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Whole Lung Irradiation in Adults with Metastatic Ewing Sarcoma: Practice Patterns and Implications for Treatment

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Background. Whole lung irradiation (WLI) is a standard treatment component for children with metastatic Ewing Sarcoma (ES), but data on WLI for adults are sparse. An adult with excellent performance status presents with primary ES in the leg and multiple pulmonary metastases. The patient achieves complete radiographic response after chemotherapy and resection of the primary. Would you give bilateral WLI to (1) this adult patient?, (2) this patient if 20 years old (yo)?, (3) this patient if 45 yo?, or (4) this patient if 60 yo? Results. 38 experts responded, including 24 adult, 1 adolescent young adult, and 13 pediatric oncologists. 63%, 63%, 62%, and 50% of respondents offered WLI to the adult, 20-year-old, 45-year-old, and 60-year-old, respectively. Pediatric oncologists more likely endorsed WLI across all ages including the adult (P = 0.01), 20-year-old (P = 0.005), 45-year-old (P = 0.01), and 60-year-old (P = 0.08). There were no significant differences between medical and radiation oncologists or between European/Australian and American providers. Conclusions. Almost two-thirds of experts surveyed supported WLI for adults with metastatic ES up to age 45 and half supported WLI for a 60-year-old. Continued collaboration across adult and pediatric oncology is needed to define evidence-based strategies across the age spectrum.

1. Introduction

Ewing Sarcoma (ES) is a mesenchymal malignancy of unclear histogenetic derivation characterized by distinct chromosomal translocations at the EWSR1 gene [1]; this disease occurs primarily in children and young adults and less commonly in older adults. Although 20–25% of patients with ES present with distant metastatic disease at diagnosis [2], some patients, such as those with limited pulmonary metastases (PM), may be cured with aggressive multimodality therapy. Whole lung irradiation (WLI) is one such treatment designed with curative-intent for patients with PM. In the Intergroup Ewing's Sarcoma Study (IESS-I) of primarily pediatric patients with localized disease, prophylactic WLI with VAC chemotherapy (vincristine, doxorubicin, and cyclophosphamide) was associated with improved survival and fewer PM relative to those treated with VAC alone [3]. Similarly, other retrospective studies have suggested benefits in disease control and survival with the use of WLI for patients with metastatic ES and clinically evident PM [4–8]. Fractionated WLI at doses between 12 and 21 Gy appears to be well tolerated with acceptable rates of toxicity [3–7, 9–11], although data across all age ranges are lacking. Despite the lack of prospective randomized studies, the available data have supported use of WLI as a component of curative therapy for the majority of pediatric ES patients with PM, and this practice is strongly supported by the U.S. National Cancer Institute (NCI) [12].
Table 1: Surveyed expert oncologists’ recommendations for whole lung irradiation for Ewing Sarcoma patients with pulmonary metastases in complete response following chemotherapy.

<table>
<thead>
<tr>
<th>Whole lung irradiation recommendation</th>
<th>N</th>
<th>Adult*</th>
<th>P</th>
<th>20-year-old</th>
<th>P</th>
<th>45-year-old</th>
<th>P</th>
<th>60-year-old</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All oncologists surveyed</td>
<td>38</td>
<td>63%</td>
<td>63%</td>
<td>62%</td>
<td>50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncologist discipline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical oncologist</td>
<td>26</td>
<td>58%</td>
<td>NS</td>
<td>58%</td>
<td>NS</td>
<td>60%</td>
<td>NS</td>
<td>46%</td>
<td>NS</td>
</tr>
<tr>
<td>Radiation oncologist</td>
<td>12</td>
<td>73%</td>
<td>75%</td>
<td>67%</td>
<td>58%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AYA/pediatric oncologist</td>
<td>14</td>
<td>92%</td>
<td>0.01</td>
<td>93%</td>
<td>0.005</td>
<td>92%</td>
<td>0.01</td>
<td>75%</td>
<td>0.08</td>
</tr>
<tr>
<td>Adult oncologist</td>
<td>24</td>
<td>48%</td>
<td>46%</td>
<td>46%</td>
<td></td>
<td>46%</td>
<td></td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Oncologist country</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe/Australia</td>
<td>15</td>
<td>57%</td>
<td>NS</td>
<td>60%</td>
<td>NS</td>
<td>53%</td>
<td>NS</td>
<td>40%</td>
<td>NS</td>
</tr>
<tr>
<td>United States</td>
<td>23</td>
<td>67%</td>
<td>65%</td>
<td>68%</td>
<td>NS</td>
<td>57%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adult age not specified.

