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Surgery for Li Fraumeni Syndrome: Pushing the Limits of Surgical Oncology

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Abstract

Objectives—Li Fraumeni syndrome is an autosomal dominant cancer syndrome due to a germline mutation in the p53 tumor suppressor gene. It results in multiple primary neoplasms in children and adults. A common question when faced with a Li Fraumeni patient who develops multiple primary cancers and/or recurrences is what is the proper treatment? Data suggests that ionizing radiation exposure increases the incidence of second malignancies in the Li Fraumeni population. Therefore, how much surgery can a cancer patient tolerate and still derive benefit from it?

Methods—We describe a representative case of a 54 year old female with Li Fraumeni syndrome with an enlarging adrenocortical hepatic metastasis, a new primary ampullary cancer, and an extensive surgical history.

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Results—We performed a simultaneous pancreaticoduodenectomy and repeat partial hepatectomy.

Conclusions—We propose that surgery is under utilized in metastatic solid organ familial cancers in general, and argue that an aggressive surgical approach should be considered in a multidisciplinary fashion for patients with Li Fraumeni syndrome and recurrent tumors. However, because of the rarity of this familial cancer there is a paucity of evidence to support this approach therefore a review of the literature is presented.

Keywords

Li Fraumeni syndrome; metastasectomy; simultaneous pancreaticoduodenectomy; hepatectomy

Introduction

Over a decade ago, Dr. Blake Cady stated that in surgical oncology, “Biology is King; selection of cases is Queen, and the technical details of surgical procedures are the Princes and Princesses of the realm who frequently try to overthrow the powerful forces of the King or Queen, usually to no long-term avail, although with some temporary apparent victories” [1]. Although this statement was proven correct on many occasions in the last century, recent technical advances, new surgical techniques, revised staging schemes, improved early diagnosis and more efficacious chemotherapy have resulted in re-examination of this historically important dictum. We report a case of a patient with Li Fraumeni syndrome (LFS) with an adrenocortical hepatic metastasis and a synchronous new primary ampullary cancer. After extensive review of the literature, we propose an aggressive surgical approach for patients with multiple cancers in the setting of LFS. Relevant literature and treatment are discussed below.

Materials and Methods

During routine screening endoscopy an asymptomatic 54 year-old female with known LFS was found to have a new ampullary mass in 2010. Biopsies revealed adenocarcinoma, moderately differentiated and invasive. Immunohistochemistries were performed and tumor cells positive for CKC, CDX-2, CK20, and negative for CK7, ER, PR, TTF-1, BRST-2. These findings supported a gastrointestinal primary. Staging imaging computed tomography (CT) imaging demonstrated a 6cm hepatic mass and a 1.6 cm ampullary mass (Figure 1A). Corresponding positron emission tomography (PET) images showed the hepatic mass to have a standardized uptake value (SUV) of 9.7 (Figure 1B). There were no other areas of significant PET avidity. The synchronous hepatic mass was biopsy proven to be metastatic adrenocortical carcinoma (ACC).

The patient’s oncologic and surgical histories date back to 1987 (24 years prior to the current presentation, Table 1) when she was diagnosed with intra-ductal carcinoma of the breast. Subsequently, she developed recurrent breast cancer along with multiple other primary cancers; adrenocortical cancer (ACC, 1989), right chest wall malignant fibrous histiocytoma (1995), multiple basal cell carcinomas and ampullary cancer. In addition to these 5 different primary cancers our patient had metastatic ACC to the lung and liver (1992,

1994, 1997, 2000). In 2008 she was diagnosed with LFS by documenting a germ line mutation in the p53 tumor suppressor gene. Relevant surgical history was: open left adrenalectomy, nephrectomy and splenectomy for ACC and prophylactic total abdominal hysterectomy and bilateral salpingoophorectomy. Relevant hepatic interventions included open non-anatomic wedge resection of segments V and IVB with cholecystectomy, margin status negative but <2mm. This was followed by a recurrence three years later and an extended right hepatectomy (metastatic ACC). The patient recurred in her hepatic remnant after three years and underwent percutaneous RFA of a solitary hepatic lesion (metastatic ACC). One year later, due to increasing size of this hepatic lesion she underwent open RFA of this solitary lesion (metastatic ACC).

The patient had an excellent performance status with an ECOG score of 0. Tumor markers were: CEA 4.7 (range 0.8–3.4), AFP 7.0 (range 0.6–6.6), CA19-9 8 (range 0–55), CA15.3 27 (range 0–30) and CA 27.9 25 (range 0–38). All other laboratory values including adrenocortical releasing hormone, serum cortisol and plasma metanephrines were within normal limits. On review of the patient's hepatic anatomy, a solitary tortuous portal vein and solitary hepatic vein were found, secondary to previous procedures and hepatic hypertrophy (Figure 1A). Of note, the ACC hepatic metastasis was abutting the solitary portal vein.

