cancer radiotherapy in LFS patients

Radiation-induced secondary malignancies (RISM) are a significant potential side effect of radiotherapy and contribute up to ~5% of all radiotherapy-associated secondary malignancies [26]. Exposure to ionizing radiation causes single- and double-strand DNA breaks (DSBs). Single-strand breaks can be converted into DSBs during cell replication, which can cause gene mutations and malignant transformation of the irradiated cell [27]. Some factors, such as age at radiation, dose and volume of the irradiated area, type of irradiated organ and tissue, radiation technique, and individual or family history of cancer, influence RISM risk [28].

Radiation-induced secondary malignancies is assumed to be far more common in LFS patients. Boyle et al. [29] previously suggested that in LFS patients, cells with or without germline *TP53* pathogenic variants may have reduced capacities for eliminating or repairing radiation-induced DNA damage, which occurs during radiation therapy. Therefore, LFS may be a predisposing factor for radiation-induced second primary cancer [29]. A retrospective study conducted by Bougeard et al. [30] on 64 French LFS patients indicated that the incidence of secondary cancers in a field after radiation of the first tumor was 30%. Specifically, second tumors typically occurred 2–26 years after radiotherapy, with a mean time to development of 10.7 years [30].

A wide range of cancer types has been observed to be associated with radiotherapy in BC patients with LFS, including small cell lung cancer [31, 32], colon cancer [31], thyroid cancer [33], breast cancer [32, 34, 35], and especially sarcoma within the radiation field

Table 2. Search strategies performed on September 22, 2022, and results from PubMed, Web of Science on the topic of Li-Fraumeni syndrome and radiotherapy and breast cancer

Database	Search terms	Research	Case Reports	Reviews
PubMed	"Li-Fraumeni Syndrome and radiotherapy in breast cancer patients"	1	4	2
Web of Science	"Li-Fraumeni Syndrome and radiotherapy side effects in breast cancer patients"	5	10	1

Table 3. Radiotherapy-induced malignancies after breast cancer radiotherapy in Li-Fraumeni syndrome (LFS) patients

References	Number of patients	RIMS	Latency
Limacher et al. [31]	1	Small-cell lung carcinoma; adenocarcinoma of the sigmoid colon	< 10 years after radiotherapy
Hisada et al. [35]	1	Mesothelioma, soft tissue sarcoma	10 years after radiotherapy
Heymann et al. [36]	2	Chest wall angiosarcoma; histiocytofibrosarcoma	13 years after radiotherapy; N/A
Barbosa et al. [37]	1	Epithelioid angiosarcoma of the right breast	N/A
Nandikolla et al. [38]	1	Spindle-cell sarcoma of the left breast	4 years after adjuvant radiotherapy
Henry et al. [39]	1	Leiomyosarcoma in the left chest wall	27 months after completing the adjuvant radiotherapy
Salomon et al. [34]	1	Malignant fibrous histiocytoma of the right clavicle; right breast cancer	40 months after the completion of radiotherapy
Ferrarini et al. [32]	1	Lung cancer (bronchoalveolar carcinoma), right breast cancer; DCIS	27 months after radiotherapy; 39 months after radiotherapy; 53 months after radiotherapy
Le et al. [33]	2	Sarcoma in the chest wall; thyroid cancer	4 years post-radiotherapy; 10 years post-radiotherapy
Petry et al. [40]	2	Fibrosarcoma in the chest wall; a low-grade leiomyosarcoma in the chest wall radiation field	6.6 years after adjuvant radiotherapy; 15.7 years after treatment
Kast et al. [41]	1	Well-differentiated liposarcoma	2 years after radiotherapy

N/A — not applicable; RIMS — radiation-induced secondary malignancies

[33, 35–40]. Sarcomas were the most frequent RIMs reported in BC patients with LFS. Another less common RIM was breast cancer (contralateral or ipsilateral). Data from studies assessing the risk of radiotherapy--induced malignancies in breast cancer LFS patients [type of RIMs and latency between radiotherapy (RT) and RIMs] are summarized in Table 3. According to the literature, the time range for development of a second malignancy was from 27 months to 22 years. In most studies, the patient's age at diagnosis was approximately 30–40 years. Clinicopathological characteristics of breast cancer LFS patients who developed RIMS and treatment strategies are shown in Table 4.

