Lack of toxicity in a patient with germline TP53 mutation treated with radiotherapy

P. Wong MD MSc* † and K. Han MD†

ABSTRACT

Li–Fraumeni syndrome is an autosomal dominant disorder characterized by germline TP53 mutation and increased susceptibility to cancer. Despite certain in vitro findings and a theoretical rationale for patients with TP53 mutation to be more radiosensitive and more prone to developing radiotherapy (RT)–induced secondary malignancies, corresponding clinical data remain elusive. Here, we report the case of a woman with TP53 mutation who was treated with adjuvant pelvic RT for stage IB uterine leiomyosarcoma in 2000, with radioactive iodine for papillary thyroid cancer in 2001, and with palliative RT to the humerus in 2010 for metastatic uterine leiomyosarcoma. She has not developed any acute or late RT-related toxicity, nor any secondary malignancies, since her first RT treatment. The literature review describes the potential risks and benefits of using irradiation in patients with TP53 mutation.

KEY WORDS
Radiation, oncology, Li–Fraumeni, toxicity, p53

1. INTRODUCTION

Initially described in 1969, Li–Fraumeni syndrome (LFS) is a rare syndrome (1 case in 5000–20,000 population)1 associated with the development of multiple cancers (mainly breast cancer, sarcoma, brain cancer, leukemia, and adrenocortical cancers)2. Approximately 75% of patients with LFS have germline TP53 mutations. Because LFS is an autosomal dominant disorder, children of a patient with LFS have a 50% chance of inheriting the syndrome2, and the penetrance is 90% by age 603. Patients with LFS are also at high risk for developing cancers at an earlier age, such that 50% of LFS-related cancers develop by age 304. Although these patients are prone to develop cancers4, published experiences on the use of radiotherapy (RT) in the treatment of cancers in this patient population are scarce because of concerns that normal cells with mutated TP53 are more sensitive to RT than are cells without TP53 mutations and that RT will induce new primary cancers in these (often young) patients.

2. CASE DESCRIPTION

A 61-year-old woman who had been diagnosed with stage IB uterine leiomyosarcoma in 2000 and with stage T2N0 papillary thyroid cancer in 2001 was referred for consideration of palliative RT to a right upper quadrant abdominal metastasis from her leiomyosarcoma that caused occasional pain and intermittent small-bowel obstruction. The leiomyosarcoma had initially been treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy followed by adjuvant pelvic RT using a 4-field box technique (45 Gy in 25 fractions). The thyroid cancer was managed with thyroidectomy and adjuvant radioactive iodine [0.75 mCi (27.75 MBq)].

The patient had no evidence of recurrence until 2007, when she developed biopsy-proven metastatic leiomyosarcoma to the lungs, heart, bone, and upper abdomen (Figure 1). She was initiated on doxorubicin and ifosfamide, which was followed by gemcitabine in the subsequent 2 years. Follow-up computed tomography imaging 3 months after the 18th cycle of gemcitabine revealed a lytic lesion of her right proximal humerus, which was subsequently treated with palliative RT for pain (35.25 Gy in 15 fractions). The thyroid cancer was managed with thyroidectomy and adjuvant radioactive iodine [0.75 mCi (27.75 MBq)].

The patient underwent further chemotherapy on trial (phase III, eribulin vs. dacarbazine; search for NCT01327885 at http://clinicaltrials.gov/ ) and received dacarbazine until her current admission. Since 2010, she has also undergone 3 bile stent procedures secondary to the enlarging right-sided upper abdominal mass, which, at the time of the current consultation, measured 18.0×18.0×9.4 cm (Figure 2).

During the course of the patient’s palliative RT to the humerus, her infant granddaughter was
diagnosed with an adrenocortical carcinoma. After genetic testing, the child was found to carry the deleterious c.473G>A (Arg158His) missense mutation in the TP53 gene that renders that gene nonfunctional. Because the child’s mother declined genetic testing, our patient was tested and was found to carry the same TP53 mutation (Figure 3).

