Radiology Case Reports 18 (2023) 3586–3591

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Case Report

Multimodality local ablative therapy of 23 lung metastases with surgical resection and percutaneous cryoablation in a patient with Li-Fraumeni Syndrome: A case report☆,☆☆

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ARTICLE INFO

Article history:
Received 4 June 2023
Accepted 20 July 2023

Keywords:
Li-Fraumeni syndrome
Cryoablation
Thermal ablation
Lung metastasis
Leiomyosarcoma

ABSTRACT

Patients with Li-Fraumeni syndrome (LFS) are prone to develop a variety of malignancies due to insufficient activity of the encoded tumor suppressor protein P53, including adrenocortical carcinoma, breast cancer, lung cancer, pancreatic cancer, and sarcoma. In the setting of LFS, local treatment options for lung metastases are limited to surgery and thermal ablation since radiotherapy and some systemic therapies predispose patients to additional future malignancies. We present the case of a 45-year-old woman with LFS with leiomyosarcoma metastases to both lungs who underwent bilateral wedge resections to treat a total of eight lung metastases followed by six percutaneous cryoablation sessions to treat 15 additional lung metastases over a period of 24 months. Our case demonstrates the option of multimodal local ablative therapies for lung metastases in patients with LFS, including percutaneous cryoablation.

☆ Acknowledgments: None.
☆☆ Competing Interests: Dr. Fintelmann received salary support from the Wood Foundation for related research. The other authors have no relevant conflicts of interest to declare.
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https://doi.org/10.1016/j.radcr.2023.07.047

Introduction

Patients with Li-Fraumeni syndrome (LFS) show insufficient activity of the *TP53-encoded* tumor suppressor protein P53 [1–3]. In healthy cells, *TP53* regulates progression through the cell cycle by arresting cell growth, signaling DNA damage repair proteins, or initiating apoptosis [4]. Patients with LFS are prone to developing malignancies, including primary and metastatic lung cancer, adrenocortical carcinoma, breast cancer, osteosarcoma, pancreatic cancer, and soft tissue sarcoma [1–3,5]. Traditional treatments for lung metastases include surgical resection, thermal ablation, radiation therapy, and systemic therapy, and surgical resection and thermal ablation for oligometastatic or oligoprogressive disease. However, radiation and some systemic therapies are not well suited in the setting of LFS [6]. Radiation therapy in patients with LFS has been linked to the development of secondary malignancies due to the inability of cells to recognize and repair double-strand DNA breaks generated by ionizing radiation [4,7–9]. The incidence of secondary tumors in a previous radiation field in patients with LFS is reported to be between 30% [10] and 37.5% [11].

Systemic therapy with genotoxic drugs can also cause iatrogenic cell damage and lead to secondary cancers [7,8,10,12,13]. While surgical resection of lung tumors is not contraindicated in the setting of LFS, the loss of lung function may limit the number of tumors, number of times, and amount of lung that can be resected [14]. Also, even a centrally located small tumor may require a lobectomy or even pneumectomy [6].

Percutaneous cryoablation is a safe and effective thermal ablation technique that has been prospectively evaluated for treating lung metastases [15,16]. Cryoablation relies on image guidance to position one or more applicators through the skin into or adjacent to the targeted tumor(s). Necrosis is achieved with a series of freezing and thawing [6,17]. Moreover, cryoablation does not lead to a measurable decrease in functional performance and quality of life [16].

While thermal ablation has been recommended for patients with LFS, cryoablation of lung metastases has not been described in this setting [3,18]. Here we present the case of a 45-year-old woman with LFS and sarcoma metastases to both lungs who underwent surgical resection and multiple percutaneous cryoablation sessions.

Case report

A 45-year-old female with Brazilian heritage presented to the Emergency Department of our hospital after ten days of worsening right upper quadrant abdominal pain and mild nausea (Fig. 1). She described her pain as constant, exacerbated by moving her right arm, and worsening over two weeks. Computed tomography (CT) showed a 23 × 16 mm lobulated mass arising from the suprarenal inferior vena cava (IVC) associated with a non-occlusive venous thrombus. The patient reported that her sister and her nephew had tested positive for a *TP53* mutation (c.1010G>A; p. Arg337His) and that her nephew had been previously diagnosed with choroid plexus carcinoma. Genetic testing revealed the same *TP53* mutation in the patient in the R337H variant known to be a disease-causing founder variant in 0.2-0.3% in Southern Brazil. Subsequently, a high-grade leiomyosarcoma was resected from the IVC, and surveillance with whole-body MRI was recommended.

