

# Radiation-induced sarcoma in thyroid: about a case report and review of the literature

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## SUMMARY

**Introduction:** Sarcomas in irradiated areas are rare diseases with an unfavorable prognosis. If complete tumor resection is the first-line treatment, the place of radiotherapy in a curative approach is not clearly defined.

**Methods:** We report a rare case of Radiation-Induced Sarcoma (RIS) that arose in the thyroid, 27 years after radiotherapy for a localized undifferentiated nasopharyngeal carcinoma (UCNT). The patient was treated in 1992 with radiotherapy and chemotherapy intended to treat curatively. Twenty-seven years after the end of radiotherapy, the patient presented with a sarcoma in thyroid for which she received an initial surgical resection with positive margins followed by adjuvant radiotherapy.

**Results:** The patient presented with a progression of her disease within one month of the end of radiotherapy.

**Conclusion:** The complete surgical resection sarcoma within the irradiated field is often difficult to achieve enhancing the risk of relapse. Radiation therapy should be discussed when faced with an unrespectable tumour or after suboptimal surgery as part of intensified local management with curative intent.

**Key words:** radiation-induced neoplasms, thyroid, sarcoma, UCNT, rhinopharynx

## INTRODUCTION

Ionizing radiation is a carcinogen as well as an agent for killing cells. When radiotherapy is used to eradicate a tumor, the radiation can cause secondary cancer related to radiotherapy, e.g. in organs adjacent to the tumor [1]. With screening resulting in patients being treated at younger ages, and with increasing patient survival times, secondary cancer is becoming of increasing concern [2]. The long-time lag between radiotherapy and secondary cancer incidence means that few direct data, or none, are available on secondary cancer induced by recently introduced treatment modalities so that model-based predictions are important. Radiation-Induced Sarcomas (RISs) occur in fewer than 1% of patients who receive radiation therapy but account for up to 5% of all sarcomas [3-8]. They have been reported after radiotherapy for tumours such as breast cancer, prostate cancer and lymphoma [9, 10]. Although many older studies have reported poor survival rates [3, 4, 11], recent work from several groups suggests that this may no longer be the case [5, 12, 13]. The cornerstone of treatment is surgery for those patients with localized disease at presentation. Excision with microscopic negative margins results in significant survival differences compared with margin-positive excision. The use of reirradiation for the treatment of radiation-associated sarcoma has been associated with better outcomes in small studies [8]. Larger studies have not seen this association. In particular, there is no consensus on the indication of radiotherapy in this pathology Gy.

## METHODS: CASE REPORT

We report here the case of a 60-year-old woman admitted to our hospital for adjuvant radiotherapy of Radiation-Induced Sarcoma (RIS) that arose in the thyroid after radiation therapy for undifferentiated rhinopharyngeal carcinoma.

At the end of 1991, when the patient was 32 years old, she had a history of progressive worsening nasal obstruction with epistaxis, and then the symptomatology Gy worsened with a decrease in visual acuity, paralysis of the sixth left cranial pair and limitation of the mouth opening with the onset of bilateral cervical adenopathies, the largest was on the left and measured 6.5 × 3.5 cm. The patient consulted and the diagnosis of undifferentiated rhinopharyngeal carcinoma was made, the tumor was initially classified as T4N3M0, then after decision of the multidisciplinary

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consultation meeting; the patient received 3 courses of neoadjuvant chemotherapy based on cisplatin+5FU+endoxon. In February 1992, she started radiotherapy; the device used was cobalt, the technique was two-dimensional radiotherapy 2D, the total dose received was 70 Gy in 35 fractions, with a dose of 2 Gy daily for 3-5 days each week, in 12.3 weeks; from 25/02/1992 to 30/03/1992 the patient received a dose of 46 Gy in 23 fractions at 2 Gy/fraction on the rhinopharynx+the jugulocarotid and spinal ganglion areas by 2 lateral fields and the supra-clavicular ganglion areas by a previous field, then from 05/05/1992 to 20/05/1992 she received a dose supplement of 24 Gy in 12 fractions at a rate of 2 Gy/fraction on the rhinopharynx by 2 lateral fields and a dose supplement on adenopathies by electrons of 10.5 MeV of ener Gy. The patient remained in good locoregional control and at a distance from her disease until 2019 when she presented a previous cervical tumefaction gradually increasing in volume with the progressive onset of dysphonia and then dyspnea. Physical examination demonstrated a well-developed and well-nourished woman (The WHO performance status was equal to 0) with mild respiratory distress. She had an 11 cm, firm, and painless, fixed, dipping thyroid mass (Figure 1). No cervical adenopathy was palpable. Laboratory evaluations including biological thyroid tests, serum tumor markers, complete blood count, electrolytes and basic metabolic profile were normal.