Our patient did not develop any grade 1 or greater toxicities (acute or chronic) during RT to the whole pelvis or the right proximal humerus, or during radioactive iodine treatments. Based on the most recent imaging (Figure 2), she also did not develop any new malignancies secondary to her previous courses of RT and 131I. Furthermore, multiple courses of DNA-damaging chemotherapies were administered with no development of hematologic malignancies. Her case suggests that patients with the Arg158His TP53 mutation might be less prone than other LFS patients (with other TP53 mutations) to secondary cancers and to RT-induced acute and chronic toxicities.

Despite some evidence that her previous courses of RT seemed efficacious, our patient opted to not receive RT because her bowel obstruction resolved after a week of no oral intake and a liquid diet. Treatment of the voluminous abdominal mass with RT would likely induce acute side effects even in non-LFS pa-

**FIGURE 1**  Timeline of diagnosis and treatments received by the patient over 13 years. TAH-BSO = total hysterectomy and bilateral salpingo-oophorectomy; Dox = doxorubicin; Ifos = ifosfamide; RT = radiotherapy.

**FIGURE 2**  Two coronal computed tomography images of the patient at the time of the last radiotherapy consultation. A right-sided mediastinal metastasis is seen to be invading the heart; a large right upper abdominal mass has a bile stent running through it; and no abnormal mass is evident within the pelvic area.

**FIGURE 3**  Pedigree chart for the patient’s family (arrow indicates the patient). At 27 years of age, the patient’s mother had abdominal and ovarian tumours surgically removed; she has not been diagnosed with cancer. The TP53 analysis was secondary to a diagnosis (dx) of an adrenocortical carcinoma in the patient’s granddaughter at 2 years of age.
patients, and our patient did not wish to receive any further treatments in the form of RT or chemotherapy. She was discharged home a week after this consultation and remained stable at 6 weeks after discharge.

3. DISCUSSION

Because of reservations connected to the administration of RT to patients known for germline TP53 mutations, clinical data describing the acute and chronic side effects of RT in this population are limited. Evidence demonstrating an association of non-cancerous cells and tissues harbouring mutated TP53 with increased sensitivity to radiation is sparse and inconsistent. Boyle et al.6 studied the effect of RT in fibroblasts derived from non-LFS, LFS (mutant TP53), and LFS (wild-type TP53) patients. The authors observed that, after irradiation, 50% more chromosomal aberrations accumulated in fibroblasts with mutant TP53 than in fibroblasts from non-LFS patients. In a case study by De Moura et al.7, reduced apoptotic death secondary to irradiation was observed in fibroblasts from a patient with mutant TP53 (Trp146X) compared with fibroblasts from controls or from the patient’s mother, who harbour the (Arg72Pro) TP53 single nucleotide polymorphism (SNP). By contrast, Alsbeih et al.8 observed increased clonogenic cell kill in fibroblasts when cells harboured more potentially radiosensitive SNP alleles in the ATM, p21, XRCC1, XRCC3, TGFN1, and TP53 (Arg72Pro) genes.

Despite certain in vitro findings and a theoretic rationale for patients with mutant TP53 to be more radiosensitive, corresponding clinical data remain elusive. Andreassen et al.9 reviewed 58 studies examining the acute and chronic RT toxicity effects of various germline gene SNPs on normal tissue. Only one study observed a correlation between a TP53 SNP (Arg72Pro) and acute skin toxicity10. In the RAPPER study, Barnett et al.11 attempted to prospectively validate 92 published RT toxicity-related SNPs (including the aforementioned TP53 SNP) by genomically profiling 1613 patients whose RT-related toxicities were prospectively recorded. None of the SNPs could be validated, which might be a result of insufficient follow-up and limitations in detecting RT-induced toxicities.