P = 2-tail Fisher Exact Test P value; NS = not significant; AYA = adolescent and young adult.

However, given the limited efficacy and toxicity data pertaining to WLI for adults, the use of WLI in adult ES patients is appropriately more controversial. Like other sarcomas that impact both adult and pediatric patients, ES presents distinct challenges with respect to forming consensus on best practice treatment strategies across the age spectrum. Clinical studies are ongoing, such as the Euro-Ewing-Intergroup EE99 (COG-AEWSO331) trial, which randomizes patients with pulmonary metastatic disease alone to standard consolidation chemotherapy with WLI or to high dose chemotherapy plus peripheral blood stem cell (PBSC) rescue in patients up to 50 years old. In the absence of robust data regarding efficacy and toxicity, there is no clear consensus on the use of WLI for adult ES patients with PM. In this context, we conducted a survey of expert sarcoma-dedicated oncologists to ascertain practice patterns regarding WLI for adults with ES and PM.

2. Methods

We developed a brief survey, in which we described the following clinical scenario: An adult with excellent performance status presents with a primary ES in the leg and multiple PM. The patient achieves a complete radiographic response after chemotherapy and resection of the primary. Participants were asked: Would you give bilateral WLI to (1) this adult patient?, (2) this patient if 20 years old?, (3) this patient if 45 years old?, or (4) this patient if 60 years old? The survey was emailed to 54 expert sarcoma-dedicated medical and radiation oncologists from adult and pediatric practices located in the US, Europe, and Australia. Experts were identified on the basis of their active involvement in sarcoma clinical trial groups such as EORTC, Children’s Oncology Group (COG), NCI Canada Clinical Trials Group, Sarcoma Alliance for Research through Collaboration (SARC), and NRG Oncology. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board.

Basic demographic information about survey participants was collected including practice discipline, country of practice, adult versus pediatric specialty, and institution. Responses among participant groups were compared using Fisher’s Exact Test.

3. Results

Thirty-eight of the 54 (70%) emailed participants responded to our survey, including 26 medical and 12 radiation oncologists; 24 adult, 1 adolescent and young adult (AYA), and 13 pediatric oncologists; and 1 from Australia, 14 from Europe, and 23 from the US. Overall, 63% of participants opted to offer WLI to the adult patient, 63% to the 20-year-old, 62% to the 45-year-old, and 50% to the 60-year-old (Table 1).

Table 1 also shows rates of WLI recommendation according to type of oncologist and geographic region. Pediatric oncologists were significantly more likely than adult oncologists to endorse WLI for the adult with no age specified (92% versus 48%, \( P = 0.01 \)), for the 20-year-old (93% versus 46%, \( P = 0.005 \)), and for the 45-year-old (92% versus 46%, \( P = 0.01 \)); the trend was similar for the 60-year-old, but the results were not statistically different (75% versus 38%, \( P = 0.08 \)). No statistically significant differences were seen between responses for medical and radiation oncologists or between oncologists in Europe or Australia versus in the US. Among all categories, WLI was recommended the least for the 60-year-old, but still approximately 50% of the time.

4. Discussion

Despite a relatively poor prognosis among patients with metastatic ES, some of these patients are potentially curable, and as such, aggressive multimodal therapy is a standard approach for metastatic ES. Since the 1970s, WLI has been a component of this aggressive therapy [13] although clear data supporting the necessity of its use, particularly for adults, are lacking.

