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Review Article

The Value of Radiation Therapy for the Treatment of Diffuse Large B-Cell Lymphoma in a New Era

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ABSTRACT

As a highly heterogeneous disease, diffuse large B-cell lymphoma shows different clinical presentations, molecular and immunophenotypic characteristics, International Prognostic Index (IPI score) and response to therapy, which consequently brings about different prognoses and survival results. In addition to surgery and chemotherapy, radiation is also one important modality to treat diffuse large B-cell lymphoma. Over the past few decades, radiation therapy has stepped forward because of technological revolutions. The role of radiation in treating diffuse large B-cell lymphoma is discussed, including: i) advances in modern-day radiation technology ii) potential toxicity from radiation, iii) indications for radiation, and iv) available studies about the efficacy of radiation.

Introduction

Lymphoma is classified into Hodgkin lymphoma and non-Hodgkin lymphoma. Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) worldwide, representing approximately 30-40% of all cases in different geographic regions [1]. The characteristic of DLBCL is its fast-growing and aggressive feature [2]. 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 [3]. With the additional use of rituximab, the efficacy of systemic treatment in DLBCL is substantially improved in the past decades [4]. The incidence has been increasing in developed regions, but fortunately, cure rates have also improved from 30%-40% in the pre-rituximab era, up to 60%-70% in the rituximab era [5]. Consequently, the RT utilization rates decreased significantly from 38.5% in 1998 to 28.8% in 2012. The decrease in RT was predominantly seen after 2002 (Rituximab era) [6]. Radiation technologies have evolved dramatically over the past decades, challenging the old concepts of RT. However, the role of radiation therapy has been controversial and the results of reported studies are contradictory [7-10]. So, it is time to rethink the value and necessity of RT in this new era.

Advances in Modern-Day Radiation Technology

I Radiation Sources

Few decades ago, cobalt was used as the radiation source to implement radiation therapy for tumors. However, in the meantime, it exposed the normal surrounding tissues to a higher level of radiation because of the high dose deposition along the path to the target [3]. Finally, machines that used cobalt as radiation sources were abandoned and replaced by the linear accelerator (LINAC) technology during 1960-1980 [11]. Other particles, such as protons and heavy-ion, are also applied to the treatment of tumors. Proton allows escalation of target tumor less exposure of normal tissues, which potentially improves local control and survival while at the same time reducing toxicity and improving quality of life [12]. Fortunately, modern personalized radiation oncology can target and treat the deep-seated tumors within the body more accurately and safely.

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II Radiation Planning

To precisely make a treatment plan, it is best to completely know about the tumor and the surroundings in 3 dimensions. However, radiation oncologists in the older days were unable to make such an ideal plan because they could only depend on the simple 2-dimensional X-ray technology. Imaging technology keeps developing and has experienced several innovations, such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET). Thus, more concepts, like gross tumor volume (GTV), clinical target volume (CTV), internal target volume (ITV), and planning target volume (PTV), were introduced into the treatment process, making it more accurate to identify the interaction between the tumor and its surroundings. The introduction of combined modality therapy (CMT) increased the rate of cured patients enormously, leaving extended-field RT (EFRT) replaced by involved-field RT (IFRT), which encompasses only the initially involved regions [13]. Nonetheless, IFRT still involves relatively large normal tissue volumes even in very limited diseases. So, two new concepts, involved-site radiation therapy (ISRT) and involved-nodal radiation therapy (INRT), have come into use.

The irradiated volume is significantly smaller with ISRT than with IFRT because all adjacent lymph nodes that appear grossly uninvolved are not purposely treated [14]. So, there are fewer radiation-induced toxicities. Meanwhile, the development of computer science, dose calculation algorithms, special computer platforms like the treatment planning systems (TPS) along with other advances, enable radiation oncologists to draw a treatment plan on a case-by-case basis. Nowadays, the rapid development of Artificial Intelligence (AI) and big data, despite their current limitations, also have a huge potential to help and improve the diagnosis, treatment and prognosis. AI does a favour in target and normal tissue image segmentation, dose optimization, clinical decision support and outcome prediction [15]. Big data plays an important role in information storage, experience extrapolation, thorough evaluation, error detection, quality assurance, and so on [16].

