Radiotherapy in the treatment of extracranial hemangiopericytoma/solitary fibrous tumor: Study from the Rare Cancer Network

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A B S T R A C T

Background and purpose: The role of radiotherapy (RT) in the treatment of hemangiopericytoma/solitary fibrous tumor (HPC/SFT) is still under debate. We aimed at investigating whether radiotherapy can improve the results in patients operated for extracranial HPC/SFT.

Materials and methods: Data from patients with HPC/SFT, treated from 1982 to 2012, were retrospectively reviewed within the Rare Cancer Network framework. Actuarial local control (LC), disease-free survival (DFS), metastasis-free survival (MFS) and overall survival (OS) were calculated with Kaplan-Meier method. Patient and tumor parameters were analyzed by univariate and multivariate analysis.

Results: Of 114 HPC/SFT, 58 (50.9%) occurred in the extremities/superficial trunk and 56 (49.1%) in intra-thoracic/retroperitoneum. Seventy-eight patients (68.4%) underwent surgery only (Sx), and 36 (31.6%) Sx and RT (Sx + RT). Median RT dose was 60 Gy (range 45–68.4 Gy) in 1.6–2.2 Gy fractions. In the extremities/superficial trunk group of patients, actuarial 5-year LC rates were 50.4% after Sx and 91.6% after Sx + RT (p = 0.008) for DFS. In the intra-thoracic/retroperitoneum group of patients, actuarial 5-year rates were 93.8% after Sx and 77.8% after Sx + RT (p = 0.002) for DFS. At multivariate analysis, the addition of RT resulted in better LC and DFS in the whole series. The advantage was confirmed for LC in the group of patients affected by extremity/superficial trunk tumors.

Conclusion: Addition of RT to Sx could improve the prognosis, in terms of LC and DFS, essentially in patients with extremities/superficial trunk tumor locations.

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Extracranial hemangiopericytomas and solitary fibrous tumors (HPC/SFT) were formerly classified as two different tumor entities. They have been merged as solitary fibrous tumors in the 2013 World Health Organization (WHO) classification [1] and represent a spectrum of disease from benign to malignant and infiltrative tumors with potential for hematogenous dissemination [2]. The NAB2-STAT6 fusion transcript is identified in most SFTs whatever their localization in the body [3,4]. Because of this complexity and their rarity (1–2% of all soft-tissue tumors)[5], controversies remain about their optimal management. Surgery is the standard
of care when feasible, but the role of radiotherapy and chemotherapy is not well established, and studies are limited [6–9].

We investigated the role of radiotherapy to reduce the risk of recurrence after surgery in the framework of the Rare Cancer Network (www.rarecancer.net) in a cohort of patients diagnosed with extracranial HPC/SFT.

Materials and methods

Data of patients treated from January 1982 to December 2012 for extracranial HPC/SFT in Rare Cancer Network centers were collected anonymously after approval by the ethical committee following the rules of the institution of each participating center. Patients had to be >18 years with pathological diagnosis of HPC/SFT of any extracranial part of the body.

Statistical analysis

Continuous variables are presented as means and range, categorical variables as percentages. Margin status after surgery was defined based on pathology reports as negative R0 (n = 73), microscopic R1 (n = 33) or macroscopic R2 (n = 12) resection, the latter ones grouped as R+. Pathology grading was defined as “low” (grade 1) or “high” (grade 2–3) following the French Federation of Comprehensive Cancer Centers (FNCLCC) score system [10]. Overall survival (OS) was calculated from the initial diagnosis and local control (LC), disease free survival (DFS) and metastasis-free survival (MFS) from the date of surgery using the Kaplan–Meier method and compared between surgery vs. surgery + radiotherapy with the log-rank test in the whole series and separately in patients with extremities/superficial trunk and in patients with intra-thoracic/retroperitoneal (including intra-abdominal/pelvic) tumor locations. Prognostic factors were identified by univariate and multivariate analyses with Cox proportional-hazards model and hazard ratios with 95% confidence intervals. In case of non-proportional hazards for specific variables, the stratified Cox regression model was applied.

Treatment (surgery vs. surgery + radiotherapy) effect was analyzed in the whole series also with the propensity score method to minimize biases related to non-random treatment assignment. A multivariable logistic regression model was fitted to estimate the probability, i.e. the propensity score, to undergo surgery + radiotherapy, considering gender, age, tumor site (extremities/superficial trunk or intra-thoracic/retroperitoneal) including intra-abdominal/pelvic tumor locations. Prognostic factors were identified by univariate and multivariate analyses with Cox proportional-hazards model and hazard ratios with 95% confidence intervals. In case of non-proportional hazards for specific variables, the stratified Cox regression model was applied.

