RESEARCH ARTICLE

# Oncologists' Perspectives on Consolidation Radiation Treatment after Chemotherapy for Lymphomas: A Survey Study by the Lymphoma Working Committee of the Turkish Oncology Group (TOG)

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## Abstract

In this study, we aimed to determine the perspectives of medical and radiation oncologists regarding consolidation radiotherapy in patients with a complete response after chemotherapy for Hodgkin's and non-Hodgkin's lymphomas. The survey was designed to identify demographic and occupational features of medical and radiation oncologists and their views on application of consolidation radiotherapy in their clinical practices, as based on a five-point Likert scale (never, rarely, sometimes, often, and always). The study covered 263, out of 935, physicians working in the oncology field as either medical or radiation oncologists; the rate of return on the invitations to participate was 28%. The majority of the participants were male radiation oncologists, with a duration of between 5 and 10 years of work as a university hospital official, and the mean age was 38 ± 14 (years). Although the most commonly followed international guidelines were NCCN, among the physicians, the majority of the respondents suggested that the guidelines were unclear regarding recommendations for consolidative radiotherapy. The administered dose for consolidative radiotherapy in lymphoma patients was indicated as 40 Gy by 49% of all the physicians and the most common cause of hesitancy concerning consolidative radiation treatment was the risk of secondary malignancies as a long-term adverse effect (54%). In conclusion, we suggest that medical oncologists could be most active in the treatment of lymphoma through a continuous training program about lymphomas and current national guidelines.

**Keywords:** Lymphoma- radiotherapy- consolidation- oncologists

*Asian Pac J Cancer Prev,* **18 (11)**, 3149-3155

## Introduction

Lymphomas are among the highly heterogeneous malignancies with a predominantly aggressive clinical course (Dorth et al., 2012; Laskar et al., 2004; Morschhauser et al., 2009; Ng et al., 2016; Tilly et al., 2015; Yeoh and Mikhaeel, 2011). Because both Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL) have a best response to chemotherapy and radiation treatment, they are known as milestones in the historical development of cancer treatment (Dorth et al., 2012; Morschhauser et al., 2009; Ng et al., 2016; Tilly et al., 2015; Yeoh and Mikhaeel, 2011).

Although the traditionally curative treatment of early-stage HL and NHL includes multimodality therapy, using any chemotherapy regimen followed by adding radiation therapy, this treatment approach is not clear in patients with advanced-stage lymphomas (Dorth et al., 2012; Laskar et al., 2004; Morschhauser et al., 2009; Ng et al., 2016; Tilly et al., 2015; Yeoh and Mikhaeel, 2011). Because of the possibility of achieving complete response with different chemotherapy regimens, strengthening the therapy by consolidation radiation treatment is an unclear issue in patients with lymphoma (Dorth et al., 2012; Morschhauser et al., 2009; Ng et al., 2016; Tilly et al., 2015; Yeoh and Mikhaeel, 2011).

Moreover, there is no current consensus regarding consolidation radiation treatment, which achieves complete response in positron-emission tomography with computerized tomography (PET/CT) after systemic chemotherapy in patients with both HD and diffuse large B-cell lymphoma (DLBCL), which is the most common type of NHL (Evens and Kostakoglu, 2014; Johnson et al., 2016; Laskar et al., 2004; Morschhauser et al., 2009;

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Yeoh and Mikhaeel, 2011).

Previous studies have indicated different results on both the effectiveness and what the administered dose would be in the consolidation radiation treatment after systemic chemotherapy in patients with lymphoma (Dorth et al., 2012; Evens and Kostakoglu, 2014; Johnson et al., 2016; Laskar et al., 2004; Morschhauser et al., 2009; Tilly et al., 2015; Yeoh and Mikhaeel, 2011).In these studies, it has been suggested that physicians avoided consolidation treatment in patients that have a complete response due to short- or long-term adverse effects of the radiation (Dorth et al., 2012; Laskar et al., 2004; Morschhauser et al., 2009; Ng et al., 2016; Tilly et al., 2015; Yeoh and Mikhaeel, 2011).