To illustrate practice patterns and to gather expert opinions on this topic, we surveyed a global sample of oncologists with dedicated expertise in sarcoma management on the use of WLI in adults with ES. Almost two-thirds of sarcoma
Sarcoma

In our survey, we identified significant differences in recommendations for WLI between pediatric and adults oncologists. These divergent practice patterns illustrate not only the challenges in the interpretation of limited data sets in rare tumors but also some of the inherent biases that may arise through a practice devoted to either adult or pediatric patients. Practice variation across adult and pediatric providers has been reported in other soft tissue cancers as well. For example, a survey of adult and pediatric oncologists on the treatment of adult medulloblastoma patients similarly demonstrated substantial variation in practice, particularly with the choice of chemotherapeutic agents, likely reflecting the limited data available relevant to older adult population [22]. Likewise, population studies have demonstrated less aggressive protocols for diagnosis, staging, and treatment for adults with Wilms’ Tumor relative to their pediatric counterparts and cited this less aggressive approach as an explanation for inferior survival outcomes among adults [23].

Together, these data call for renewed and continued collaboration across the artificial divide of adult and pediatric oncology to define evidence-based treatment strategies and appropriate prospective trials across the age spectrum. A vibrant form of this collaboration is seen in the emergence of interest in adolescent and young adult (AYA) oncology as a resource-dedicated discipline dedicated to bridging service and survival gaps in the young adult population and in
cancers affecting many age groups which span the traditional “lines” demarcating pediatric and adult oncology [24–26]. Efforts of the AYA Oncology Progress Review Group and others have produced an increased understanding of the distinct survival outcomes, survivorship concerns, barriers to care, and challenges to clinical trial enrollment relevant to these patients [26–28]. Increased participation by AYA providers in both patient care and in clinical trial development will undoubtedly expand our understanding of these understudied populations and encourage inclusion of these patients in forthcoming clinical studies.

The ongoing Euro-Ewing-Intergroup EE99 (COG-AEWSO33I) trial comparing standard consolidation chemotherapy with WLI to high-dose chemotherapy plus peripheral blood stem cell (PBSC) rescue in patients up to 50 years old with EW and PM is one example of such interdisciplinary collaboration, which promises to help elucidate the role of WLI across a broad range of ages. As we await those results, our survey suggests that the majority of expert oncologists would offer WLI for most adults with ES and PM in complete response, particularly for younger patients up to the age of 45. While it may be reasonable to treat younger adults with WLI outside of a clinical trial, we would recommend caution in older adults with comorbidities due to limited safety data in this patient population. For clinical scenarios of localized disease, PM with comorbidities due to limited safety data in this patient clinical trial, we would recommend caution in older adults for younger patients up to the age of 45. While it may be

doubt whether a trial across all age groups. These data call for continued collaboration across adult and pediatric oncology to define evidence-based treatment strategies and appropriate prospective trials across the age spectrum. As we await the results of the ongoing Euro-Ewing-Intergroup EE99 study investigating the role of WLI, these data suggest that the majority of expert oncologists would offer WLI for most adults with ES and PM, particularly for younger patients up to the age of 45.

5. Conclusion

In this survey of worldwide expert sarcoma-oncologists, approximately two-thirds of respondents supported WLI for adult patients with metastatic ES up to 45 years old, and half supported WLI for patients 60 years old. Pediatric oncologists were most likely to recommend WLI at nearly double the rate across all age groups. These data call for continued collaboration across adult and pediatric oncology to define evidence-based treatment strategies and appropriate prospective trials across the age spectrum. As we await the results of the ongoing Euro-Ewing-Intergroup EE99 study investigating the role of WLI, these data suggest that the majority of expert oncologists would offer WLI for most adults with ES and PM, particularly for younger patients up to the age of 45.

Conflict of Interests

The authors have declared no conflict of interests.

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References


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