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]. However, 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].

Hendrickson et al. [43] analyzed a group of 40 LFS patients. The most common first cancer diagnosis in this group of patients was breast cancer (11 patients — 27.5%). Among breast cancer LFS patients, 3 (18.8%) received radiotherapy as part of their cancer treatment, and 8 (33.3%) were not treated with radiotherapy. None of the malignancies that occurred in patients who received radiotherapy were classified as 'radiotherapy-associated'. However, the median follow-up time in this particular study may have been too short to capture radiation-associated secondary malignancies. The median dose of radiation in the study group was 50.4 Gy (range, 15–66 Gy), and all but one patient received radiotherapy at standard fractionation of 1.8–2 Gy per fraction. There used radiation techniques included 3-dimensional (3D) conformal and intensity-modulated radiation therapy (IMRT) and intraoperative radiotherapy with a Harrison-Anderson-Mick (HAM) applicator (one patient) [43].

Le et al. [33] also found a lower risk of RISMs in patients with LFS and BC compared with that previously reported in the literature, which was a 33% risk of radiation-induced sarcoma. The study group included 18 patients with LFS and BC who received radiation in a curative setting. The authors reported radiation-induced sarcoma in one patient (6%) and thyroid cancer in the radiation field in another patient (6%). By contrast, among non-LFS patients with BC, only 17 (0.5%) and 1 (0.03%) developed thyroid cancer and radiation-induced sarcoma, respectively. The radiation-induced sarcoma was observed significantly less often ($p < 0.001$) in patients with BC without LFS compared with those with LFS. Similarly, there was also a lower tendency to develop thyroid cancer in the radiation field in patients without LFS ($p = 0.08$). According to propensity score weighted analyses, LFS was found to be associated with a significant increase in the risk of thyroid cancer ($p = 0.001$) and a non-significant increase in the risk of sarcoma ($p = 0.22$) following radiation

Table 4. Characteristics of breast cancer patients with Li-Fraumeni syndrome (LFS) and radiation-induced secondary malignancies (RIMS) — literature review

References	Number of patients	Age	ER/PR	HER2 overexpression	TNM	Histology	Surgical treatment	Contralateral breast cancer	CT
Limacher et al. [31]	1	25 years	N/R	N/R	N/R	N/R	Mastectomy	No	Adjuvant CT — FAC
Hisada et al. [17]	1	30 years 36 years	N/R N/R	N/R N/R	N/R N/R	N/R N/R	N/R N/R	N/R	N/R
Heymann et al. [36]	2	22 years 39 years	N/R ER negative/ /PR negative ER positive/ /PR positive ER positive/ /PR positive	N/R HER2 positive N/R HER2 negative	TxN0M0 N/R TisN0M0 N/R	Phyllodes sarcoma Ipsilateral breast cancer DCIS local relapse – invasive ductal carcinoma	Conservative breast surgery Mastectomy Lumpectomy Mastectomy	Yes No	No Trastuzumab No Adjuvant chemotherapy
Barbosa et al. [37]	1	38 years	ER positive/ /PR positive	HER2 positive	pT2N0M0	Invasive ductal carcinoma of the right breast	Sectorectomy	DCIS of the left breast	Adjuvant CTH — anthracycline-based CT and trastuzumab
Nandikolla et al. [38]	1	28 years	ER negative PR negative	HER2 negative	pT2N1miM0	Invasive ductal carcinoma of the right breast	Mastectomy	Phyllodes tumor of the left breast	Adjuvant CT — AC-P
Henry et al. [39]	1	24 years	ER positive PR positive	HER2 positive	N/R	Invasive ductal carcinoma of the left breast	Lumpectomy	No	Adjuvant CTH — AC-P and trastuzumab
Salomon et al. [34]	1	27 years	ER positive ER positive	N/R	T2N1M0 T1NxM0	Invasive ductal carcinoma Invasive ductal carcinoma	Left mastectomy Right lumpectomy	Bilateral breast cancer	Adjuvant chemotherapy AC
Ferrarini et al. [32]	1	32 years	ER negative/ /PR negative	HER2 positive	N/R	Ductal infiltrating carcinoma of the right breast	Mastectomy	DCIS of the left breast	Adjuvant CTH — docetaxel, carboplatin and trastuzumab
Le et al. [33]	2	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Petry et al. [40]	2	40 years 52 years	N/R N/R	N/R N/R	N/R N/R	DCIS Invasive ductal carcinoma	Mastectomy Conservative breast surgery	No No	No Adjuvant CT — not specified
Kast et al. [41]	1	40 years	PR positive	HER2 positive	N/R	Bilateral invasive ductal carcinoma	Bilateral breast-conserving tumor extirpation	No	Neoadjuvant CT TH

