

Radiation Therapy for Choroid Plexus Carcinoma Patients with Li-Fraumeni Syndrome: Advantageous or Detrimental?

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Abstract. *Background: Choroid plexus carcinomas (CPCs) are rare pediatric tumors often associated with Li-Fraumeni Syndrome (LFS), a germline mutation in the TP53 tumor-suppressor gene, predisposing to cancer. Materials and Methods: We performed a systemic literature review from 1990-2013 to evaluate the hypothesis that radiation therapy should be avoided in patients with CPC and LFS. Overall survival (OS) was compared using Kaplan–Meier curves and log-rank tests. Results: Twenty-eight patients were documented with CPC and LFS. Eleven out of 17 patients received radiation therapy. The survival of patients receiving radiation was inferior to that of those without radiation [median ($\pm 95\%$ confidence interval) 2-year OS=0.18 \pm 0.12% versus 0.58 \pm 0.12%]. The log-rank tests suggested the difference to be marginally significant ($p=0.056$). Conclusion: This finding provides evidence for pursuing treatment approaches that do not include radiation therapy for patients with LFS.*

According to the World Health Organization, choroid plexus carcinomas (CPCs) are classified as central nervous system tumors of grade III (1). They are often associated with Li-Fraumeni syndrome (LFS) (2-4). In most cases of LFS, an underlying germline *TP53* mutation can be detected (5).

Prior to the advent of gene analysis techniques, criteria for classical LFS were proposed based on phenotypic cancer characteristics. In 1988, this cancer phenotype was observed in 24 families (6). Classical LFS families were initially characterized as those in which sarcoma occurred before the age of 45 years and with at least one first-degree relative younger than 45 years with cancer, or a close relative with

cancer before the age of 45 years or sarcoma at any age (3, 7). Most recently, additional criteria for identifying germline *TP53* mutation carriers allow for the possibility of testing children with sentinel tumors such as CPC or adrenocortical carcinoma with a negative family history (3, 5, 8). Despite these criteria, some family cases remain with phenotypic characteristics of LFS that lack the *TP53* mutation. These phenotypic criteria include family history of cancer diagnoses at a young age, a synchronous diagnosis of another type of cancer, or a metachronous diagnosis of a second cancer at a later date (9). This strongly suggests that genetic factors other than *TP53* mutations may contribute to familial predisposition to cancer in families with LFS (10).

CPC is a malignant tumor primarily affecting infants and children under two years of age (11). Current recommendations for the treatment of CPC include surgical resection followed by adjuvant therapy. Although radiotherapy improves survival for many with high-grade embryonal brain tumors, its use remains controversial due to its irreversibly detrimental effects on brain development, especially for young children (12, 13).

Dysregulation by mutant P53 may allow tumor cells to escape genotoxic signals, including gamma-radiation, by circumventing programmed cell death, senescence and even non-canonical metabolic anti-tumoral mechanisms (14, 15). Based on the molecular function of P53, we proposed that patients with LFS, specifically those that harbor the *TP53* mutation, will present with primary radioresistance. This theory was demonstrated in a family with LFS with *TP53* mutation, in which exposure to ionizing radiation resulted in increased fibroblast culture and increased resistance associated with reduced permanent G₁ arrest (5). *TP53* germline mutations have also been reported to negatively impact the survival for patients with CPC due to increased resistance to chemotherapy and irradiation (7). We, therefore, performed a literature analysis to evaluate the hypothesis that radiation therapy should be avoided in the sub-group of patients with CPC and LFS.

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Key Words: Li-Fraumeni syndrome, choroid plexus carcinoma, *TP53* mutation, radiation.

Table I. Demographics, treatment, and outcome of patients with choroid plexus carcinoma and Li-Fraumeni syndrome.

