

The AYA gap for rhabdomyosarcoma.

Simone Hettmer¹ and L. H. Lindner²

¹University of Freiburg

²LMU University Hospital

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Simone Hettmer¹ and Lars H. Lindner²

Division of Pediatric Hematology and Oncology, Department of Pediatric and Adolescent Medicine, University Medical Center Freiburg, University of Freiburg, Freiburg, Germany.

Department of Medicine III, LMU University Hospital, LMU Munich, Marchioninstr. 15, 81377, Munich, Germany.

To whom correspondence should be addressed. Email: simone.hettmer@uniklinik-freiburg.de. Phone: +49 761 270-45140; Fax: +49 761 270-4518

Cancer is the leading cause of death among adolescents and young adults (AYAs). Cancers diagnosed during the AYA period - defined by the National Cancer Institute as the age from 15 to 39 years - account for approximately 5% of all cancers [1]. As per the national report on the status of cancer (study period 2015-2019, [1]), 5-year relative survival rates for both children and AYAs suffering from cancer are high (85.1% for children and 85.8% for AYAs), and improvements in survival over time appear to be similar for both age groups [1]. Yet, the spectrum of cancer types diagnosed in AYAs varies widely. The most common malignancies are female breast cancer (15%), thyroid cancer (15%), testicular cancer (8%) and melanomas (7%) [1], but AYAs may also suffer from so-called pediatric cancers with peak incidence during childhood. When compared to their childhood counterparts, worse outcomes were reported for AYAs diagnosed with pediatric cancers, including but not limited to leukemias [2] and sarcomas [3]. This „AYA gap“ is of concern to both pediatric and adult oncologists.

The accompanying paper by Harrison et al examines a cohort of 2151 patients with rhabdomyosarcomas (RMS) enrolled in consecutive Children’s Oncology Group (COG) trials, including 19% AYAs aged 15-39 years and 81% children aged 0-14 years [4]. Compared to children with RMS, AYAs experienced significantly lower 5-year event-free survival (EFS; 44% vs. 67%) and 5-year overall survival (OS; 52% vs. 78%). These observations are in line with a recent retrospective analysis of nearly 2000 patients treated on European paediatric Soft Tissue Sarcoma Group (EpSSG) protocols [3]. Importantly, relative survival of AYAs with RMS treated on EpSSG and COG protocols appears to be better [3, 4] than the survival observed in epidemiological studies such as EURO CARE-5 (39,6% 5-year relative survival among RMS patients aged 15–19 years, and 36,4% for those aged 20–39 years; study period 2000-2007 [5]). Survival benefits for AYA patients treated on pediatric RMS protocols are consistent with previous observations in AYAs receiving treatment according to pediatric acute lymphoblastic leukemia (ALL) protocols [2] or at pediatric cancer centers/ sites with pediatric oncology expertise [6]. AYA cancer patients appear to benefit from chemotherapy dose intensities higher than what is generally prescribed to older patients. They may also draw advantages from pediatric standards with respect to planning of multimodal treatment and cancer staging. For example, the bone marrow (rarely ever involved in adult-type soft tissue sarcomas (STS)) is the most frequent site

of metastases in AYAs with RMS treated within the COG cohort reported by Harrison et al [4] and should always be considered when planning pre-treatment examinations of AYAs with RMS. All taken together, adult oncology providers of AYA patients with RMS are well advised to consult their pediatric oncology colleagues and/ or consider referral to an institution with pediatric oncology expertise.

AYA cancer patients treated on pediatric protocols – including those suffering from RMS - still experience worse outcomes than their pediatric counterparts [2]. There is ample evidence to support higher risk biology, more aggressive clinical phenotypes and higher rates of early treatment failures in AYAs diagnosed with pediatric cancers – including leukemias and sarcomas- compared to children diagnosed with the same malignancies [2-4]. For RMS tumors, higher rates of alveolar histology tumors and metastatic disease in AYAs were observed in the COG cohort reported here [4], as well as in the EpSSG and other retrospective studies [3, 7]. In addition to higher-risk disease manifestation, more frequent treatment-related toxicities and higher rates of withdrawal from treatment contribute to worse outcomes of AYAs compared to children with cancer [2]. There is a direct association between age and treatment-related deaths for patients undergoing ALL treatment on pediatric protocols [2]. Harrison et al do not comment on differences in treatment-related toxicities between children and AYAs with RMS, but higher rates of vincristine neurotoxicity, nausea and pain were previously reported in older adolescents undergoing RMS treatment on pediatric protocols. Even in the absence of higher-grade toxicities, a high burden of low-grade adverse events can have a major impact on the ability to function in daily life, continue education, maintain employment or participate in social activities. Many AYAs with cancer need to rely more on their parents/ support persons, which threatens their age-appropriate strive for autonomy and may result in them rebelling against treatment recommendations or failing to self- manage complex medication plans [8]. Active involvement of AYAs in the development of a care plan, which considers dignity, normalcy and family/ social relationships may improve compliance and, ultimately, treatment success.

RMS is the most common STS in children and adolescents and often referred to as a pediatric cancer. Nevertheless, it occurs at any age, and up to 40% of all cases are diagnosed in adults (including seniors) [9]. The molecular and histological heterogeneity of pediatric RMS was studied intensively in recent years [10]. However, the insights provided by Harrison et al [4] and Ferrai et al [3] emphasize that the remarkable diversity apparent across the RMS spectrum is multidimensional. Distinct clinical and biological characteristics of RMS diagnosed in different age groups deserve further attention. The two main pediatric RMS subtypes are embryonal and alveolar RMS, whereas pleomorphic RMS and RMS not otherwise specified are predominant in older adults and considered fundamentally different cancers [9]. To obtain a better understanding of RMS diagnosed in AYAs, future study efforts should aim at investigating the full spectrum of the disease and differentially consider the molecular underpinnings and therapeutic requirements of RMS diagnosed at opposite ends of the AYA age range.

(917 words, max 1000 words)

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