AC-P — doxorubicin, cyclophosphamide and paclitaxel; CT — chemotherapy; CTH — chemotherapy and trastuzumab; DCIS — ductal carcinoma in situ; ER — estrogen receptor; FAC — fluorouracil, doxorubicin and cyclophosphamide; HER2 — human epidermal growth factor receptor 2; N/R — not reported; PR — progesterone receptor; TH — taxan and trastuzumab; TNM — tumor-node-metastasis staging system

for primary BC. These findings suggest that LFS may not be an absolute contraindication for the radiotherapy of breast cancer. Therefore, the potential risk for loco-regional recurrence without radiotherapy must be weighed against the long-term risk for radiation-induced malignancies when considering adjuvant radiotherapy for BC patients with LFS [33].

Similar results were also reported by Petry et al. [40], who evaluated the occurrence of RISMs after adjuvant radiotherapy in LFS patients treated for localized BC in a Brazilian cohort. A total of 10 (62.5%) of 16 patients were found to be harboring the p.R337H germline *TP53* pathogenic variant. The majority of patients (12/16, 75%) received adjuvant radiotherapy, of whom 16.6% (2/12) developed RISMs after a median follow-up of 52.5 months. Specifically, the authors reported fibrosarcoma in one patient in the chest wall in the radiation field 6.6 years after adjuvant radiotherapy, whereas the other patient developed low-grade leiomyosarcoma 15.7 years after treatment. In addition, one distant recurrence with bone metastasis was diagnosed (1/12) in the group treated with radiotherapy 46.6 months after the initial diagnosis. No loco-regional recurrence occurred in this group. In the group of LFS patients (*TP53* p.R337H variant), the presence of RISMs after therapy of localized BC was lower compared with that reported in the previous literature. However, the authors recommended early molecular diagnosis and careful assessment of treatment risks and benefits for these patients [40].

Radiotherapy in patients with LFS and breast cancer

If radiotherapy must be applied in LFS patients, a protocol should be adapted to minimize the risk of a second malignant neoplasm. Adaptation may be achieved through the reduction of irradiated volumes using proton therapy, non-ionizing diagnostic procedures, image guidance, and minimal stray radiation [44]. The comparison of hadrontherapy (protons, helium, or carbon ions) with conventional radiotherapy was evaluated in various preclinical studies. High linear energy transfer radiotherapy induces intense focal damage caused by ions passing through the nucleus. By contrast, DNA damage induced by hadrontherapy is more complex in structure; it is multifocal, condensed, and may be more difficult to repair. This therapeutic method also reduces the volume of radiation normal tissues due to dose deposit patterns. The more finite dose deposit is caused by the loss of kinetic energy. The spread-out Bragg peak is used to cover the entire tumor thickness, ensuring that little or no radiation is leaked beyond that area [45]. In addition, irradiated volumes from proton radiation are two-fold smaller compared with those from a photon, which was associated with second malignant neoplasm reduction [45]. The risk of secondary malignant neoplasm was 2–10-fold lower with proton therapy compared with intensity-modulated radiation therapy [46]. However, the risk-benefit ratio of intensity-modulated radiotherapy, stereotactic body radiotherapy, or 3D radiotherapy should be estimated. The differences between photons and carbon ions revealed increased cell death by apoptosis in a p53-dependent manner *in vitro*, with high linear energy transfer (higher LET) with carbon ions. Phosphorylation of p53 at serine 37, involved in apoptosis induction, was much higher after high LET irradiation [47]. Carbon ions will typically induce larger DNA double-strand break clusters and therefore more lethal DNA damage compared with proton therapy and X-rays [48]. Therefore, heavy ion therapy cannot be recommended for patients with heritable *TP53*-associated cancer syndromes. There have been studies reporting a superior response with hypofractionation compared with conventional fractionation in tumors with *TP53* pathogenic variants. However, there are also no arguments in favor of altering the radiotherapy fraction in patients with *TP53*-pathogenic variants in comparison to patients with wild-type *TP53.* In LFS patients, non-ionizing imaging should be prioritized for the diagnosis and designation of a radiotherapy regimen [49].