III Radiation Delivery

Each tumor has its unique shape of different length, width and depth. The 3D-conformal radiotherapy (3D-CRT) has an advantage of measuring the depth and highly matching the shape of the tumor compared to 2D radiotherapy. Nevertheless, density is another essential element that should never be forgotten. Each radiation beam from the three axes is of the same dose, in another word, they have the same energy. As a result, due to the different densities inside the tumor, some parts may not achieve enough radiation while some parts get over irradiated, which weakens the efficacy of radiation and causes damage to the normal tissues at the same time. Intensity-modulated Radiation Therapy (IMRT), an advanced delivery modality based on the 3D-CRT, combines the function of shape adjustment and dose modulation together. It ensures that high-dose needed regions can get higher-dose radiation and low-dose needed regions can get lower-dose radiation.

Volumetric-modulated Arc Therapy (VMAT) can deliver the radiation continuously without an interval by rotating around the patient. VMAT is an extension of IMRT and it shortens the radiation time significantly and balances the radiation damage. And then, Image-guided radiotherapy (IGRT), a 4D-radiation approach, comes into clinical use gradually. It has a unique on-board imaging capability by integrating different imaging technologies, including CT, MRI and PET, with the linear accelerators, which brings the ability to take the small errors into consideration that are created by respiration, peristalsis, position error and target area contraction, and so on. IGRT provides real-time images and surveillance of the tumor and the surrounding tissues, helping the radiation oncologists to better adjust to the changed target area. Other modern technologies are also under development. Flattening-filter-free linear accelerator (FFF LINAC), especially for stereotactic body radiation therapy (SBRT), can reduce the radiation delivery time substantially. So, these technologies take a further step to spare the healthy area and perfect the individual optimization.

Potential Toxicities from Radiation

Due to high RT doses and large RT fields, devastating toxicities such as secondary malignancies and cardiovascular effects were commonly observed in Hodgkin lymphoma (HL) patients, which finally led to the reduction of modern RT for patients with NHL [17]. Radiation oncologists and patients tended to avoid RT even fundamental changes have taken place in RT technology. So, it is not a feasible way to conclude that it is the same situation in NHL. The toxicities of RT depend especially on the location of involved lymph nodes or tissue [13]. Most toxicities, such as epithelitis, mucositis, diarrhea and dysphagia, were mild and tolerable, and RT-induced interstitial pneumonitis did not lead to the long-term dysfunction of the respiratory system or requirement of assisted ventilation [18]. One two-institutional study assessed the adverse effects of radiotherapy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0) [2]. No grade 4 non-hematologic toxicity was observed.

RT-induced toxicities were mild and tolerable, with most toxicities limited to grades 1-3, which made the completion of scheduled radiotherapy, without any possible interruption [19]. Another study proved that toxicity was increased for patients receiving longer courses of chemotherapy [20]. It evaluated 131 patients diagnosed with stage I-IV DLBCL to examine the influence of consolidative RT on outcome and toxicity. There was a lower rate of more than ten kinds of toxicity, comparing patients who received 3-4 cycles of chemotherapy with radiation to patients who received 6 to 8 cycles of chemotherapy alone. And it showed statistical differences in the incidence of anemia and neuropathy between the two groups (p=0.008, p=0.273 respectively).

Indications for Radiation in DLBCL Patients

I Bulky or Residual Disease

Although the exact definition of bulky disease is still under debate, ranging between 5 and 10 cm, it has been proven that RT contributes significantly to locoregional control (LRC) and survival for patients with bulky or residual disease after chemotherapy [18, 21-24]. In multivariate analysis, bulky disease was associated with better PFS and OS (HR=0.02, p=0.009) [18]. Øystein Fluge *et al.* analysed 211 DLBCL patients and divided patients into complete remission (CR) group (n=73) and any residual mass group (n=138), which included partial response

(PR) and CR unconfirmed (Cru) [23]. Among 138 patients with any residual mass after chemotherapy, 57 patients did not receive RT and 81 patients received RT. It was reported that the 5-year overall survival (OS) was 59% in those who did not receive RT and 82% in those who did receive RT (P=0 .005). The 5-year cancer-specific survival (CSS) events were 69% in patients not receiving RT and 89% in patients receiving RT (P<0.001). Subgroup analysis of 94 patients with stages II/III/ IV and a residual mass after chemotherapy was carried out.