Two years later, a mammogram revealed calcifications in the right upper outer breast, and a needle biopsy showed atypical ductal hyperplasia. The patient opted for bilateral prophylactic mastectomy, and the final pathology was consistent with grade 3 ductal carcinoma in situ. Two months after the bilateral mastectomy and two years after resection of the primary sarcoma, chest CT revealed eight enlarging bilateral solid lung nodules measuring up to 16 mm in the posterior basal segment of the left lower lobe. The patient was evaluated by thoracic surgery and underwent bilateral thoracoscopy-assisted wedge resections removing eight metachronous leiomyosarcoma metastases within the next eight months (Table 1). A left paraspinal mass and a scalp mass corresponding to additional leiomyosarcoma metastases were also surgically removed four months after the third wedge resection. The patient enrolled in chemotherapy-based clinical trials and also tried immunotherapy and monotherapy with off-label Lurbinectedin since previous phase II studies had suggested potential benefits of Lurbinectedin for patients with leiomyosarcoma (Fig. 1) [19].

While on systemic therapy and eight months after the third wedge resection, CT demonstrated six bilateral new and enlarging solid lung nodules measuring up to 9 mm, consistent with metachronous sarcoma lung metastases. The patient was referred to a multidisciplinary clinic to discuss the option of thermal ablation. After image review and discussion with input from thoracic surgery, radiation oncology, and interventional radiology, percutaneous cryoablation was determined to be the most appropriate treatment option for this young patient with excellent performance status to prolong survival while preserving quality of life.

The patient stopped systemic therapy one week before the cryoablation procedure and resumed five days afterward. For this and subsequent cryoablation procedures targeting lung metastases, the patient was positioned on the table of a CT scanner, and either moderate sedation or general anesthesia was administered, as previously described [20]. For the first of six cryoablation sessions, CT images obtained immediately before the ablation demonstrated an increase in the size of a 13 mm solid left pleural nodule (Fig. 2), which was treated with a 17.5 cm IcePearl 2.1 CX cryoprobe (Boston Scientific) using a triple freeze protocol (3 minute freeze, 3 minute passive thaw, 7 minute freeze, 3 minute passive thaw, 10 minute freeze) followed by 2 minute active thaw. The patient underwent five additional cryoablation sessions two, three, four, eight, and ten months after the first ablation to treat 14 additional lung metastases (Fig. 3). The patient experienced transient intercostal neuritis after the fourth session because the ice ball encompassed the intercostal nerve during the treatment of a subpleural tumor (Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0 Grade 1). No additional adverse events occurred following the cryoablation procedures.

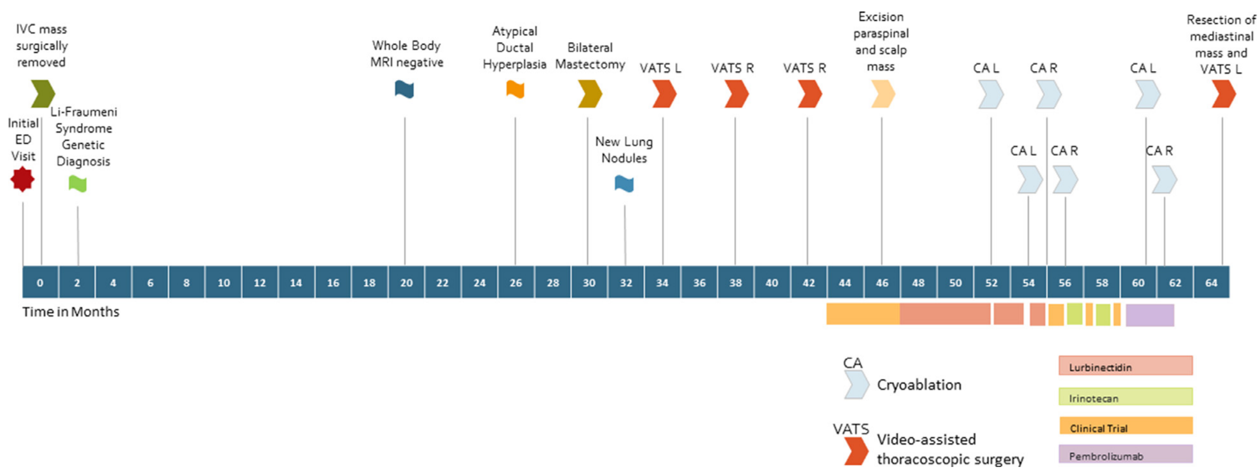

Fig. 1 – Timeline illustrating the diagnosis and multimodality management of neoplasms in the retroperitoneum, breast, and lungs in a woman with Li-Fraumeni syndrome. Abbreviations: ED, emergency department; IVC, inferior vena cava; L, left lung; MRI, magnetic resonance imaging; R, right lung; VATS, video-assisted thoracoscopic surgery.