Reference	Age (months)/sex	TP53 mutation	Initial XRT	XRT at recurrence	Initial Cx	Surgery	Outcome
7	NA	Yes	Yes	Yes	NA	NA	DOD
7	NA	Yes	Yes	No	NA	NA	DOD
20	NA/M	Yes	Yes	No	CPT-SIOP 2009	GTRx	DOD×10 months
21	6/M	Yes	Yes	No	NA	GTRx	DOD×20 months
22	96/M	Yes	Yes	No	NA	GTRx	NED×16 years
22	12/F	Yes	Yes	No	NA	PRx	NED×8 years
7	NA	Yes	Yes	No	NA	NA	DOD
7	NA	Yes	No	Yes	NA	NA	DOD
7	NA	Yes	No	Yes	NA	NA	DOD
9	10/M	Yes	No	Yes	HDCx/AHCR	GTRx	DOD 34 months, MDS mets
23	8/F	Yes	No	Yes	VNC/5-FU	GTRx	DOD 1 year, 2 months (rhabdo)
7	NA	Yes	No	No	NA	NA	DOD
7	NA	Yes	No	No	NA	NA	DOD
7	NA	Yes	No	No	NA	NA	DOD
7	NA	Yes*	No	No	NA	NA	DOD
7	NA	Yes*	No	No	NA	NA	DOD
9	12/M	Yes	No	No	CCG-99703	GTRx	NED×83 months
9	48/M	Yes	No	No	CCG-99703	GTRx	NED×60 months
9	14/M	Yes	No	No	HSIII	GTRx	NED×12 months
9	54/M	No, pheno ⁺	No	No	Cx*	GTRx	DOD (AML 39 months)
21	12 /M	Yes	No	No	NA	GTRx	NED×15 years
22	11/F	Yes	No	No	No	GTRx	DOD×NA weeks
24	24/F	Yes	No	No	Yes1	GTRx	NED×52 months
25	12/F	Yes	No	No	HDCx AST	GTRx	NED×5 years
8	12/M	Yes	No	No	Yes/BMT	GTRx	DOD×1 year
8	12/M	Yes	No	No	NA	GTRx	NED×11 years
26	3/M	Yes	No	No	No	GTRx	NED×42 months
27	8/M	No, pheno ⁺	No	No	Yes2	GTRx	NED×2 months

Cx: Chemotherapy; Cx*: combination of cisplatin, vincristine, cyclophosphamide, etoposide, and carboplatinum; CPT-SIOP 2000: six cycles of etoposide, vincristine (VNC), and two cycles of local radiotherapy (XRT) with 54 Gy; HDCx/AHCR: high-dose (myeloablative) chemotherapy with autologous hematopoietic cell rescue; 5-FU: fluorouracil; CCG-99703: Children's Oncology Group protocol [3 cycles of induction chemotherapy (VNC, cisplatin, cyclophosphamide, and etoposide) followed by three cycles of HDCx/AHCR (thiotepa and carboplatin)]; HSIII - Headstart III protocol (5 cycles of induction chemotherapy of VNC, cisplatin, cyclophosphamide, etoposide, and high-dose methotrexate); DOD: dead of disease; GTRx: gross total surgical resection of primary tumor; NED: no evidence of disease; NA: not available; PRx: partial resection of primary tumor; pheno+: phenotypically positive for Li-Fraumeni syndrome; Yes*: TP53 staining-positive but negative for TP53 mutation; Yes¹: cyclophosphamide, etoposide and carboplatin; Yes²: 20 weeks of cyclophosphamide, vincristine, cisplatin, followed by 21 days of oral etoposide; AML: acute myeloid leukemia; AST: autologous stem cell rescue; BMT: bone marrow transplantation; M: male; F: female; MDS: myelodysplastic syndrome; mets: metastatic; rhabdo: rhabdomyosarcoma.

Materials and Methods

We used a pre-existing choroid plexus tumor literature database which consisted of 1,004 patients with choroid plexus tumors. We then further expanded our database with a systemic literature review on Medline, Cochrane, Embase, Scopus, and Web of Science from 1990-2013. Search words included "Li Fraumeni syndrome and choroid plexus carcinoma". We restricted the analysis to patients with CPC identified by the presence or absence of TP53 dysfunction or presence of phenotypic characteristics of LFS. In total, our final database consisted of 11 articles, which included 28 patients. We evaluated patients treated with radiation therapy, chemotherapy or surgery alone and compared their overall survival. Overall survival was defined as the time interval between initial diagnosis and the last follow-up visit or death due to any cause. The database was analyzed using the stratified sub-group analysis technique with SPSS® (Version 19; SPSS

Inc, San Francisco, CA, USA). Survival was analyzed using the Kaplan–Meier estimates and compared with log-rank tests.