Patients were divided into RT group (n=44) and non-RT group (n=50). The 5-year CSS was 88% in RT group versus 68% in the non-RT group (P=0.003). Five-year OS was 84% in RT group versus 57% in non-RT group (P=0.014). This indicated that consolidative RT also do favour for patients with DLBCL of the advanced stage with a residual mass after chemotherapy. Naresh Jegadeesh *et al.* analysed 89 stage III or IV DLBCL patients who met the inclusion criteria [25]. Bulky disease was defined as any presenting mass ≥ 5 cm in CT maximum diameter, including in patients with multiple bulky sites. The LRC rate at 5 years was 47.4% in the bulky disease group versus 74.7% in the non-bulky group (P=0.01). On multivariate analysis, the presence of bulky disease was linked with an increased risk for the development of local recurrence (LR) (P<0.01).

II Relapsed/Refractory Disease

Although systematic chemotherapy has greatly improved the treatment, it should not be forgotten that about 30-40% of patients with DLBCL will have either primary refractory disease or relapse after chemotherapy [8]. Eric Grignano *et al.* made a conclusion that RT should remain a treatment option for relapsed/refractory DLBCL patients [18]. Among the 51 selected patients, 16 patients responded insufficiently to chemotherapy, 18 patients were refractory and 17 patients had relapsed. The 5-year progression-free survival (PFS) was 62% and OS was 72%. Brendan G. Coutu *et al.* reviewed 72 patients who underwent autologous stem cell transplantation (ASCT) because of relapsed/refractory DLBCL [26]. 31 experienced a relapse (43%) and 16 died (22%) within 2 years of ASCT. In the relapsed, 20 (65%) occurred at the previous sites, which indicated the failure of LRC. 19 had residual disease ≥ 2 cm on post-ASCT imaging, but finally, 8 patients chose to receive consolidative IFRT. 5 patients with a residual tumor volume < 2 cm also underwent consolidative RT. Therefore, 13 patients received consolidative IFRT and 59 patients were observed. IFRT was associated with the statistical difference in 2-year LRC (92% vs. 68%; P=0.04). Subgroup analysis of the 19 patients with the residual disease was performed to figure out the utility of consolidative IFRT. The 2-year LRC rate was 100% for 8 patients receiving consolidative IFRT and 36% for 11 patients not receiving (P<0.01). Correspondingly, the 2-year PFS rate was 88% and 27%, respectively (p=0.01). The 2-year OS was 100% and 45% respectively (p=0.01).

III Sites Benefiting from RT

Survival for patients with DLBCL differs according to the site of presentation.

i Skeletal Involvement (SI)

The role of radiation is still going on debate under this scenario, but it has been proven that patients with primary bone DLBCL can have better outcomes, with prolonged PFS and OS, after standard chemotherapy followed by RT [27]. RT should still function as an important option for patients with SI even in the era of rituximab because RT can exactly improve the outcome while rituximab cannot [28]. Nicola Lehners *et al.* did retrospective research of 75 patients showing SI at first diagnosis to find out the influence of chemotherapy and RT on the progression-free survival (PFS) and overall survival (OS) [10]. All the patients received chemotherapy (46 with CHOP, 27 with intensified chemotherapy, 2 with palliative chemotherapy) and 37 received RT. Survival analysis showed a 3-year PFS of 73% and a 3-year OS of 83%. In univariate analysis, the use of rituximab did not improve the survival (p = 0.87 for OS, and p = 0.58 for PFS), neither did the intensified chemotherapy (p = 0.21 for OS, and p =0.10 for PFS), on the contrary, RT had a positive effect on OS (p = 0.02) but not on PFS (p = 0.23). In multivariate analysis, RT significantly improved the PFS (p = 0.0006) and OS (p =0.002), rituximab prolonged the PFS (p = 0.008) but not OS, and intensified chemotherapy did no help to survival.

ii Primary Testicular Diffuse Large B-cell Lymphoma (PT-DLBCL)