The computerized tomography (CT) scan of the neck with contrast confirmed a voluminous thyroid mass spread over 100 × 60 mm, contrasting heterogeneously, containing numerous areas of necrosis, slightly protruding at the thoracic level, compressing the trachea backward and pushing the jugulocarotid vessels laterally (Figure 2).

On this CT scan, there was no cervical adenopathy. CT scan of the chest and abdomen did not reveal any metastases. The patient underwent a total thyroidectomy without lymph node dissection (see the surgical part in Figure 3, without preoperative cytolgy). The postoperative course was uneventful.

The anatomopathological and immunohistochemical analysis returned in favour of a low-grade myxofibrosarcoma of the thyroid, with a positive surgical margin (R1). After five weeks of surgery and good healing of the surgical wound, the patient was admitted to our hospital for adjuvant radiotherapy as the surgical margins were positive. Indeed, after the decision of the multidisciplinary consultation meeting, the patient was received normofractionated



Fig. 1. Image showing the thyroid mass in the patient

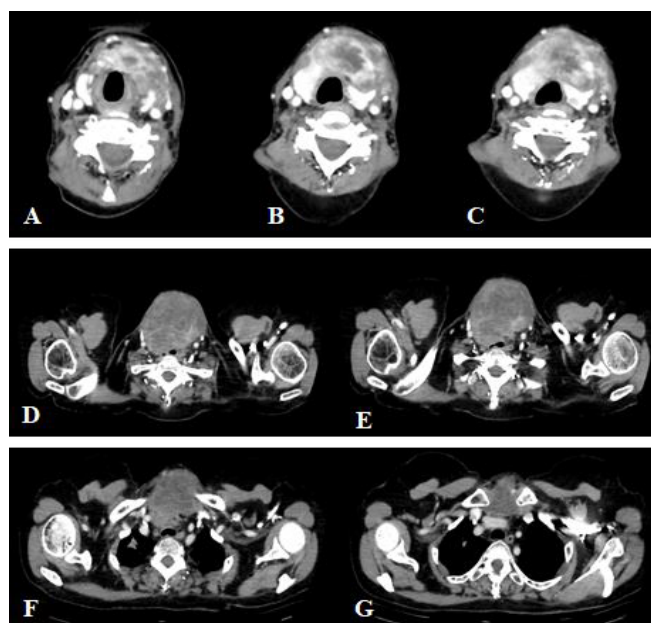


Fig. 2. Axial CT scan slides with an injection of contrast product showing the tumour mass at different levels of its extension