Results

Surgical Approach

After appropriate staging workup and multidisciplinary discussion, a surgical approach to render the patient disease free was decided. We brought the patient to the operating theater, three attending surgeons and one surgical fellow participated. Initially an extensive lysis of adhesions was performed after which, we focused our attention on resection of the hepatic mass. Intra-parenchymal aspects of the tumor were identified by intra-operative ultrasound, palpation and confirmatory frozen section biopsy. In-flow control was then obtained (Figure 2A). Due to the patient's previous hepatic surgeries and resulting peri-hepatic adhesions, we felt it unsafe to dissect her solitary hepatic vein; therefore, we did not gain outflow control. Consistent with imaging, the tumor was found to be directly adjacent and abutting for 6cm the patient's solitary inflow, intra-hepatic portal vein, which was freed via meticulous dissection. A non-anatomical wedge resection was then performed. Pringle maneuver lasted nine minutes. Since this was a non-anatomical resection her future liver remnant would be greater than 85% of her current remnant (what was left after her extended right hepatectomy). Following the hepatic resection, we proceeded with a standard pancreaticoduodenectomy (PD). All resection margins were grossly clear. Total procedural time was 13 hours and approximate blood loss was 1.5 liters.

Pathology

On microscopic examination the hepatic mass was confirmed to be metastatic ACC with the patient's primary. The intra-hepatic portal vein margin was focally involved microscopically. The ampullary mass was moderately differentiated ampullary adenocarcinoma confined to the Ampulla of Vater, Stage I. All resection margins were negative for tumor.

Follow Up

The patient tolerated the procedure well and was discharged on a low fat diet on postoperative day 17. Early in her post-operative course she was found to have a superficial wound infection at the lateral aspect of her chevron incision. This was opened and healed by secondary intention. She was followed with CT imaging every 3 months and received 12 cycles of adjuvant cisplatin. Due to this regimen patient developed grade 3 peripheral neuropathy after cycle 10. Follow-up is now at 23 months and imaging remains stable. Patient has no nausea, vomiting or bowel dysfunction and her weight remains stable.

Discussion

LFS is a rare autosomal dominant neoplastic syndrome characterized by a wide spectrum of primary malignancies in children and adults. This syndrome has now been linked to germline mutations of p53, a tumor suppressor gene on the short arm of chromosome 17. These mutations allow for the accumulation of genetic damage, in effect leading to genomic instability and neoplastic formation [2]. Criteria for LFS have been developed and include: (1) a proband with any bone or soft tissue sarcoma before age 45, (2) a first degree relative with any cancer under the age of 45, and (3) a first or second degree relative in the same lineage with any cancer under age 45, or sarcoma at any age [2]. Upwards of 75% of LFS patients develop cancers before the age of 45 as compared to 10% in the general population [2]. Moreover, cancer risk is estimated to be 90% by age 60 in patients with LFS [2]. Malignancies include sarcoma, breast, brain, leukemia, adrenal, lung, prostate, gastric, pancreatic, ampullary, lymphoma, germ cell tumors and Wilms' tumor [2].

Recent National Comprehensive Cancer Network (NCCN) guidelines in oncology for genetic and familial high risk assessment have addressed testing for LFS [3]. Testing criteria was divided into the classic LFS criteria and the Chompret criteria [3]. Classic criteria stated that testing should occur in individuals diagnosed with a sarcoma less than age 45 who also have a first degree relative diagnosed less than age 45 with cancer and also an additional first or second degree relative in the same lineage with cancer diagnosed less than age 45, or a sarcoma at any age [3]. Chompret et al revised this criteria stating TP53 mutation screening should be implemented in, an individual with a tumor from the LFS tumor spectrum before age 46 and at least one first or second degree relative with any cancer of the LFS tumor spectrum other than breast cancer (if the proband has breast cancer) before the age of 56; an individual with multiple primaries at any age, an individual with adrenocortical carcinoma or choroid plexus carcinoma at any age of onset, regardless of family history, or an individual with early onset of breast cancer less than 30 years of age with a negative BRCA1/BRCA2 test [4].