In PT-DLBCL, most cases present with localized disease, but disappointedly, the outcome is poor due to the high risk of relapse at contralateral testis and the central nervous system (CNS). Combined treatment of R-CHOP chemotherapy with radiation therapy to the contralateral testis remains the standard management for PT-DLBCL patients [29]. The study carried out by Jennifer C. Ho *et al.* suggested that prophylactic testicular RT should be offered to all patients with PT-DLBCL to improve survival, even in the modern era of rituximab [30]. Among 120 selected patients, 84 (70%) patients received testicular radiation and 36 (30%) patients did not receive testicular radiation. The 5-year PFS rate was 65% for patients who received RT versus 30% for patients who did not receive RT (p=0.001). The 5-year OS was borderline (73% vs. 52%, p=0.065). With regard to testicular relapse-free survival (TRFS), patients who received RT had a higher TRFS rate (5-year TRFS rate of 98% and 10-year TRFS rate of 91%) compared to those who did not (5-year TRFS rates of 79% and 10-year TRFS rate of 73%) (p=0.001).On univariate analysis, RT was associated with PFS and trended toward improved OS. On multivariate analysis (MVA), RT was significantly associated with improved OS and PFS. Subgroup analysis of 64 patients who received rituximab and anthracycline chemotherapy indicated that RT was a significant predictor of improved PFS in univariate and multivariate analysis. There was also a statistical difference in 5-year TRFS rate (100% vs. 82%, p=0.033).

iii Other Sites

RT offers significant benefits for survival of patients with primary breast diffuse large B- cell lymphoma (PB-DLCBL), with better 5-year OS in the RT group (78.1% versus 66.0% in non-RT group, P = 0.031), indicating the therapeutic value of RT in the rituximab era [31]. Treatment outcomes of DLBCL involving the head and neck treated with R-CHOP followed by radiotherapy were satisfactory with excellent local

control and tolerable toxicity [2]. Moreover, consolidative RT could also be applied to diseases located in the para-spinal area, para-sinus, or base of the skull in case of future recurrence at the original site, which could cause irreversible damage [3].With the continuous advances in radiation technology, RT could be more powerful and practicable for patients with DLBCL occurring in different sites, even in the rituximab era.

IV Several Studies in Favour of RT

The aforementioned studies have figured out the fact that adding RT to the treatment of DLBCL improves LRC, PFS, and OS. Several other studies consistent with the conclusion of the above studies were summarized below (Table 1).

Table 1: Recent studies indicating the value of RT for DLBCL.

Study with Reference Citation	Year	Number of Patients	Number of Patients Receiving Radiation Therapy	Chemotherapy	Results
Bouthaina S. Dabaja *et al.* [32]	2001-2008	841 (I-IV)	293	6-8 R-CHOP	5 years OS rates: 91% for patients who had received RT vs. 83% for those who did not (P=0.01) 5 year FFS rates: 83% for patients who had received RT vs. 76% for those who did not (P=0.05)
John A. Vargo *et al.* [33]	1998-2012	59,255 (I-II)	23,340	unreported	5-year and 10-year OS rates, respectively 79% and 59% for all patients 75% and 55% for patients receiving chemotherapy alone 82% and 64% for patients receiving chemotherapy followed by RT (P=0.001).
Waqar Haque *et al.* [34]	1992-2011	34,680 (I-II)	10999	unreported	RT was associated with improved OS in both the pre-Rituximab era (HR = 0.797; 95% CI 0.756–0.841) and the post-Rituximab era (HR = 0.745; 95% CI 0.702–0.789). Propensity-score matched analysis confirmed that.
Yoo-Kang Kwak *et al.* [2]	2006-2015	56 (I-IV)	56	6 R-CHOP	the 5-year RFS and OS rates were 72% and 61%, respectively local control rate 94%
Jeanny Kwon *et al.* [35]	2004-2012	198 (I-II)	43	Median 6 R-CHOP	RT was associated with improved PFS (HR=0.23, P=0.021) and OS (HR=0.15, P=0.014)

Abbreviation: R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone; RT: Radiation Therapy; HR: Hazard Ratio; CI: Confidence Interval; PFS: Progression-Free Survival; OS: Overall Survival; RFS: Recurrence-Free Survival; FFS: Failure-Free Survival.

Conclusion

i. It is a fact that technologies have made such dramatic progress that modern imaging and conformal RT can target the tumor more accurately and irradiate more safely with less radiation to the normal tissues and lower risk of later toxicities.
ii. There is a huge potential of RT with the development of big data and AI; besides, RT was associated with better survival, so it is not the right thing to say RT has been replaced in the rituximab era.
iii. RT can provide a high level of LRC and omission of RT will result in a shorter PFS and OS. RT should therefore remain standard practice. There are many indications for the use of RT. Patients, who can benefit from RT, should be identified in time.
iv. More prospective studies should be carried out to confirm the value of RT.

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Conflicts of Interest

None.

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