A p-value ≤0.05 was chosen as statistical significance. Statistics were performed using SAS software, v9.4 (SAS Institute).

Results

Of 151 patients with extracranial HPC/SFT from 17 RCN centers and 10 countries over 20 years, 37 cases were excluded, leaving 114 patients available for the analysis: 13 cases were excluded for non-curative treatment mainly because of metastatic spread, 11 for unknown margin status after surgery, 9 for lack of follow-up and 4 for inhomogeneities of treatment modalities.

Main patient and treatment characteristics of the whole series (N = 114) and of the patients with extremities/superficial trunk (N = 58; 50.9%) and intra-thoracic/retroperitoneal tumors (N = 56; 49.1%) are reported in Table 1.

Diagnostic workup included computed tomography (CT) for local and distant staging in 99/114 cases (86.8%) (chest only in 72 cases and chest/abdomen in 27 cases), magnetic resonance imaging (MRI) for primary tumor site in 48/114 cases (42.1%), 18F-fluorodeoxyglucose positron emission tomography (PET) in 13/114 cases (11.4%) and pre-operative angiography in 5/114 cases (4.4%).

Surgical resection resulted in pathological R0 in 70/114 cases (61.4%), R1 in 32/114 cases (28.1%), and R2 in 12/114 cases (10.5%). It resulted R0 in 31/58 (53.4%) and 39/56 (69.7%) cases, R1 in 19/58 (32.8%) and 13/56 (23.2%) cases, and R2 in 8/58 (13.8%) and 4/56 (7.1%) cases for extremities/superficial trunk and for intra-thoracic/retroperitoneal tumor locations, respectively.

For radiotherapy purposes, clinical target volume (CTV) was defined by CT alone in 17/36 (47.2%) patients and by CT + MRI in 19/36 (52.8%) patients, and planning target volume (PTV) was obtained by adding 5–10 mm (median 10 mm) margin, depending on tumor site. Two-, three-dimensional radiotherapy and intensity-modulated radiotherapy was used in 13/36 (36.1%), 19/36 (52.8%) and 4/36 (11.1%) patients, respectively.

Median total dose of radiotherapy was 60 Gy for the whole series (range 45–68.4 Gy), and for the two patient groups with extremities/superficial trunk (range 45–66.6 Gy) and intra-thoracic/retroperitoneal (range 50–68.4 Gy) tumors with the same median dose/fraction of 2 Gy for the whole series (range 1.6–2.2 Gy) and for extremities/superficial trunk (range 1.6–2.2 Gy) and intra-thoracic/retroperitoneal (range 1.8–2 Gy). All patients received at least 45 Gy equivalent total dose in 2 Gy/fraction (EQD2) considering an α/β value of 10 Gy.

After median follow-up of 5.8 years (range 1–29.8 years), 85/114 patients (74.6%) were alive and 29 (25.4%) had died. Actuarial OS, DFS, MFS and LC curves for the whole series and for extremities/superficial trunk and intra-thoracic/retroperitoneal tumors are displayed in Figs. 1–3. Corresponding actuarial data are reported in supplementary material.

Notably, actuarial 5-year LC rate was 72.5% after surgery and 88.0% after surgery + radiotherapy (p = 0.03) in the whole series, 50.4% after surgery and 91.6% after surgery + radiotherapy in extremities/superficial trunk tumors (p < 0.0001), and 89.3% after surgery and 77.8% after surgery + radiotherapy in intra-thoracic/retroperitoneal tumors (p = 0.99). In total, LC occurred in 16/71 (22.5%) R0 and in 21/45 (46.7%) R+ of which 12/33 (36.4%) R1 and 9/12 (75.0%) R2.

Four patients developed “in field” recurrence after median dose of 60 Gy (range 55–64 Gy). Considering the R+ cases with high-grade tumors, 6/6 patients had recurrence after surgery only and 1/6 after surgery + radiotherapy in the group of extremities/superficial trunk locations, while 4/9 had recurrence after surgery only and 1/3 after surgery + radiotherapy in the group of intra-thoracic/retroperitoneal locations.

