ORIGINAL ARTICLE

Ethical Analysis As a Tool for Addressing Treatment Controversies: Radiotherapy Timing in Children With Orbital Rhabdomyosarcoma As a Case Example

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Abstract

Purpose: The treatment of orbital rhabdomyosarcoma is a topic of debate between North American and European clinicians, with the utility of radiation therapy as part of initial management in question. Despite differences in philosophy, the dominant North American approach of upfront radiation and the dominant European approach of radiation only in the event of recurrence yield a similar rate of overall survival. We sought to identify the ethical arguments for each approach.

Methods: Established moral principles and appeals in contemporary medical ethics were utilized to identify the ethical arguments supporting each treatment approach. The potential for technologic advances to alter the analysis was considered.

Results: Emphasizing the principle of beneficence, the North American approach seeks to reduce recurrence rates. In contrast, the European approach seeks to avoid radiation-induced sequelae, emphasizing the principle of nonmaleficence. Both approaches are based on well established ethical principles, evidence, and clinical experience. Thus, both approaches currently appear to have legitimacy and should be included in the informed consent process. However, if treatment-related toxicity is reduced through improvements in radiation delivery, the North American approach could emerge as ethically superior.

Conclusions: Ethical analysis can aid in addressing challenges that arise when professional practices and perspectives differ in the management of cancer patients.

Key Words: Rhabdomyosarcoma, ethics, orbit, pediatric, radiotherapy, late effects

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INTRODUCTION

As the most common pediatric soft-tissue sarcoma, rhabdomyosarcoma (RMS) can develop in a variety of sites. Approximately 10% of cases arise in the orbit [1]. Historically, patients with orbital RMS were treated with surgical resection alone, with a mortality rate of greater than 70% [2]. In the contemporary management of orbital RMS, chemotherapy has become the standard of care, with radiotherapy used for local control in most cases. The current approach of combined modality treatment has shown 5-year overall survival rates of more than 85% in most reports [3]. Despite the excellent overall survival rates, the treatment of orbital RMS remains a topic of debate, with the utility of radiation therapy as part of initial management in question [4].

The difference in treatment philosophies is best seen among pediatric oncologists in Europe and North America, as exemplified by the following cooperative studies: the International Society of Pediatric Oncology's (SIOP) malignant mesenchymal tumor studies (MMT-89 and MMT-84), representing the European approach; and the Intergroup Rhabdomyosarcoma Study Group's (IRSG) IRS-IV study, and Children's Oncology Group Study D9602, representing the North American approach [5-8]. Major differences between the approaches are outlined in Table 1. Briefly, the North American approach attempts to minimize disease recurrence through upfront radiation for most patients, often

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Table 1. Comparison of European and North American approaches to treating rhabdomyosarcoma, as exemplified by pediatric oncologists

Factor Evaluated	European Approach (Defer Radiotherapy)		North American Approach (Upfront Radiotherapy)	
Philosophy	Decreased late toxicity from radiotherapy		Decreased rate of local recurrence	
Risk	Increased local failure		Late toxicity of radiotherapy	
Studies	MMT-84 [5]	MMT-89 [6]	IRS-IV [7]	D9602 [8]
5-year OS (%)	88	85	100	96
5-year EFS (%)	65	53	93	86

Note: EFS = event-free survival; IRS = Intergroup Rhabdomyosarcoma Study Group; MMT = malignant mesenchymal tumor; OS = overall survival; SIOP = International Society of Pediatric Oncology.

with the associated cost of increased patient vulnerability to treatment-induced sequelae. By comparison, the European approach aims to prevent these treatment effects by avoiding the use of upfront radiation and instead utilizing an intensive chemotherapy regimen, often with the associated cost of increased patient vulnerability to disease recurrence.

Although the differences in approach have come under intense scrutiny and debate in recent years, ethical aspects have been largely ignored. We explore the potential for ethical analysis to (1) provide insight into the nature of the tradeoffs involved with each approach, and (2) guide clinicians in counseling patients and parents in the face of this controversy. In addition, we address the implications of the 2 approaches for the informed consent process. We hope to establish that ethical analysis is an important resource to address challenges that arise when professional practices and perspectives differ across groups of physicians, and in this case, regional borders, in the management of cancer patients.

METHODS

In the ethical analysis that follows, we examine the ethical basis for each treatment approach. Our analysis rests upon established moral principles and appeals, which we more completely characterize in the context of our analysis. Briefly, Beauchamp and Childress [9] identify a set of 4 pivotal moral principles relevant to health care: respect for autonomy (respecting and supporting patients' decisions); nonmaleficence (avoiding the causation of harm); beneficence (relieving, lessening, or preventing harm and providing benefits); and justice (fairly distributing benefits, risks, and costs).

Brody [10] describes a range of distinct moral appeals that draw attention to morally salient properties or features of actions, including the appeal to consequences, the appeal to rights, and the appeal to virtues. Some of the principles are related to particular appeals. For example, respect for autonomy aligns with the appeal to rights, and nonmaleficence and beneficence align with the appeal to consequences. Our analysis is based on the idea of moral pluralism, meaning that a number of independent ethical considerations may be relevant in determining the appropriateness of a particular action or practice.

RESULTS

Ethical Analysis

North American approach. Health care professionals have a fiduciary obligation to protect and promote the health-related interests of their patients. This obligation is often expressed in terms of the *principle of beneficence*, which entails that physicians have an ethical obligation to recommend the treatment option with the most favorable outcome, which in clinical terms most often translates to overall survival. Overall survival rates with the North American approach have ranged from 96% to 100%, compared with 85% to 88% seen with the European approach [5-8]. An international workshop examining both approaches failed to find a statistically significant difference in overall survival, but a lower local recurrence rate was observed with the North American approach: 7% versus 36% [3].

This 5-fold increase necessitates salvage therapy, which is not always successful, carries increased morbidity, and requires more-toxic treatment than initial therapy [11]. Indeed, high-dose chemotherapy followed by autologous stem-cell rescue has not improved outcomes for these patients, and total cumulative doses of some chemotherapeutic agents carry increased risks, such as infertility [12,13]. Many chemotherapeutic agents used in the treatment of orbital RMS are known to cause ophthalmic complications that are often attributed to radiation, such as keratitis and cataract formation [14]. Additionally, delaying upfront radiation may potentially increase the risk of metastatic disease: Several studies have reported distant metastasis with rates as high as 15% in select patients [1,3,15,16].

Citing decreased recurrence rates, and therefore less salvage therapy, proponents of the North American approach advocate for upfront radiation as the optimal treatment option. Considering the psychological distress of disease recurrence for both patient and parent, advocates of