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Successful role of radiation therapy: Account for every single gray and make every single gray count

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ABSTRACT

Combined-modality treatment involving immuno-chemotherapy with or without radiation has become the mainstay of treatment for aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL). Long-term goals in the treatment of DLBCL are to keep improving the therapeutic ratio and to extend survival; these goals have been accomplished largely by (a) gaining insight into disease biology and developing biologically based criteria to guide choice of therapy, (b) avoiding unnecessarily long courses of chemotherapy, and (c) reducing both the size of the radiation fields and the radiation dose. Here I review the available literature on which clinical presentations can benefit the most from radiation; how the availability of advanced imaging has led to radical changes in the use of radiation therapy in DLBCL; and examples of best-practice radiation planning and delivery.

1. Introduction

The radiosensitivity of hematologic malignancies in general, and lymphoma in particular, has underscored the pivotal role of radiation therapy for this disease for more than half a century.

The current state of the art for treating aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL) relies on a combination of immunotherapy and chemotherapy, with or without radiation. The evolution of each aspect of this therapy has led to marked improvements in the overall survival (OS) of patients with DLBCL [1–3]. Additional improvements in patient outcomes will require ongoing improvements in the therapeutic ratio. An important aspect of such efforts has included the development of biologically based criteria to guide choice of therapy [4–6]; another important approach has been to reduce the intensity and duration of both chemotherapy [7] and radiation therapy. Indeed, the latter is achieved chiefly through reducing both the size of the radiation fields and the radiation dose by using treatment planning procedures that are based on advanced imaging technologies. Reduction of treatment intensity has been shown to be effective at saving lives that had been previously lost to long-term toxicity in patients with Hodgkin lymphoma [8]. Although one might be tempted to take the knowledge gained and lessons learned on radiation therapy for Hodgkin lymphoma and apply them to DLBCL, that is not advisable given the differences between DLBCL and Hodgkin lymphoma in terms of their biology, demographics, response to therapy, and survival. Therefore, a different set of strategies is needed for DLBCL.

Many of the published reports on the role of radiation in treating aggressive lymphomas began decades ago by advising against its use for fear of long-term toxicity, even though many of those reports cited evidence from randomized and non-randomized trials showing consistent benefits from the use of radiation. Moreover, the reports of toxicity are based largely on the several-decades-old experience with treating patients with Hodgkin lymphoma, in which the radiation was given to large nodal fields. Because radiation-induced toxicity depends on which normal tissues are exposed to it, the use of modern-day techniques involving delivery of radiation

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only to involved sites is associated with considerably less toxicity [9,10], radiation causes side effects only and only to where it lands, thus, and when using modern involved site radiation therapy (ISRT) as opposed to the several decades old large nodal and subtotal nodal fields the occurrence of these side effects should no longer be seen.

I will start this review somewhat unconventionally, first by addressing the issue of toxicity, which has driven most of the large studies conducted to date, followed by describing successful attempts to mitigate the presumed toxicity and discussing ways to interpret the available findings in light of recently acquired knowledge on modern-day radiation, with helpful examples. The review concludes with a brief summary of recommendations and indications for the use of radiation for DLBCL.

2. Potential toxicity from radiation for the treatment of aggressive lymphoma

The pervasive and longstanding belief that radiation should not be used for lymphoma because of toxicity can be traced back to the time when radiation was given as the sole treatment for most subtypes of lymphoma, particularly Hodgkin lymphoma. In the mid-twentieth century, before chemotherapy or combination chemotherapy was available, radiation was considered a kind of "systemic therapy" in that it addressed the entirety of the lymphatic system. The radiation fields used in this approach are now referred to as total lymphoid and subtotal lymphoid irradiation (Fig. 1). Although this approach did cure the lymphoma in a large number of patients, decades later it became clear that the large radiation fields used, which included most of the bone marrow as well as other critical normal organs, could cause long-term side effects such as cardiac disease and second malignancies. Hence lives were lost from the treatment as much as, if not more than, from the disease itself [11–13]. Notably, this experience arose largely from the treatment of Hodgkin lymphoma, and thus every subsequent change made in treatment was specific to that disease. Again, one must bear in mind that knowledge gained from treatment of Hodgkin lymphoma is not necessarily transferable to other types of lymphoma; indeed, lymphomas are quite diverse and have radically different etiologies and outcomes.

Eventually, in the case of Hodgkin lymphoma, chemotherapy was introduced as a systemic treatment, radiation therapy fields and doses were reduced, and patient survival improved drastically, with unprecedented high cure rates [8]. Interestingly enough, many medical oncologists could not overcome an instinctive avoidance of radiation therapy because of its potential side effects even after radical changes in radiation delivery, even though early chemotherapy regimens, particularly those including alkylating agents, were also found to cause infertility and secondary hematologic malignancies. Of course use of these early agents has been abandoned and replaced with more modern, less toxic forms of chemotherapy; yet in the minds of some, the assumption remains that radiation is radiation. For that reason, this is an ideal time to describe how 21st-century radiation therapy differs from that used in the 20th century.

3. Differences between older techniques and modern-day radiation therapy planning and delivery

3.1. Radiation sources

Machines that used cobalt sources have been abandoned, meaning that radiation can now reach depths within the body without depositing high doses along the path to the target; in other words, use of cobalt for deep-seated tumors involved delivering a higher radiation dose to normal tissues than to the target intended to be treated. We now use linear accelerators that, as the name implies, accelerate the radiation particles such that they can be delivered precisely to targets. Other advances include therapy with heavier particles such as protons, which can deliver high-dose radiation doses still more precisely to tumor targets with much less exposure of surrounding normal tissues and with no exit dose beyond the target [14].

3.2. Radiation planning

In the past, radiation planning was done by drawing targets on simple 2-dimensional X-ray films. Obviously this limited the ability of radiation oncologists to precisely tailor the intended therapy, without the ability to visualize the tumor and its surroundings in 3 dimensions. In current practice, plans are based on computed tomography (CT) scans rather than simple X-ray films, and computer algorithms are used for dose calculations rather than manual means. In other words, when delivering radiation, the computer planning system can factor in various interactions between the radiation beams and tissues of different densities (e.g., air, bone, or muscle) along the radiation path; in this way, highly accurate doses are "painted" onto the target (Fig. 2). Indeed, radiation therapy has gone one step further, to create software with mathematical iterations akin to artificial intelligence that can generate solutions on how to best plan each case. These techniques are the basis for the now widely available planning and delivery techniques such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT).

3.3. Radiation delivery

Another advance in radiation therapy is the ability to not only plan where radiation is to go but also to visualize where it is actually being deposited. This capability, termed "on-board imaging," had not been possible until CT capabilities were incorporated into the linear accelerators that deliver the radiation. Such set-ups allow the actual delivered daily dose to be visualized, providing reassurance and confirmation that the tumor is still being covered appropriately while irradiation of the surrounding normal organs is avoided or minimized (Fig. 3).