Distant metastasis occurred mostly in lungs and liver with similar actuarial 5-year survival rates after surgery only (85.0%) and after surgery + radiotherapy (84.7%), as reported in supplementary material.

Prognostic factors are reported in Tables 2 and 3 and supplementary material. In the whole series, the addition of radiotherapy to surgery resulted in better LC (p = 0.007) and DFS (p = 0.02) at multivariate analysis. This result was confirmed by propensity score analysis for LC (p = 0.005). Moreover, multivariate analysis showed that maximum tumor diameter >7 cm (median) was associated with poorer OS (p = 0.004), DFS (p = 0.02) and MFS (p = 0.005) and margin status influenced LC (p = 0.02), DFS (p = 0.001) and MFS (p = 0.02). In the 36 patients treated by surgery + radiotherapy, total dose < or ≥60 Gy did not influence LC.

Multivariate analysis in the two groups of patients with different tumor location showed that the addition of radiotherapy resulted in better LC (p = 0.003) and in a trend for better DFS
Table 1
Characteristics of all patients (N = 114), patients with extremities/superficial trunk (N = 58) and patients with intra-thoracic/retroperitoneal tumor locations (N = 56).

<table>
<thead>
<tr>
<th></th>
<th>All (N = 114)</th>
<th>Extremities/superficial trunk (N = 58)</th>
<th>Intra-thoracic/retroperitoneum (N = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S (%)</td>
<td>S + RT (%)</td>
<td>S (%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46 (59.0)</td>
<td>24 (75.0)</td>
<td>22 (47.8)</td>
</tr>
<tr>
<td>Male</td>
<td>32 (41.0)</td>
<td>8 (25.0)</td>
<td>4 (40.0)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Median*</td>
<td>39 (50.0)</td>
<td>18 (56.2)</td>
<td>23 (50.0)</td>
</tr>
<tr>
<td>&gt;Median*</td>
<td>39 (50.0)</td>
<td>14 (43.8)</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>Tumor site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremities/superficial trunk</td>
<td>32 (41.0)</td>
<td>15 (65.2)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td>Intra-thoracic/retroperitoneum</td>
<td>46 (39.0)</td>
<td>8 (34.8)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Maximum diameter (94/114)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;Median**</td>
<td>36 (57.1)</td>
<td>15 (65.2)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td>&gt;Median**</td>
<td>27 (42.9)</td>
<td>8 (34.8)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Margins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R+</td>
<td>29 (37.2)</td>
<td>17 (53.1)</td>
<td>12 (26.1)</td>
</tr>
<tr>
<td>R0</td>
<td>49 (62.8)</td>
<td>15 (46.9)</td>
<td>34 (73.9)</td>
</tr>
<tr>
<td>Grading (99/114)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (2–3)</td>
<td>29 (44.6)</td>
<td>8 (30.8)</td>
<td>21 (33.8)</td>
</tr>
<tr>
<td>Low (1)</td>
<td>36 (55.4)</td>
<td>18 (69.2)</td>
<td>18 (67.2)</td>
</tr>
</tbody>
</table>

Abbreviations: S = surgery; RT = radiotherapy; H&N = head and neck; R+ = residual tumor (R1 + R2); R0 = no residual tumor; *median age: whole series = 57.5, extremities/superficial trunk = 52, intra-thoracic/retroperitoneum = 59.5; **median maximum diameter: whole series = 7 cm, extremities/superficial trunk = 4.6 cm, intra-thoracic/retroperitoneum = 10 cm.

Fig. 1. Actuarial overall (a), disease-free (b), metastasis-free (c) survival and local control (d) in the patients (N = 114) who underwent surgery only (radiotherapy no) or surgery + radiotherapy (radiotherapy yes).
in the group with extremities/superficial trunk, but not in the group with intra-thoracic/retroperitoneal locations (Tables 2 and 3).

Acute radiation-related toxicity was reported in 22/36 patients (61.1%) treated by surgery + radiotherapy (grade 1 in 11 patients, grade 2 in 10, and grade 3 in 1). It mainly consisted of dermatitis, mucositis and salivary gland toxicity.

Late radiation-related toxicity was reported in 17/36 patients (47.2%) after surgery + radiotherapy (grade 1 in 9 patients, grade 2 in 4, grade 3 in 3, and grade 4 in 1). Grade 3 toxicity was observed in the subcutaneous tissue, lung and small bowel. The sole grade 4 toxicity was observed in the small bowel.