Iwasaki et al. [50] presented the use of proton therapy in an LFS patient to treat re-irradiation- or radiation-induced secondary cancer. A 2-year-old girl was diagnosed with rhabdomyosarcoma (RMS) in the region between the neck and shoulder on the right side. She received surgical resection followed by chemotherapy and photon radiotherapy, delivered at 45 Gy in 25 fractions. Two years after the initial treatment, another RMS appeared in the right anterior chest. Surgery, chemotherapy, and radiotherapy (36 Gy in 20 fractions) were used. In total, 5 years after the initial treatment, when the patient was 7 years old, osteosarcoma was observed in the right shoulder blade and a malignant fibrous histiocytoma formed in the left chest wall, both of which were considered to be secondary cancers caused by previous irradiation. Therefore, proton therapy, which in these cases is thought to be more useful compared with photon radiotherapy, was proposed. To achieve local control, she received proton therapy delivered at 66 Gy in 30 fractions for both tumors. Grade 1 dermatitis was the only observed acute radiation toxicity. Ultimately, 23 months after the proton therapy, magnetic resonance imaging (MRI) showed an increase in the tumor on the right shoulder.

Discussion

Based on the literature data, recommendations for the follow-up and treatment of LFS patients were proposed. The presence of pathogenic germline *TP53* variants should be taken into account during decision-making for the local treatment of BC.

Heymann et al. [36] previously recommended that adjuvant radiation therapy for localized BC should only be the last resort or prohibited altogether if the risk/benefit ratio is doubtful. The possibility of both mastectomy and contralateral prophylactic mastectomy with immediate reconstruction should be discussed with the patient as in the case of BRCA1/2 mutations [36]. Barbosa et al. [37] suggested that mastectomy without radiation should be prioritized in patients with BC and LFS to minimize the risk of developing secondary malignancy. However, in cases where conservative therapy and/or radiotherapy were to be used, then intensive monitoring is of paramount importance [37].

Nandikolla et al. [38] recommended that radiation as part of adjuvant therapy should be delivered carefully in LFS patients. Risk-benefit assessment of chemotherapy and radiotherapy is required due to the risk of treatment resistance and RISM [38].

Kumammoto et al. [3] suggested that the use of radiation should be avoided where possible due to RISM risk. Surgical treatments, such as risk-reducing bilateral mastectomy, warrant further investigation. Nevertheless, the LFS follow-up protocol should include whole-body, brain, and breast MRI and abdominal ultrasonography immediately after the diagnosis [3]. By contrast, Hendrickson et al. [43] reported that the rate of the development of RISM did not significantly differ between LFS patients treated with radiotherapy and those without such therapy. Therefore, they recommended that radiotherapy should be considered as part of the treatment algorithm in cases with clinical indications and after multidisciplinary scrutiny [43]. The conclusions for adult patients with *TP53*-associated BC are presented in Table 5, separately for each study**.**