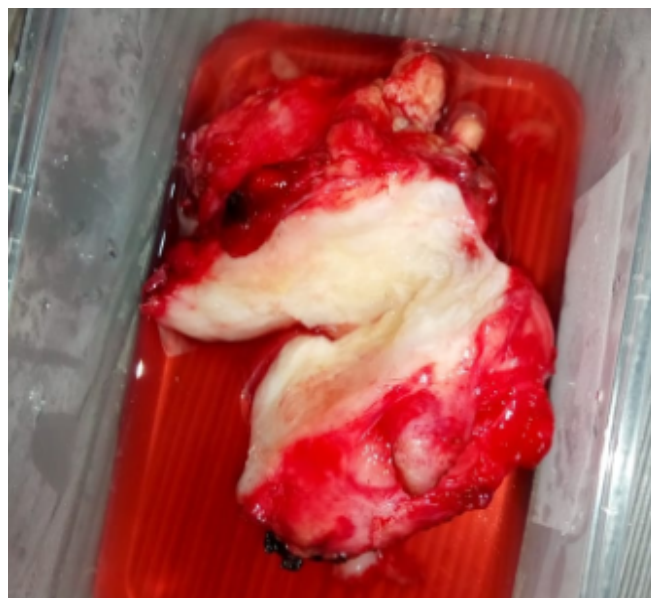


Fig. 3. Image showing surgical part just after excision in the operating room

re-irradiation of the cervical floor, delivered by a linear accelerator with 6 MV X-rays. The total dose was 60 Gy in 30 fractions, with a dose of 2 Gy daily for 5 days each week, in 6 weeks. This re-irradiation was received by the technique of Intensity-Modulated Radiation Therapy (IMRT) with fields prescribed to the 100% isodose line (Figures 4 and 5).

The cumulative dose of radiotherapy to organs at-risk was taken into account, especially to the spinal cord, right carotid and left carotid, whose maximum doses were 15.21 Gy, 35.4 Gy and 31, 85 Gy, respectively (Figures 6 and 7).

The patient received treatment according to plan and the tolerance was good. She was reviewed weekly during the treatment by our team. There were no significant side effects observed except moderate skin reactions on the irradiated skin and slight dysphagia.

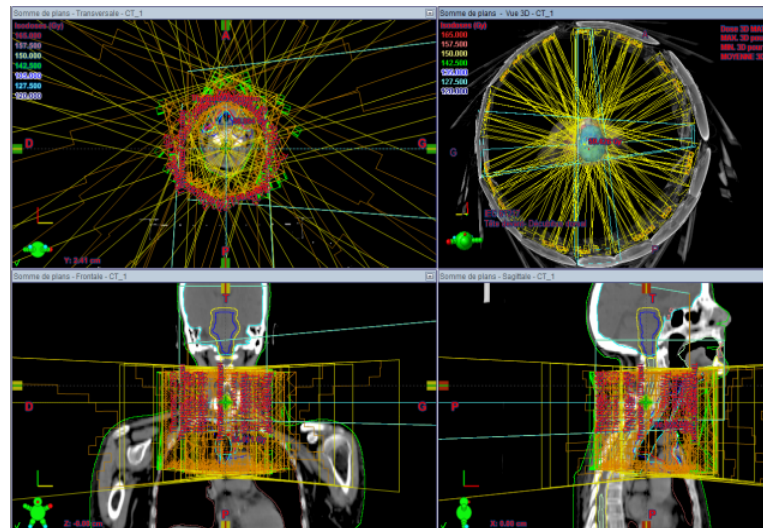


Fig. 4. Disposition of multiple IMRT beams on the three planes (axial, sagittal and coronal)