Discussion

In this series of extracranial HPC/SFT, all patients underwent surgery and about one third of them (31.6%) surgery + radiotherapy, providing the opportunity to study the role of adjuvant radiotherapy. Moreover, the presence of patients with various tumor locations allowed to analyze separately cases from extremities/superficial trunk and from intra-thoracic/retroperitoneum. Data collection over a long-time period allowed to assemble a large series with long follow-up of such rare disease. However, long accrual time and retrospective study design were probably the causes of the relative heterogeneity of cases and treatment approaches, which were probably influenced by local expertise and treatment policy of participating centers. To reduce such heterogeneity, we excluded from the analysis all cases treated with non-curative intent, unknown margin status, adjuvant chemotherapy and lack of adequate follow-up.

Several literature studies did not specifically address the role of radiotherapy in multidisciplinary treatment setting [6,7,11,12–16]. In our series, OS rates were similar in patients undergoing surgery or surgery + radiotherapy, but radiotherapy improved both LC and DFS as shown by multivariate analysis and confirmed by propensity score analysis with a significant value for LC. Of note, late local recurrences were observed even after 10 years [12].

In accord with other studies [14,17], the radicality of surgery resulted significant prognostic factor for LC and DFS. Salas et al. [12] reported that margin status after R0-R1 resection did not influence outcomes. In our series, the influence of margin status was probably emphasized by the presence of few R2 cases that had very high recurrence rate (75%). To address potential attrition biases, we performed propensity score analysis that adjusted for possible biases related to different characteristics between the patients treated by surgery and by surgery + radiotherapy, that confirmed the benefit of radiotherapy in our series. In this regard, literature data show equivocal results. Salas et al. [12] reported that postoperative radiotherapy can improve LC without influencing OS, as reported in head and neck series [11,14]. Wushou et al.
analyzing the “Surveillance, Epidemiology, and End Results (SEER)” database, observed that DFS was worse after postoperative radiotherapy compared to surgery only. They commented that radiation is usually added in case of unfavorable tumor characteristics, which can adversely influence the prognosis.

Considering the two groups of patients with different tumor location, radiotherapy was able to significantly improve LC in patients with extremities/superficial trunk, but not in those with intra-thoracic/retroperitoneal tumors. Our results are in accord with other literature data showing that radiotherapy can reduce local recurrence in operated extremities high-grade sarcoma, especially after R+ resection [18]. On the other hand, it is still unclear whether retroperitoneal sarcoma can benefit from the addition of radiotherapy to surgical resection [19,20]. Due to the limited number of patients, our study did not allow to clarify this issue for HPC/SFT, although the rate of recurrence was slightly lower (1/3 vs. 4/9) after radiotherapy in R+ patients with high-grade intra-thoracic/retroperitoneal tumors. Of note, in the group with R+ and high-grade extremities/superficial trunk tumors, 6/6 patients recurred after surgery and only 1/6 after surgery + radiotherapy.

Among the other prognostic factors, univariate and multivariate analyses confirmed what observed in other studies [12,18–20], showing that margin status, grading, and maximum tumor diameter have a prognostic role for survival parameters and LC, and could be considered in the decision of adding radiotherapy. In particular, independent prognosticators for DFS were margin status in extremities/superficial trunk and grading in intra-thoracic/retroperitoneum.

Recent literature focused on predictive models to identify patients at higher risk of metastatic spread by using age, tumor size, mitotic activity [21] and tumor necrosis [12,22]. In this regard, preliminary data of our study [23] were used by Salas et al. [12] to validate their model that found that age <60 years, visceral involvement and high mitotic count can identify patient classes with different risk levels for developing local recurrence and metastatic spread.

The present study analyzed also acute and late radiation side effects and found a relatively low percentage of patients who experienced grade >2 acute and late toxicities. However, toxicity data could be underestimated in a retrospective series like this and the multiple tumor sites could have influenced the incidence in patient subgroups.

The main limitations of our study were related to its retrospective design, to the potential biases in case selection due to the patient accrual in radiation oncology centers, and to the availability of some tumor and treatment parameters, such as tumor size and grading, in less than 100% of cases and definition of CTV margins. Moreover, the long-time span of patient accrual could represent a bias for both pathology diagnosis, that could not be centralized for organizational reasons, and treatment modalities,

![Fig. 3. Actuarial overall (a), disease-free (b), metastasis-free (c) survival and local control (d) in the patients with intra-thoracic/retroperitoneal tumors (N = 56) who underwent surgery only (radiotherapy no) or surgery + radiotherapy (radiotherapy yes).]
Table 2  
Univariate (UA) and multivariate analysis (MA) for prognostic factors in overall survival (OS), disease-free survival (DFS), metastasis-free survival (MFS), and local control (LC) in patients with extremities/superficial trunk tumors (N = 58).