Table 1 – Characteristics and sequential treatments of 23 lung metastases in a woman with Li-Fraumeni syndrome and leiomyosarcoma metastases to both lungs.

Lesion number	Treatment session	Tumor size at time of treatment (mm)	Treatment intent	Tumor location (peripheral, intermediate, central)	Tumor location (lobe)
1	Wedge VATS Resection 1	15	Eradication	Peripheral	LLL
2		5	Eradication	Peripheral	LUL
3	Wedge VATS Resection 2	2	Eradication	Peripheral	RUL
4		7	Eradication	Intermediate	RML
5	Wedge VATS Resection 3	18	Eradication	Peripheral	LUL
6		16	Eradication	Peripheral	LUL
7		4	Eradication	Peripheral	LUL
8		9	Eradication	Peripheral	LUL
9	Cryoablation 1	13	Eradication	Peripheral	LUL
10	Cryoablation 2	6	Eradication	Intermediate	LLL
11		8	Eradication	Peripheral	LLL
12	Cryoablation 3	7	Eradication	Peripheral	RLL
13	Cryoablation 4	3	Eradication	Intermediate	RLL
14		7	Eradication	Peripheral	RLL
15		8	Eradication	Peripheral	RLL
16	Cryoablation 5	4	Eradication	Peripheral	LLL
17		5	Eradication	Peripheral	LLL
18		4	Eradication	Peripheral	LLL
19		10	Eradication	Peripheral	LLL
20		18	Debulking	Central	LLL
21		9	Eradication	Peripheral	LLL
22	Cryoablation 6	7	Eradication	Intermediate	RML
23		7	Eradication	Peripheral	RLL
20*	Wedge VATS Resection 3	Partially ablated	Eradication	Central	LLL

Abbreviations: LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; VATS, video-assisted thoracoscopic surgery.

* This lesion was partially ablated due to proximity to the heart and resected 8 weeks later.

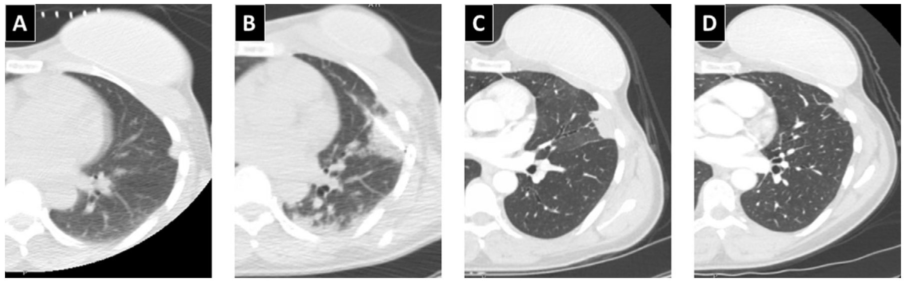

Fig. 2 – 45-year-old woman with Li-Fraumeni syndrome and leiomyosarcoma metastases to both lungs. CT images show (A) a solid 13 mm left upper lobe subpleural metastasis (arrow); (B) uncomplicated cryoablation (arrow) and expected postablation changes (C) 1 week (arrow) (D) and 6 months (arrow) following cryoablation.