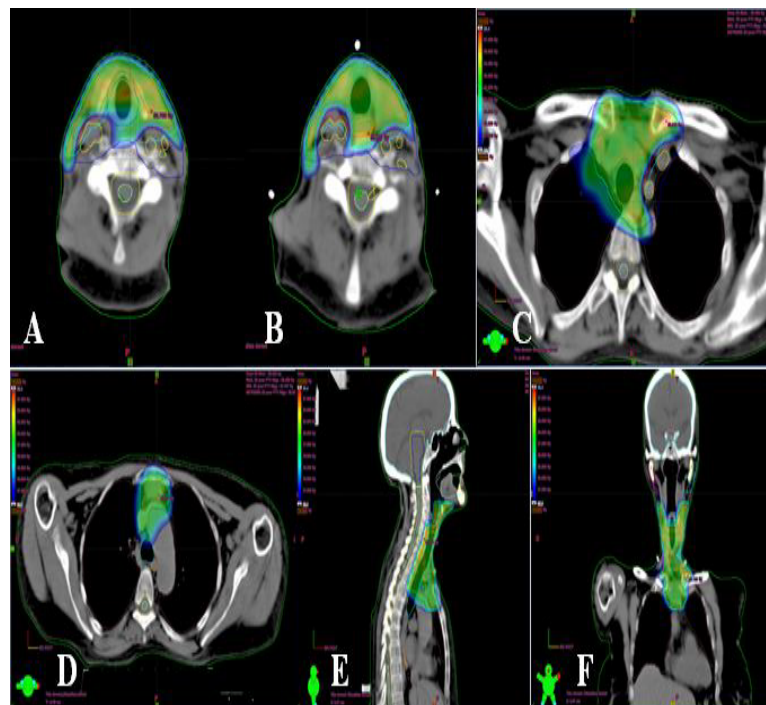


Fig. 5. (A-D): Axial view of the conformity of the prescribed dose to the target volume (magenta) and the respect for carotid arteries (yellow) and the spinal cord (light green); (E): sagittal plan; (F): coronal plan

## RESULTS

One month later, the patient presented with the appearance of subcutaneous nodules in the surgical bed, with dysphagia and cervical pain. Clinical examination detected a local disease evolution with palpation of a 2-cm neck mass (Figure 8).

Whole-body computed tomography (CT) scan revealed the presence of a large mass centered on the thyroid compartment, poorly limited, heterogeneous, with areas of necrosis, measuring approximately  $70 \times 48 \times 150$  mm. this mass encompasses and exerts a mass effect on the laryngotracheal axis by reducing its light, with irregularity of the tracheal wall testifying to its invasion. There is also infiltration of cervico-thoracic peri-lesional fat. Behind it invades the hypopharynx and the cervical esophagus (Figure 9).

On the chest and abdominal levels, there were no secondary

locations. Instead of surgery because of the impossible radical resection we opted for chemotherapy.

## DISCUSSION

Approximately 50% of patients with malignant neoplasms receive radiation therapy as part of their oncologic treatment [14]. Although radiation therapy can be effective at preventing disease recurrence, patients can also experience significant radiation-associated morbidity. One of the most feared late complications of radiation therapy is the development of secondary malignancies due to the carcinogenic effect of ionizing radiation. Secondary malignancy types include carcinoma (eg, breast and thyroid), mesothelioma, and sarcoma. Radiation-associated sarcomas are rare, occurring in fewer than 1% of patients who receive radiation therapy, but account for up to 5% of all sarcomas [3-8]. As the use of radiation therapy increases and the efficacy of oncologic therapy



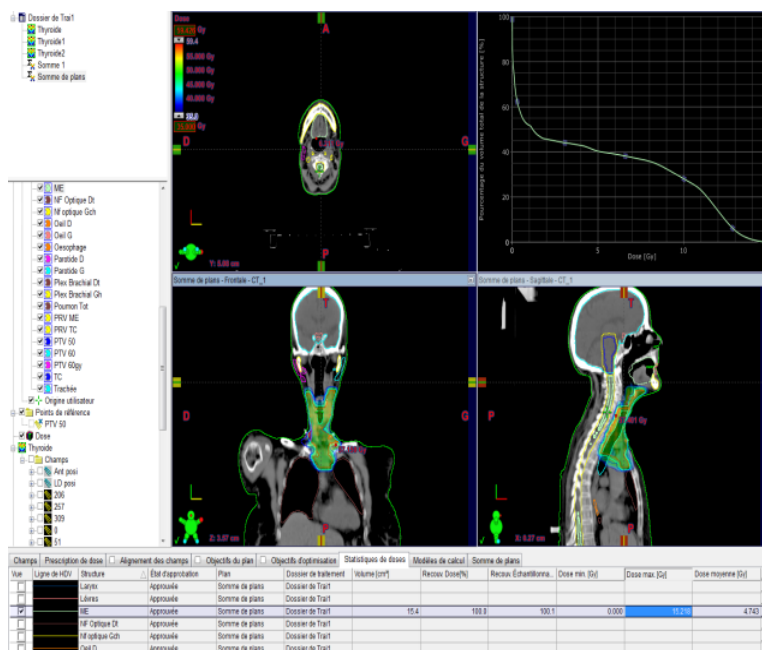


Fig. 6. Image showing the Dose-Volume Histogram (DVH) of the spinal cord at the top right, as well as the maximum dose received by the latter