In this survey study, we attempted to determine both the approaches and the perspectives of medical and radiation oncologists on consolidation radiation treatment in lymphoma patients with complete response after systemic chemotherapy.

## Materials and Methods

*Methods and individuals*

*Study design*

This study was conducted as a cross-sectional survey study on staff physicians in medical and radiation oncology. It was presented as a project at the 11th National Oncological Studies Workshop (2015, Antalya) and was accepted as a study of the Lymphoma Working Committee. Researchers who were members of the Lymphoma Working Committee created and revised the methods of measurement and the tools of the study.

*Study sample*

The target population for this study consisted of 410 medical oncology fellows and specialists and 525 radiation oncologist residents and specialists who were actively working in Turkey, between January 2015 and June 2015. A link to an electronic questionnaire was e-mailed to members of both the Turkish Society of Medical Oncology and the Turkish Society of Radiation Oncology. The invitation e-mail was sent every three weeks during this 6-month period.

*Ethical considerations*

Ethics committee approval was received from the Mugla SK University Scientific Research Ethics Board and the study started after this approval. The invited physicians who agreed to participate in the study through an e-mail were required to read and sign consent forms prior to being accepted into the study.

*Measures and tools*

The questionnaire had three purposes: 1) to collect demographic and occupational data, 2) to assess the perceptions, attitudes, and hesitations of physicians on their position in the treatment, dosing, and adverse effects of consolidation radiation treatment in advanced-stage lymphoma patients with complete response after systemic chemotherapy, and 3) to determine the position of medical oncologists regarding lymphoma treatment and the status of the use of international guidelines. The expected time needed to complete the survey was approximately 15 minutes.

The first portion of the questionnaire included questions regarding demographic and occupational data, such as age, gender, professional title (fellowship, resident, specialist, and academic degree), workplace, and number of years of work experience.

In the second portion of the survey, questions assessed how the physicians approached consolidation radiation treatment in terms of indication, dose of radiation, and adverse effects. This part contained questions about approaches and attitudes in the clinical practice of medical and radiation oncologists; it consisted of 5-point Likert scale questions (strongly agree, agree, no idea, disagree, strongly disagree).

The final portion of the questionnaire asked about whether the physicians follow-up the patients with lymphomas in their hospital and whether they use an international guideline for the treatment of lymphoma or not.

*Statistical analysis*

The data were indicated as the mean ± standard deviation or the median and interquartile range (25–75%). The distribution of the study variables was assessed using the Kolmogorov-Smirnov test. A descriptive analysis was expressed for all study variables. The advanced statistical analyses included the use of the two tailed independent Student's t-test, the Mann-Whitney U test, and either a chi-squared or a Fisher's exact test. The value of $P < 0.05$ was determined as statistically significant. The statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) version 18.

## Results

The study was finished with contributions from 263 physicians: 118 (45%) were medical oncologists and 145 (55%) were radiation oncologists. The rate of return to invitation was 28%.

The majority of the participants were radiation oncologists (55%), non-academic (34%), and male (56%), as well as working at a state hospital (43%), for a duration of between 5 and 10 years (36%). The mean age was 38 ± 14 years (range 24–67). Given the features regarding age, gender, occupational status, and workplace, there was no significant difference between the radiation and the medical oncologists ($P = 0.215$, $P = 0.156$, $P = 0.197$, and $P = 0.114$, respectively) (Table 1).

Only 11% (n = 29) of the physicians indicated that treatment and follow-up of lymphomas was never done in their workplace. However, the majority of the physicians (44%, n = 115) said that their workplace was a center where patients with lymphomas were treated and only 24% of them were medical oncologists. Additionally, 59% of the physicians who treated and followed-up on patients with lymphomas in their workplace were hematologists; this ratio was no different between medical and radiation oncologists (P=0.141) (Table 1).