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>DFS</th>
<th>MFS</th>
<th>LC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UA MA</td>
<td>UA MA</td>
<td>UA MA</td>
<td>UA MA</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male vs. female</td>
<td>2.20 (0.66–7.29)</td>
<td>0.20</td>
<td>1.56 (0.34–7.23)</td>
<td>0.57</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (0.98–1.07)</td>
<td>0.28</td>
<td>1.01 (0.97–1.07)</td>
<td>0.54</td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgery + RT vs. surgery</td>
<td>2.22 (0.64–7.64)</td>
<td>0.21</td>
<td>1.03 (0.87–2.63)</td>
</tr>
<tr>
<td>Margins</td>
<td>R+ vs. R0</td>
<td>1.25 (0.35–4.48)</td>
<td>0.73</td>
<td>0.83 (0.16–4.30)</td>
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<tr>
<td>Grading</td>
<td>high (2–3) vs. low (1)</td>
<td>1.83 (0.38–2.75)</td>
<td>0.45</td>
<td>1.40 (0.24–2.80)</td>
</tr>
</tbody>
</table>

Abbreviations: HR = hazard ratio; CI = confidence interval; RT = radiotherapy; R+ = residual tumor; R0 = no residual tumor.

Table 3  
Univariate (UA) and multivariate analysis (MA) for prognostic factors in overall survival (OS), disease-free survival (DFS), metastasis-free survival (MFS), and local control (LC) in patients with intra-thoracic/retroperitoneal tumors (N = 56).

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>DFS</th>
<th>MFS</th>
<th>LC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UA MA</td>
<td>UA MA</td>
<td>UA MA</td>
<td>UA MA</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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</tr>
<tr>
<td>Male vs. female</td>
<td>2.66 (0.87–8.09)</td>
<td>0.09</td>
<td>2.69 (0.75–9.63)</td>
<td>0.13</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (0.99–1.09)</td>
<td>0.06</td>
<td>1.03 (0.97–1.10)</td>
<td>0.29</td>
</tr>
<tr>
<td>Treatment surgery + RT vs. surgery</td>
<td>1.35 (0.46–3.98)</td>
<td>0.58</td>
<td>0.96 (0.29–3.13)</td>
<td>0.94</td>
</tr>
<tr>
<td>Margins</td>
<td>R+ vs. R0</td>
<td>1.34 (0.50–3.64)</td>
<td>0.56</td>
<td>0.80 (0.27–2.44)</td>
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<tr>
<td>Grading (50/56)</td>
<td>High (2–3) vs. low (1)</td>
<td>5.35 (1.19–23.98)</td>
<td>0.03</td>
<td>4.46 (0.85–23.40)</td>
</tr>
</tbody>
</table>

Abbreviations: HR = hazard ratio; CI = confidence interval; RT = radiotherapy; R+ = residual tumor; R0 = no residual tumor; * assessed by stratified Cox regression model based on gender for LC and on grading for MFS because these variables showed evidence of non-proportional hazards; ** assessed by log-rank test because grading variable showed evidence of non-proportional hazards.
including surgical resection and radiation techniques. Finally, the non-uniform case distribution in the patient subgroups influenced the power of statistics, especially in the intra-thoracic/retroperitoneum group where a larger number of patients could allow to draw firmer conclusions.

In conclusion, this study showed that the addition of radiotherapy could improve LC and DFS rates in patients operated for extracranial HPC/SFT as it emerged from multivariate analysis. The separate analysis of the two different tumor locations showed that the advantage of adding radiotherapy was for extremities/superficial trunk rather than for intra-thoracic/retroperitoneum tumors. Margin status, grading, and maximum tumor diameter resulted also significant prognostic factors. Although challenging for the rarity of extracranial HPC/SFT, the conduct of prospective trials should be seriously considered in the future to better define the role of adjuvant radiotherapy and possible systemic drug therapy.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the University Hospital “Maggiore della Carità”, Novara, Italy (Prot. 874/CE, Study N. CE 144/15). The study was performed in accordance with the Declaration of Helsinki.

Conflict of interest

No conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.11.011.

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