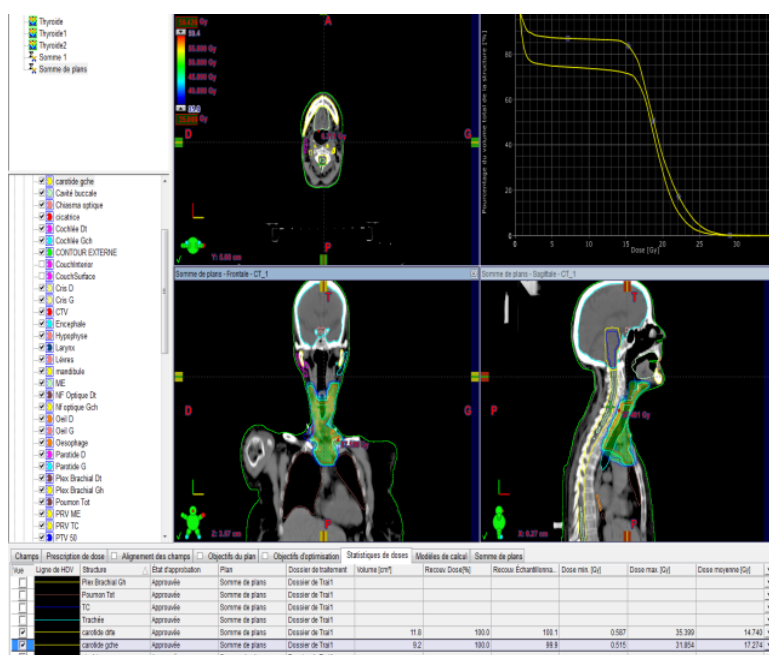
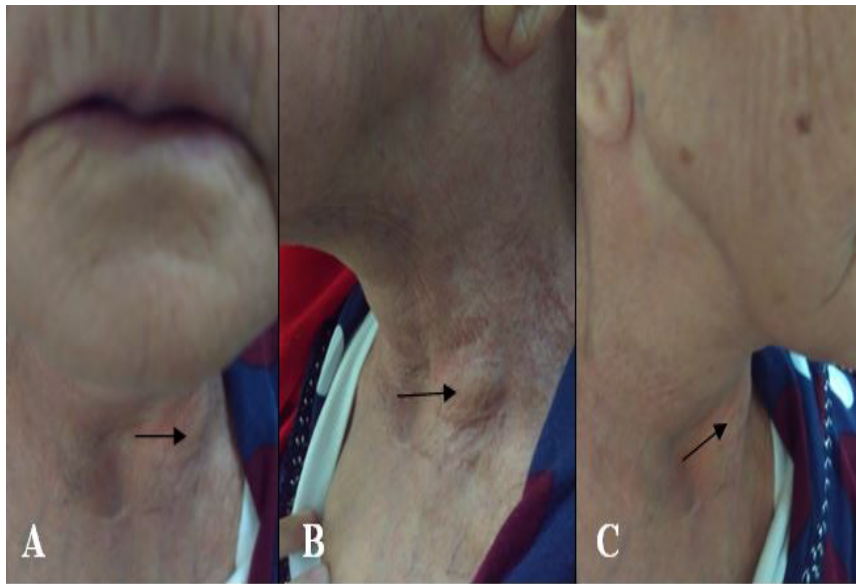


Fig. 7. Image showing the dose-volume histogram (DVH) of the carotid arteries at the top right and top, as well as the maximum dose received by them