Data on RT-induced cancers in LFS patients are limited because of the syndrome’s rarity, the associated unfavourable prognosis, and the time delay to the development of secondary cancers12. And yet Li and Fraumeni13, as well as others12,14–20, observed cancers developing more frequently in patients after RT. For example, Heymann et al.14 noted 8 new cancers in 6 patients treated with adjuvant breast RT, compared with 1 new cancer in 2 patients treated without RT. In another study of 27 LFS patients, 9 developed 13–18 new primary cancers (8 in the RT field) after a median of 11 years21, which might be more frequent than the 24–32 new tumours in patients (n = 18) who never received RT. Pierce and Haffty suggested that, compared with nonirradiated LFS patients, those receiving RT are at higher risk, by a factor in the 2–6 range, to develop RT-induced malignancies22, corroborating the data derived from murine models23.

4. CONCLUSIONS

Radiotherapy is an efficacious and inexpensive treatment modality for cancer patients24. More than half of all patients diagnosed with cancer will undergo RT during their lifetime with either curative or palliative intent25,26. With more than 12 million cancers diagnosed annually worldwide27, an increasingly important need to better estimate RT-related toxicities in relation to patient genomic profiles is emerging. In addition to enabling proper pro–con discussions for RT, an improved understanding of radiogenomics will help in tailoring the cancer treatment dose by allowing physicians either to reduce the dose in patients who are radiosensitive or to increase the dose to improve the tumouricidal effect of RT in patients at low risk of developing toxicities. Individual mutations and polymorphisms within specific genes might affect a particular person’s sensitivity to RT differently. The ongoing GENEPI and REQUITE projects aim to examine this topic, and the results will yield insights into how to best tailor RT according to an individual patient’s genetic background, age, comorbidities, performance status, and disease characteristics.

Guidelines from the U.S. National Comprehensive Cancer Network28 suggest that individuals be tested for TP53 mutation if they are members of a family with a known TP53 mutation; people meeting the classical Li–Fraumeni syndrome or Chompret criteria; or people diagnosed with breast cancer at age 35 or younger, with a negative BRCA1/2 test. Testing should be performed before RT start, because the results might alter patient management. Furthermore, Villani et al.29 demonstrated that surveillance of asymptomatic LFS family members was associated with improved rates of survival at 3 years (100% vs. 21%, p = 0.0155). The authors suggested that the strategy resulted in earlier diagnosis of cancers and premalignant lesions that were more treatable and amenable to the reduced use of systemic and RT treatments.

In conjunction with the National Comprehensive Cancer Network recommendations, therapeutic RT for cancer should be used with caution, and be kept as an option, in patients with a known TP53 mutation or LFS undergoing treatment with curative intent28. The risks of toxicities and secondary malignancies have to be carefully weighed on a case-by-case basis against the evidence-based benefit of RT. In the absence of alternative therapies, and when high-level evidence supports RT, RT treatment should not be withheld. For patients undergoing RT with palliative intent, the threshold of...
RT use in patients with germline TP53 mutation should be lower, because the association between toxicities and TP53 is not as robust, and the consequences of secondary malignancies are less critical.

5. CONFLICT OF INTEREST DISCLOSURES

PW and KH are recipients of Canadian Association of Radiation Oncology–Elekta fellowship awards and the Canadian Institutes of Health Research Terry Fox Foundation Strategic Training Initiative for Excellence in Radiation Research of the 21st Century.

6. REFERENCES


Correspondence to: Philip Wong, Département de radio-oncologie, Centre hospitalier de l’Université de Montréal, Hôpital Notre-Dame, Pavillon Lachapelle, 1560 rue Sherbrooke est, Montreal, Quebec H2L 4M1. E-mail: Philip.wong.chum@ssss.gouv.qc.ca

* Radiation Medicine Program, Princess Margaret Cancer Centre, and Department of Radiation Oncology, University of Toronto, Toronto, ON.
† Département de radio-oncologie, Centre hospitalier de l’Université de Montréal, Hôpital Notre-Dame, Montreal, QC.