Ninety-two percent of all the physicians indicated that

Table 1. Demographic and Occupational Features of the Physicians in the Survey

| | All of participants | Medical Oncologists | Radiation Oncologists | P* |
|---|---|---|---|---|
| n, (%) | 263 | 118 | 145 | 0.248 |
| Age (years) | 38±14 | 40±13 | 36±12 | 0.215 |
| Gender, n (%) | | | | |
| Male | 147 (56) | 62 (53) | 85 (59) | 0.156 |
| Female | 116 (44) | 56 (47) | 60 (41) | |
| Occupational title, n (%) | | | | |
| Residents/Fellows** | 84 (32) | 34 (29) | 50 (34) | 0.197 |
| Non-Academic Specialist | 108 (41) | 44 (37) | 64 (44) | |
| Academic Specialist | 71 (27) | 40 (34) | 31 (22) | |
| Workplace, n (%) | | | | |
| State hospital | 113 (43) | 29 (25) | 84 (39) | 0.114 |
| University hospital | 84 (32) | 49 (43) | 35 (32) | |
| Education Hospital | 58 (22) | 34 (29) | 24 (27) | |
| Private Hospital | 8 (3) | 6 (3) | 2 (2) | |
| Work for a duration, n (%) | | | | |
| 1-4 years | 84 (32) | 34 (29) | 50 (34) | 0.241 |
| 5-10 years | 110 (42) | 54 (46) | 56 (39) | |
| 11-15 years | 60 (23) | 28 (24) | 32 (22) | |
| 16-20 years | 9 (3) | 2 (1) | 7 (5) | |
| The physicians who treated and followed-up on patients with lymphomas in their workplace, n (%) | | | | |
| Haematologists | 155 (59) | 64 (54) | 91 (63) | 0.145 |
| Medical Oncologists | 11 (4) | 8 (7) | 3 (2) | |
| Haematologists and Medical Oncologists | 68 (26) | 35 (30) | 33 (23) | |
| Never done | 29 (11) | 11 (9) | 18 (12) | |

*, The value of $P < 0.05$ was determined as statistically significant; **, Residents, physicians who in training on radiation oncology after the post-graduate; Fellows, physicians who in training on medical oncology after specialisation for internal medicine

they followed international guidelines to treat patients with lymphomas and the National Comprehensive Cancer Network (NCCN) (89%) was the most commonly followed international guideline for this issue. Other international guidelines that were followed include the American Society for Radiation Oncology (ASTRO) (48%), the European Society of Medical Oncology (ESMO) (38%), the American Society of Hematology (ASH) (26%), and the American Society for Clinical Oncology (ASCO) (19%). However, here, there was no difference between the radiation and the medical oncologists ($P = 0.241$) (Table 1).

Sixty-one percent of all of the participants indicated with strongly agree that there was not a clear consensus in the international guidelines for DLBCL regarding consolidative radiation treatments for patients with complete response after chemotherapy and 40% felt with strongly agree that there was not a clear consensus for HL. Whereas there was no difference between the perspectives of the radiation and the medical oncologists regarding this issue for DLBCL ($P = 0.245$), there was a significant difference for HL ($P = 0.031$) (Table 2).

The administered dose for consolidative radiotherapy in patients with lymphoma was indicated as 40 Gy by 49% of all physicians but it was 30 Gy among radiation oncologists (67%). This result was a significant difference between the radiation and the medical oncologists ($P = 0.035$) (Table 2).

Among all of the physicians, the causes of hesitancy regarding consolidative radiation treatment were risk of secondary malignancies as a long-term adverse effect (54%), unclear recommendations in international guidelines and the results of previous studies (47%), the lack of national guidelines (41%), the risk of the cardiotoxicity (24%), and unclear administered dose (14%). However, there was no difference on this between the radiation and the medical oncologists ($P = 0.198$) (Table 2).

## Discussion

In this study, we found that medical oncologists avoided consolidation radiation treatment due to the probability of adverse radiation-induced effects. In addition, there was no consensus among either the medical or the radiation oncologists on consolidation radiation treatment in patients who have HL and NHL with complete response after systemic chemotherapy.