Medical guidelines for managing LFS according to the Toronto Protocol include recommendations for children (from birth up to 17 years old) and adults (> 18 years old). The children's follow-up protocol recommended a full check-up every 3–4 months to obtain various parameters, including blood pressure, growth curve (general evaluation), abdominal and pelvic ultrasound (for adrenocortical carcinoma), brain MRI every year, starting with contrast MRI (for brain tumor) and whole-body MRI every year (for bone and soft tissue tumor). The recommendation for adults stated a full physical check-up every 6 months (general evaluation), breast exam twice a year from age 20 years onwards, and breast MRI every year from age 20 to 75 years. Risk-reducing mastectomy should be considered, and brain MRI performed every year, starting with contrast MRI (for brain tumor), whole-body MRI every year, and abdominal and pelvic ultrasound every 12 months from the age of 18 years (for bone and soft tissue tumor). Upper and lower gastrointestinal endoscopy should be performed every 2–5 years from the age of 25 years onwards (for gastrointestinal cancer) and dermatological examination every year from the age of 18 years (for malignant melanoma). In addition, it is suggested that radiation exposure during diagnostic imaging [such as computed tomography (CT) and positron emission tomography-computed tomography (PET-CT)] and radiation therapy should be avoided where possible. However, irradiation is allowed in LFS patients if the risk/benefit balance indicates its utility. Secondary cancers may develop as a result of radiation exposure in patients with *TP53* pathogenic variants. Therefore, radiation should be avoided if other viable options are available [3].

According to the National Comprehensive Cancer Network recommendations (Guidelines Version 1.2023), radiotherapy for cancer should be avoided when possible, instead, it should be considered an option. In addition, diagnostic radiation should be minimized to the extent that is feasible without sacrificing accuracy [11]. The risk of toxicities and secondary malignancies has to be carefully considered individually based on estimated radiotherapy benefits. However, in the absence of alternative therapies and/or when clinical data support radiotherapy, then therapy should not be interrupted. In patients with germline *TP53* mutations undergoing palliative radiotherapy, the threshold of radiotherapy use should be lower because the association between toxicities and *TP53* mutations is not as robust and the consequences of secondary malignancies are less critical. In addition, an annual breast MRI should be performed between the ages of 20 and 29 years. Recommendations for patients in the 30–75 age group include annual breast MRI screening with contrast and mammogram. For patients aged > 75 years, management should be considered on an individual basis. Other cancer risk recommendations include colonoscopy and upper endoscopy every 2–5 years starting at the age of 25 or 5 years before the earliest known colon or gastric cancer in the family, annual dermatological examination starting at 18 years of age, annual whole-body MRI, annual brain MRI (or as a part of whole body MRI) and a comprehensive physical exam (including neurologic examination) in cancer survivors every 6–12 months [11].

European Reference Network for Rare, Low Prevalence, and Complex Diseases also prepared Guidelines for LFS and heritable *TP53*-associated cancers. In adults, these recommendations include annual clinical examinations, whole-body MRI, breast MRI in women aged 20–65 years, and brain MRI until the age of 50 years. In patients with cancer and disease-causing germline *TP53* variants, radiotherapy and conventional genotoxic chemotherapy will predispose them to the development of subsequent primary neoplasms, especially within the radiotherapy field. The option of risk-reducing mastectomy should be discussed on a case-by-case basis [44]. According to European Reference Networks, genetic testing of the *TP53* gene before the start of treatment is essential. This is to avoid, where possible,

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
Thariat et al. [49]	Radiotherapy should be avoided whenever other similarly curative treatment options are available. In other cases, it should be adapted in such a way as to minimize the risk of a second malignant neoplasm	Mastectomy and immediate reconstruction in case of *in situ* breast cancer. Invasive breast cancer: intraoperative external-beam radiotherapy may be discussed for early primary node-negative tumors; hadrontherapy. IMRT might not be better than three-dimensional external-beam radiotherapy if proton therapy is not available
Limacher et al. [31]	Radiotherapy should be discussed individually and should take into account the risk of secondary neoplasms arising in the radiation fields	Germline p53 mutation screening in affected members of families with LFS to define better the indications for and modalities of radiation therapy
Salmon et al. [34]	Radiotherapy application should be reconsidered taking into account the uncommon, but clinically significant risk of RISMs	In the case of young breast cancer patients (even with no family history of cancer), it is reasonable to carry out *TP53* and *BRCA1/2* molecular testing
Ferrarini et al. [32]	Strongly consider the potential deleterious influence of radiotherapy in the rapid development of second primary cancers	N/A
Le et al. [33]	The potential risk for locoregional recurrence without radiotherapy must be weighed against the long-term risk for radiation-induced malignancies in consideration of adjuvant radiotherapy for LFS breast cancer patients	N/A
Petry et al. [40]	Adjuvant radiotherapy for patients with *TP53* pathogenic germline variants should be avoided	*TP53* testing is recommended in all cases of female breast cancer diagnosed under the age of 31 years