Surveillance was also addressed by the NCCN guidelines in oncology for genetic and familial high risk assessment. Due to the prevalence of breast cancer among those with LFS they advocated breast self-exam training and education starting at 18 years of age, clinical breast exams every 6–12 months, starting at age 20–25 years or 5–10 years before the earliest known breast cancer in the family [3]. Further, LFS patients should have annual mammography and breast MRI screening starting at age 20–25 years or individualized based on the earliest age of onset in family [3]. With respect to other cancer risks, the NCCN

guidelines addressed the limitations of screening for many cancers associated with LFS and made a general statement that because of the remarkable risk of additional primary neoplasms, screening should be entertained for cancer survivors with LFS who have a good prognosis from their primary tumor [3]. As per NCCN LFS patients should have annual comprehensive physical examinations (including careful skin and neurologic exams) with a high index of suspicion for rare cancers and second malignancies in cancer survivors [3]. Colonoscopy should be considered every 2–5 years starting no later than age 25 [3]. Participation in novel screening approaches using technologies within clinical trials when possible, such as whole-body MRI, abdominal US and brain MRI is favored [3]. Overall, surveillance should be targeted based on individual family histories.

Three percent of LFS patients will develop ACC [5, 6]. Although chemotherapy (Mitotane) is commonly used, it has little impact on disease progression [7]. Therefore, it is hypothesized that an aggressive surgical approach for ACC is associated with prolonged survival [6] [7]. Recently, Ripley et al. published the largest series to date of patients undergoing hepatic resection for metastatic ACC. This series found a median overall survival of two years which was superior to historical controls [7]. Extrapolating this data to our patient, we thought it prudent to take an aggressive surgical approach to the metastatic ACC hepatic lesion. In addition, we felt the hepatic disease would be a rate-limiting step in this patient's overall survival. Fassnacht et al recently published results of cytotoxic therapy in advanced ACC. They compared cytotoxic agents (etoposide, doxorubicin, cisplatin) plus mitotane versus streptozocin plus mitotane and found higher response rates (23.2% vs 9.2%, $p < 0.001$) as well as increased progression free survival (5.0 vs 2.1 months, $p < 0.001$) in the cytotoxic group (fassnacht m 2012). Adjuvant cisplatin-mitotane was implemented in our patient and may have suppressed a recurrence at her solitary portal vein in-flow.

We advocated for a synchronous resection of the ampullary cancer with the patient's hepatic tumor. Currently, there are approximately 200 cases of combined pancreaticoduodenectomy (PD) and partial hepatectomy published. Recent reports stated that the procedure is safe and does not significantly increase ones morbidity as compared to PD alone [8] [9]. Singh et al. analyzed seven cases showing an increase in the amount of blood loss compared to PD alone; however, the overall complication rates and duration of hospital stay were not significantly affected [8].

PD itself carries a significant morbidity and mortality. Some believe that combining another procedure such as hepatectomy with PD makes it a formidable scenario [8]. However with current improvements in surgical technique combined with improved perioperative and postoperative management, the morbidity and mortality of PD have decreased [8]. With these encouraging developments the limits of PD are being extended. Multi-visceral resections combined with PD are now increasingly reported and have been proven safe when performed at experienced centers [10, 11]. Results of a systematic review of 103 patients undergoing synchronous PD and hepatectomy found that this procedure can be performed with low morbidity and mortality[12]. Furthermore, De Jong et al analyzed 5,025 patients who underwent PD at two large U.S. hepatobiliary centers. Of this cohort, 126 patients underwent either staged or synchronous liver directed therapy along with PD. It was concluded that a simultaneous approach should be used when possible for the incidence of

hepatic abscess was increased in patients undergoing staged liver directed therapy [9]. Although, the operative time may be prolonged and the complexity of the operation increased, the overall outcome remains relatively unaffected.

Radiation-associated cancers are typically rare, arising 10 years after irradiation and carry an incidence less than 2% [13]. However, data suggests that LFS patients are at a higher risk of secondary radiation-induced malignancies [13–17]. Using breast cancer as an example, population analysis holds that the risk of loco-regional relapse after breast surgery and adjuvant radiotherapy is reported to be 1% per year [13]. In a small cohort of LFS patients treated with breast conserving therapy for breast cancer, 3/8 patients developed a second malignancy (chest wall angiosarcoma, malignant histiocytofibroma, and papillary thyroid cancer) in the radiation field and 3/8 patients developed an in-field, ipsilateral breast relapse [13]. Hasada et al. also documented a relationship between radiotherapy and second malignancies in a cohort of 200 LFS patients. This study found that 8 solid cancers were diagnosed in 6 patients who had received radiotherapy [14]. The role of radiation stress in human cells containing heterozygous germ-line p53 mutations leads to a defective cell cycle arrest in G1/S and a lesser apoptotic response of lymphocytes [13]. These cellular features promote radiosensitization and potentially carcinogenesis [13]. In vivo analysis of Trp53 heterozygous null mice have found an accelerated emergence of solid tumors following ionizing radiation [18]. Due to the increased incidence of radiation-induced malignancy, a conservative approach should be undertaken for radiation therapy.