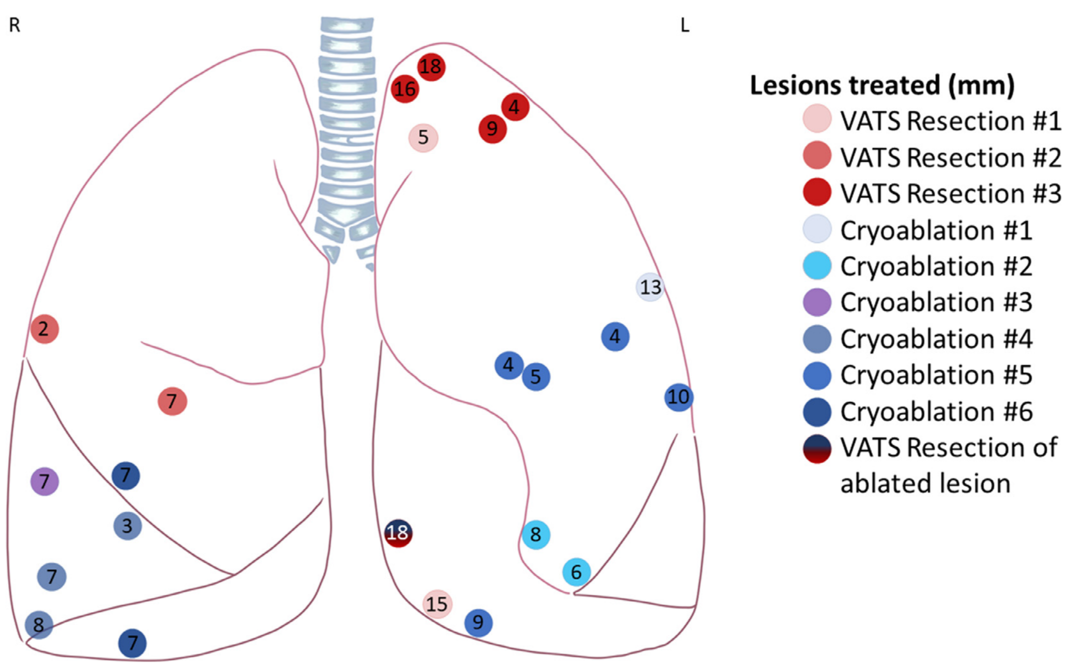

Fig. 3 – Location and treatment of leiomyosarcoma metastases to both lungs in a woman with Li-Fraumeni syndrome. Abbreviations: VATS, video-assisted thoracoscopic surgery.

Two months after the most recent cryoablation session the patient underwent resection of a 27 mm leiomyosarcoma metastasis located anterior to the heart combined with a fourth VATS resection targeting an 18 mm peridiaphragmatic left lower lobe nodule (metastasis #20, Table 1). This tumor was within 1 cm from the heart and had intentionally been partially treated with cryoablation. For the 14 ablated lung metastases treated with the goal of eradication, no local recurrence was observed at 16 months.

Discussion

This case highlights the option of multimodal local ablative therapy in a patient with LFS and multiple lung metastases. Surgical resection was combined with percutaneous cryoablation since neither treatment modality increases the risk of secondary cancers, contrary to radiation therapy. Primary technical success was achieved for all treated lung metastases, and no local progression was observed. The only adverse event related to percutaneous cryoablation was transient intercostal neuritis (CTCAE Grade 1).

Our experience with this case supports the safety and efficacy of treating lung metastases with percutaneous cryoablation. Cryoablation is safe and particularly effective for sarcoma lung metastases smaller than 1 cm with local control rates of 99% and 98% at 1 and 2 years [20]. Cryoablation has distinct advantages for patients with multiple lung metastases as it is (i) minimally invasive [20,21], (ii) preserves lung function [6], (iii) has lower complication rates than surgery [15], and (iv) is repeatable [22].

Prior studies showed that cryoablation of up to eight lung tumors in a single session is safe [20]. While data regarding the incidence of nerve injury due to percutaneous lung cryoablation are limited, [23] neuropathic pain following video-assisted thoracic surgery (VATS) has been described in about 25% of cases [24].

In general, the possibility of repeat percutaneous ablation is an important advantage compared with surgery and SBRT, since repeat pulmonary metastasectomy is associated with prolonged survival in patients with sarcoma [25]. Not only is the number of surgical interventions a patient can tolerate limited by the lung parenchyma lost, but resection of even small central lung nodules may also require lobectomy or even a pneumonectomy [17,26]. On the contrary, no decrease in lung function has been demonstrated following percutaneous thermal ablation, regardless of the tumor location. Therefore, percutaneous cryoablation provides the ability to control more pulmonary metastases than surgery alone [27]. Furthermore, cryoablation does not preclude subsequent surgical resection, as shown in this case of uneventful VATS following multiple lung cryoablation sessions. Although local ablative therapies cannot provide a definitive cure for metastatic leiomyosarcoma, they may prolong survival [27]. In this young patient with excellent performance status, the combination of surgery and thermal ablation-controlled disease burden while minimizing morbidity and preserving quality of life.

Patients with LFS are prone to developing multiple malignancies and management focuses on the surveillance, recognition, and early local treatment of emergent tumors [3,28]. Managing patients with LFS with lung metastases is complex and should involve a multidisciplinary team, including pulmonology, thoracic surgery, and interventional radiology [3,6,27]. This case report highlights the role of percutaneous lung cryoablation as a safe and effective treatment option for lung metastases in patients with LFS, where radiation is ideally avoided.

Authors' contributions

Case report conception and design: J. Saenger, F. Fintelmann; data collection: J. Saenger, G. Cote, A. Muniappan; draft manuscript preparation: J. Saenger, I. Tahir, F. Fintelmann. All authors reviewed the results and approved the final version of the manuscript.

Availability of data and materials

Not applicable.

Patient consent

Written informed consent for research and publication was obtained.

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