IMRT — intensity-modulated radiation therapy; LFS — Li-Fraumeni syndrome; N/A — not applicable; PET/CT — positron emission tomography-computed tomography; RISM — radiation-induced secondary malignancies; RT — radiotherapy

radiotherapy and genotoxic chemotherapy. If there is no other alternative in the conventional treatment repertoire, then drugs, radiation dose adjustment, or even proton therapy should be considered. The reason for this is that proton therapy will provide more focused radiation delivery compared with photonic radiation and may be more therapeutic for carriers of the pathogenic, germinal *TP53* gene variant. *TP53* mutation carriers treated with radiotherapy or chemotherapy for cancer as their primary disease have an exceptionally high risk of developing a second primary cancer, which is $\geq 40\%$ [45]. In children, the recommendations are to perform clinical examination and abdominal ultrasound every 6 months, annual whole-body MRI, and brain MRI from the first year of life, if the *TP53* variant is known to be associated with childhood cancers. In adults, the surveillance should include annual clinical examination, whole-body MRI, and breast MRI

in females from the age of 20 until 65 years and brain MRI until the age of 50 years [44].

For carriers of *TP53* mutations, as for other patients at high risk based on family history or predisposing mutations in other genes (e.g., BRCA1/2, partner, and localizer of BRCA2, checkpoint kinase 2 and ataxia telangiectasia mutated) and for those at risk because of the personal history of therapeutic radiation, annual surveillance is recommended. Different diagnostic methods e.g. whole-body MRI should be discussed with LFS patients. For women who did not undergo salpingo-oophorectomy, gynecologic surveillance every 6 months is recommended. In addition, different diagnostic methods for staging and follow-up (e.g., whole-body MRI) should be considered for women harboring pathogenic germline *TP53* variants (LFS). Fludeoxyglucose-PET-CT is currently under evaluation for LFS patients [51].

According to an expert panel consisting of members of the American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology, for patients with germline *TP53* mutations, mastectomy is advised. By contrast, radiation therapy is contraindicated except for those with a significant risk of loco-regional recurrence. *TP53* mutation carriers appear to be less efficient at repairing tissue damage caused by radiotherapy, so they are at higher risk of significant radiotherapy-associated sequelae [52, 53].

According to Thariat et al. [49], radiotherapy should be avoided whenever other similar treatment methods are available. In other cases, the risk of RISM in patients who still require radiotherapy should be minimized, given its potential benefit. Adaptations may be achieved through the reduction of irradiated volumes using proton therapy, non-ionizing diagnostic procedures, image guidance, and minimal stray radiation. Non-ionizing imaging should be considered more often. The risk of second malignant neoplasms after radiotherapy in terms of germline TP53 variants should be assessed during specialized multidisciplinary staff meetings [49]. The dose of radiation to the tumor should be standardized and irradiating normal tissue volumes should be reduced. This can be attained by improving tumor targeting and limiting low non-target doses from image guidance and stray radiation [49]. The recommendations, guidelines and expert opinions statements of the scientific societies for adult patients with TP53-associated breast cancer are summarized in Table 6.

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

Conclusions

Radiotherapy for patients with breast cancer and LFS should be used with caution, taking into account its potential benefits. In patients with BC undergoing palliative radiotherapy, the consequences of secondary malignancies are less critical, so radiotherapy can be used with fewer restrictions. However, the use of radiotherapy should always be assessed by a multidisciplinary team. According to international recommendations, the use of radiotherapy should generally be avoided in individuals with a *TP53* P/LP variant, and clinical decision-making should take into account the availability of other curative treatment options. The risk of a second malignant neoplasm following radiotherapy should be minimized. This may be achieved by the reduction of irradiated volumes, non-ionizing diagnostic techniques, image guidance, and minimal stray radiation.

Article Information and Declarations

Author contributions

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Supplementary material

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