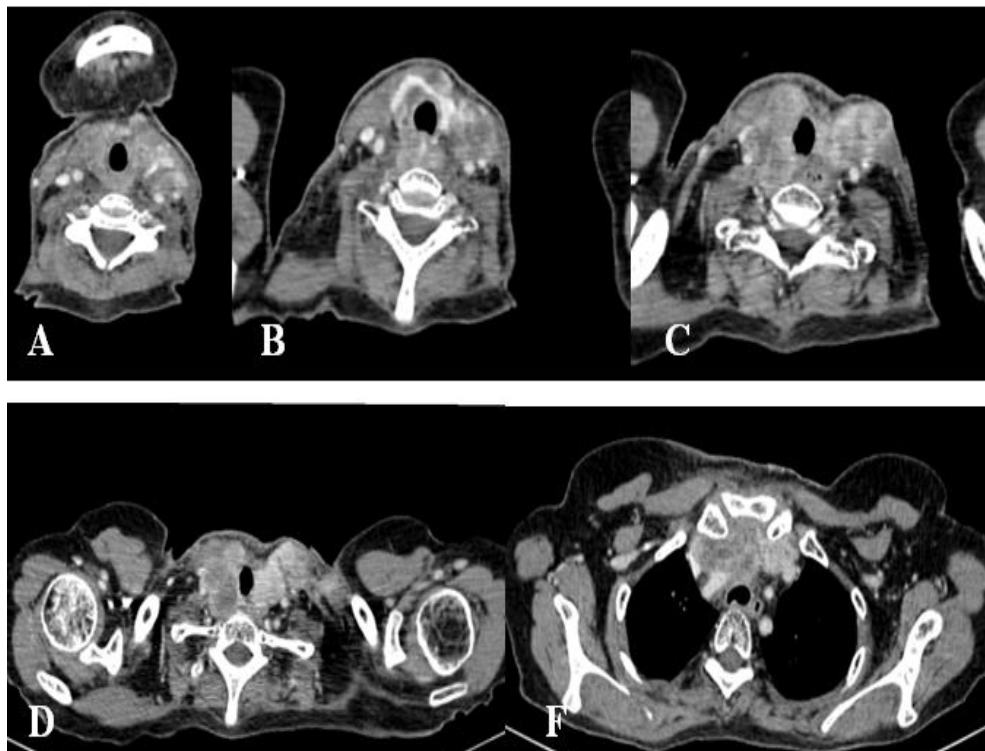
improves, there is a growing population of radiation-exposed cancer survivors from which the incidence of radiation-associated sarcomas is expected to grow [15]. Although many older studies have reported poor survival rates [3, 4, 11] recent work from several groups suggests that this may no longer be the case [5, 12, 13]. The median age of patients with radiation-associated sarcoma is approximately 60, but the range is wide because of the variable latency period between initial and secondary malignancy (months to >50 years) and the diverse patient population who receive radiation therapy. For instance, pediatric patients may develop radiation-associated sarcomas in their 20s, whereas those who receive radiation therapy for malignancies more common in older adults may develop radiation-associated tumors into their 80s

or beyond. In a recent study, the median latency from primary malignancy to diagnosis of radiation-associated sarcoma was 11 years, with a significantly shorter median latency for patients with radiation-associated angiosarcoma of the breast compared with patients with other types of radiation-associated sarcomas (8 years vs. 15 years, respectively) [13]. Our patient is 60 years old and has developed radiation-induced thyroid sarcoma after 27 years from the end of radiotherapy for a localized undifferentiated nasopharyngeal carcinoma (UCNT).

Currently, the most common primary malignancy for which patients received radiation therapy and subsequently developed radiation-associated sarcoma is carcinoma of the breast [13, 16]. This reflects the high incidence of this diagnosis and common



**Fig. 8.** Images showing clinical evolution of the disease with palpation of a 2-cm neck mass



**Fig. 9.** Scan sections in the axial plane, with contrast injection, showing the recurrent tumour mass, as well as its extensions and its relationship with the surrounding organs

use of breast-conserving therapy with lumpectomy followed by breast radiation [17]. The second most common group of patients with radiation-associated sarcoma is those who received radiation therapy for treatment of lymphoma [13, 16]. It is likely, however, that the size of this population will diminish with time as treatment paradigms have shifted away from high-dose, large-volume radiation treatment fields, with many patients no longer receiving any radiation therapy due to the use of newer, effective, and well-tolerated chemotherapy agents. The remaining patients include those with primary Gynecologic or prostatic primaries, unrelated sarcoma types, head and neck cancers, and colorectal cancer or germ cell tumors, all of which are commonly treated with radiation therapy. The anatomic sites in which radiation-