Results

Twenty-eight patients were documented with CPC and LFS. Twenty-four patients had documentation of germline TP53 mutations, two had phenotypic characteristics of LFS (there was no TP53 mutation in one patient and this was not tested in the other) and two patients had positive p53 staining but no TP53 mutation (7). The male to female ratio was 2:1 (12 males, 6 females, 10 unknown). The median and mean age at diagnosis was 12 months (range=3-98 months) (Table I). Locations of tumors were predominantly in the lateral ventricle (10 cases; 18 unknown).

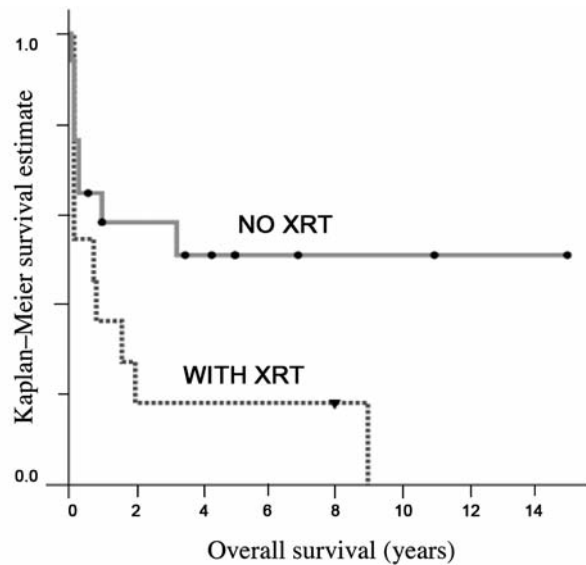


Figure 1. Kaplan-Meier survival curve of patients with Li-Fraumeni Syndrome (LFS) receiving radiation therapy (XRT) vs. those that did not receive radiation therapy ($p=0.056$).

All patients were treated with surgical resection. Gross total resection of the primary tumor was achieved in 15 cases, partial resection in one case (unknown in 10 cases).

A total of 27 cases were treated with chemotherapy at initial diagnosis. Various chemotherapy regimens were used including combinations of cisplatin, vincristine, cyclophosphamide, etoposide, and carboplatin.

Eleven patients received radiation therapy. Five out of the 11 patients received radiation therapy after tumor recurrence. Radiotherapeutic doses were 22.5 to 23.4 Gy craniospinal, and 54 Gy locoregional to primary tumors or to metastatic nodules (three cases of craniospinal radiation, one of local radiation, and five unknown). Of the eleven patients that received radiation therapy, six died from disease recurrence or progression, three died from secondary malignancies, and two were alive without disease at the time of the study. Seventeen patients did not receive radiation therapy. Out of these patients, one developed secondary malignancy (acute myeloid leukemia); seven died of disease progression and the others were alive at the time of the study.

The median [95% confidence interval (CI)] overall survival duration of the whole cohort of studied patients with LFS and CPC was 1 ± 0.76 years. The survival of patients receiving radiation was inferior to that of those without radiation (2-year overall survival $0.18 \pm 0.1\%$ versus $0.58 \pm 0.12\%$, respectively). Kaplan-Meier curves (Figure 1) showed survival advantages for patients that did not receive radiation. The log-rank tests suggested the difference to be marginally significant ($p=0.056$).