Long term survival is achievable for LFS with multiple primaries and metastatic lesions when surgery is implemented in a multidisciplinary approach (Table 2) [15] [19] [20] [21] [22] [23]. For example, Izawa et al. published their experience with one patient who had 9 separate primary malignancies. Utilizing surgery the patient survived for over 20 years following her diagnosis of LFS [21]. Nutting et al. described a patient with LFS who had 17 different primary malignancies [15]. Again, surgery was implemented and the patient had an overall survival of 41 years from her first malignancy [15]. Although the seven cases depicted in table 2 are anecdotal reports without historical controls, we

We propose, based on limited but promising data, that an aggressive surgical approach for tumor eradication should be undertaken in the LFS population with the principal aim of prolonging survival. In spite of the paucity of data, and until proven otherwise, LFS patients presenting with multiple cancers and/or recurrences should undergo operations for each primary and/or recurrence as if it were the first cancer diagnosed. In essence, for a given cancer, one should treat LFS patients as one would treat non-LFS patients regardless of past occurrences; and, radiation therapy should be used conservatively, if at all, following thorough discussion with the patient.

Acknowledgments

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List of Abbreviations

ACC	adrenocortical cancer
RFA	radiofrequency ablation
ECOG	eastern cooperative oncology group
CEA	carcinoembryonic antigen
AFP	alpha fetoprotein
CA	cancer antigen
CT	computed tomography
PET	positron emission tomography
SUV	standardized uptake value
LFS	Li Fraumeni syndrome
PD	pancreaticoduodenectomy

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FIGURE 1.

A, CT imaging displaying a solitary tortuous portal vein (black arrow) in relation to the metastatic adrenocortical hepatic tumor (white arrow). B, PET imaging documenting a SUV of 9.7 of the metastatic adrenocortical hepatic tumor.

Figure 2.
In flow control: The portal vein is skeletonized (black arrow) from the hepatic artery and bile duct

Table 1

Complete oncologic and surgical history for our 54-year old female with Li Fraumeni syndrome

	Medical/Surgical History
1987	Left breast intraductal carcinoma: left breast lumpectomy
1989	Left ACC: Left adrenalectomy, left nephrectomy, splenectomy
1990	Right lung ACC metastasis: Right thoracotomy, segmental resection
1991	Right breast intraductal carcinoma: right breast lumpectomy
1992	Left lung lesion: left thoracotomy, benign pathology
1993	Bilateral mastectomy
1994	Liver lesion metastatic ACC: liver wedge resection
1995	Right chest wall malignant fibrous histiocytoma: right chest wall resection
1997	New liver disease (ACC): Extended right hepatectomy
1999	Left pleural effusion: left thoracentesis, pleurodesis
2000	New liver disease (ACC): Percutaneous RFA of solitary liver lesion
2001	Increasing size of liver lesion: open RFA of solitary liver lesion
2006	Basal cell carcinoma (right temporal lesion): wide local excision
2007	Basal cell carcinoma (scalp): wide local excision
2008	Diagnosed Li Fraumeni Syndrome
2008	Prophylactic hysterectomy, bilateral salpingoophorectomy
2009	DIEP flap bilateral breast reconstruction
2010	Ampullary cancer and increasing liver lesion

Table 2

Literature search depicting Li Fraumeni patients with multiple primary malignancies who underwent repeat surgical resections correlating with a prolonged overall survival. (+) indicates ongoing survival

Manuscript (year)	Organs Involved	Number of Surgical Resections	Overall Survival from Initial Malignancy
King et al (1993)	Soft Tissue Sarcoma, Bone, Skin (melanoma)	3	17 years
Nutting et al (2000)	Skin, Ovary, Soft Tissue Sarcoma, Breast, Endometrium, Lung, Kidney	14	41 years
Vranic et al (2006)	Muscle, Breast	Multiple/NOS	8 years
Izawa et al (2008)	Bone, Breast, Colon, Soft Tissue Sarcoma, Lung	8	20 years
Landolsi et al (2010)	Bladder, Soft Tissue Sarcoma, Pancreas, Bone	2	8 years
Curiel- Lewandrowski et al (2011)	Bone, Skin (melanoma)	6	5 years+
<i>Langan et al (2012)</i>	Breast, Adrenal, Lung, Liver, Soft Tissue Sarcoma, Skin, Ampulla	15	24 years+