associated sarcomas arise reflect the initial radiation field, and, therefore, superficial locations on the chest wall or an extremity are most common, followed by deep cavity body sites (intrathoracic and intra-abdominal/pelvic) and head and neck [13, 16]. Radiation dose and field are believed to play a significant role in the likelihood of developing a radiation-associated sarcoma. These parameters are affected by disease biology, anatomic location, and the overall oncologic management strategy (including the use of systemic therapy and surgical resection). Most cancer patients receive conventionally fractionated radiation administered 1.8 Gy to 2 Gy per day over the course of 5 weeks to 8 weeks; patients receiving definitive radiation without plans for surgical resection typically receive higher doses of radiation than patients receiving

preoperative or postoperative radiation therapy. These results from the literature are consistent with the case of our patient who was irradiated at the time by two-Dimensional Radiotherapy (2DRT) with large irradiation fields, the limits of which were based on bone landmarks, with a high dose of radiotherapy up to 70 Gy. Patient-specific factors also play an important role in the risk of secondary malignancy after radiation therapy. Inherited germline variants, such as deficiencies in the double-strand break repair pathway, result in uniquely high rates of secondary malignancy, such that radiation therapy is rarely used in these patients [18]. The 2 most common histologic subtypes of radiation-associated sarcoma are angiosarcoma and unclassified sarcoma [13, 19]. Less common subtypes are Malignant Peripheral Nerve Sheath Tumor (MPNST), leiomyosarcoma, osteosarcoma (either arising in soft tissue or bone), and, rarely, chondrosarcoma, dedifferentiated liposarcoma, and pleomorphic liposarcoma [3, 5, 7, 13, 16, 19]. Our patient has a low-grade myxo-fibrosarcoma. Radiation-associated sarcomas have generally been considered to have a particularly poor prognosis among sarcomas, predominantly based on older literature reporting 5-year survival rates of 14% to 33% [3, 4]. However, 2 recent studies have suggested that outcomes may be improving, with 5-year survival rates of 58% to 68% [5, 13]. In the few large studies examining outcomes of patients with radiation-associated sarcomas, the following clinical and histologic features have been significantly associated with worse overall survival: positive margins, deep tumor location (intrathoracic or intra-abdominal), and high grade [3, 5, 13, 16]. Correspondingly, low or intermediate tumor grade, superficial location, and margin negative excision are associated with improved outcomes. The strongest driver for better outcome is complete surgical excision, and, therefore, amenability to complete excision is also associated with improved outcome. Our patient has had surgery with positive margins, which is a poor prognostic factor that may explain the progression of the disease in her. The cornerstone of treatment is surgery for those patients with localized disease at presentation. Excision with microscopic negative margins results in significant survival differences compared with margin-positive excision. The use of reirradiation for the treatment of radiation-associated sarcoma has been

associated with better outcomes in small studies [8]. Larger studies have not seen this association. Riad et al. showed a significantly higher proportion of local recurrence in patients with sarcoma in irradiated territory only operated on compared to those who were operated on and irradiated (34.5% versus 7.7%;  $p=0.043$ ) [8]. The indication for radiotherapy must be brought to a multidisciplinary consultation meeting dedicated to the management of sarcomas, depending on the risk-benefit ratio which must take into account the status of the surgical margins, the target volume, the dose previously received, the surrounding organs at risk and the volume of healthy tissues already irradiated. The informed consent of the patient is essential for decision-making. Re-irradiation should ideally be carried out using the most modern techniques in order to minimize the risk of late sequelae. Contemporary radiation techniques that allow more accurate targeting of the radiation dose may make this modality a more appropriate treatment in the future.

## CONCLUSION

Vigilant serial examinations of patients who have received radiation are therefore encouraged. The present case highlights the importance of being aware of this complication.

Therapeutically; as in sporadic sarcomas, complete surgical resection is the cornerstone of sarcoma management in irradiated areas. However, the high proportion of incomplete resection observed in this type of tumor increases the risk of local recurrence. Radiation therapy using modern irradiation techniques should be discussed after suboptimal surgery or in the case of sarcoma in irradiated territory that cannot be resecured for curative purposes.

## COMPETING INTERESTS

The authors state that they have no Conflict of Interest.

## AUTHORS' CONTRIBUTIONS

All authors read and approved the final version of the manuscript.

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