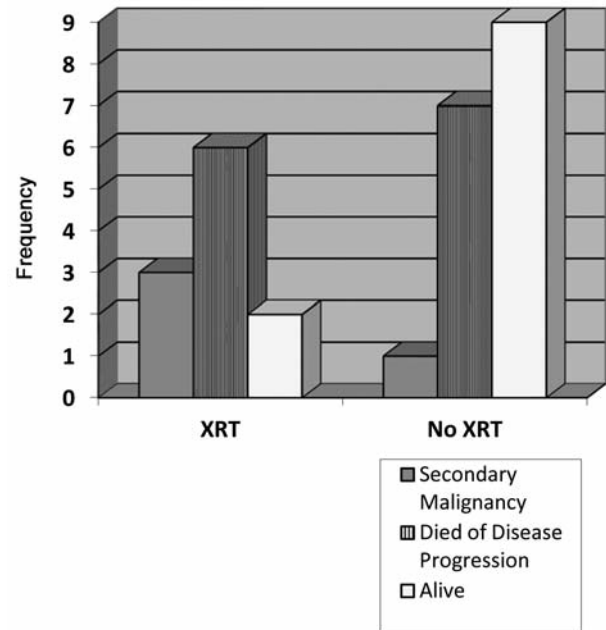


Figure 2. Distribution of outcomes: Increased secondary malignancies in patients receiving radiation therapy (XRT).

We acknowledge that death from disease in the patients that received deferred radiotherapy may actually reflect radioresistance at relapse rather than primary failure of radiotherapy. To further explore the effects of radiation, our data were re-analyzed by excluding the five out of the 11 patients who received radiation at tumor recurrence. Kaplan-Meier survival curves continued to show a survival advantage for patients treated without radiation therapy, however, the statistics did not reach significance ($p=0.3$) likely due to an insufficient sample size.

Discussion

CPCs are highly invasive tumors, with a poor prognosis. Due to the rarity of this tumor, there exist no current guidelines for the treatment of patients with LFS with CPC. Surgical treatment is generally considered the most important factor, however, the role of radiation therapy remains controversial (12). This meta-analysis assessed the effect of radiation therapy on CPC in the LFS population. Due to detrimental effects on brain development, certain studies recommend radiation therapy as a treatment modality for all patients with CPC over the age of 3 years (12). However, these studies did not demonstrate whether their specific patients carried the TP53 mutation in association with LFS. The present results suggest that there is a survival disadvantage with the use of radiation therapy for patients with LFS with CPC. Thus, we propose that

patients with CPC with *TP53* mutations should be classified as a separate entity and treated differently with irradiation-sparing protocols.

The acute toxicity of radiotherapy in patients with LFS may be tolerable (16) but late toxicities include an increased cumulative risk for secondary malignancies (Figure 2). Depending on the tumor type and underlying *TP53* mutation, different mechanisms may lead to treatment failure. Loss-of-function ('disruptive') *TP53* mutations predicted radiotherapy failure in a study of head and neck cancer (17), while gain-of-function ('non-disruptive'), *TP53* mutation led to a shorter overall survival in patients with advanced non-small cell lung cancer independent of epidermal growth factor receptor (*EGFR*) mutations (18).

The increased rate of tumor progression or relapse following radiotherapy in our analysis is disturbing. As a possible explanation, the study by Boyle *et al.* (5) suggests that gamma irradiation of LFS-derived cells with doses below those required for definite cell kill may induce and select for cells with additional genetic aberration, enabling accelerated growth potential. Furthermore, regardless of *TP53* mutation, the reduced capacity to eliminate or repair chromosomal damage of the type induced by ionizing radiation may contribute to cancer predisposition in this syndrome (19).

This study has the limitations of a retrospective literature review. We cannot produce the level of evidence as reliable as that of a prospective randomized study since there is publication bias from case reports and case series. However, a prospective clinical study would also not allow us to produce this level of evidence, given the rarity of this tumor type. Thus a literature review provides the best possible evidence to date.

Given the data that LFS-derived cells display radioresistance, the increased risk of secondary malignancies associated with radiation therapy in patients with LFS and the detrimental neurological sequelae of radiotherapy, we propose that radiation therapy should be avoided in all patients with LFS with CPC.

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Received February 12, 2015

Revised February 23, 2015

Accepted February 25, 2015