In the literature, it has been reported that DLBCL constituted from 30 to 58% of the NHL series and that it has a very aggressive clinical course (Dorth et al., 2012; Miller et al., 1998; Ng et al., 2016). Historically, radiotherapy has been an important treatment option with 85 to 95% complete response rates for localized control

Table 2. Perspectives and Attitudes of Medical and Radiation Oncologists on Consolidative Radiotherapy in Patients with Complete Response from DLBCL and HL

| Questions | All Physicians (n=263) | Medical Oncologists (n=118) | Radiation Oncologists (n=145) | P* |
|---|---|---|---|---|
| There is no consensus in the international guidelines associated with consolidation radiotherapy in DLCBL patients with complete response after chemotherapy; n (%) | | | | |
| Strongly agree | 166 (61) | 67 (57) | 99 (68) | 0.245 |
| Agree | 37 (14) | 20 (17) | 17 (12) | |
| No idea | 5 (4) | 3 (2) | 2 (1) | |
| Disagree | 29 (11) | 15 (13) | 14 (10) | |
| Strongly disagree | 26 (10) | 13 (11) | 13 (9) | |
| There is no consensus in the international guidelines associated with consolidation radiotherapy in HL patients with complete response after chemotherapy; n (%) | | | | |
| Strongly agree | 105 (40) | 36 (31) | 69 (47) | 0.031* |
| Agree | 45 (17) | 16 (14) | 29 (20) | |
| No idea | 29 (11) | 27 (23) | 2 (2) | |
| Disagree | 52 (20) | 24 (20) | 28 (19) | |
| Strongly disagree | 32 (12) | 15 (12) | 17 (12) | |
| I act according to the international guidelines to determine treatment decisions regarding consolidative radiation treatment in DLBCL and NHL patients with complete response after chemotherapy; n (%) | | | | |
| Strongly agree | 242 (92) | 107 (91) | 135 (93) | 0.041* |
| Agree | 16 (6) | 10 (8) | 6 (4) | |
| No idea | 0 (0) | 0 (0) | 0 (0) | |
| Disagree | 5 (2) | 1 (1) | 4 (3) | |
| Strongly disagree | 0 (0) | 0 (0) | 0 (0) | |
| What is your preferred administered dose for consolidative radiation treatment?; n (%) | | | | |
| 20 Gy | 3 (1) | 3 (3) | 0 (0) | 0.035* |
| 30 Gy | 102 (39) | 5 (4) | 97 (67) | |
| 40 Gy | 129 (49) | 85 (72) | 44 (30) | |
| I am not treating to lymphoma | 29 (11) | 25 (21) | 4 (3) | |
| I am not receiving consolidative radiotherapy | 0 (0) | 0 (0) | 0 (0) | |
| What is your reason for not choosing consolidative radiation treatment in lymphoma patients?; n (%) (multiple choose) | | | | |
| Unclear international consensus | 124 (47) | 50 (42) | 74 (51) | 0.198 |
| Secondary malignancies | 142 (54) | 54 (46) | 88 (61) | |
| Cardiotoxicity | 63 (24) | 25 (21) | 38 (26) | |
| Unclear administered dose | 37 (14) | 19 (16) | 18 (12) | |
| Unclear national consensus | 108 (41) | 45 (38) | 63 (43) | |
| Which international guidelines do you follow on consolidative radiation treatment?; n (%) (multiple choose) | | | | |
| NCCN | 234 (89) | 104 (88) | 130 (90) | 0.241 |
| ASTRO | 126 (48) | 51 (43) | 75 (52) | |
| ESMO | 100 (38) | 41 (35) | 59 (41) | |
| ASH | 68 (26) | 29 (25) | 39 (27) | |
| ASCO | 50 (19) | 23 (19) | 27 (19) | |
| EHA | 8 (3) | 3 (2) | 5 (3) | |

* The value of $P < 0.05$ was determined as statistically significant; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; NCCN, the National Comprehensive Cancer Network ; ASTRO, the American Society for Radiation Oncology; ESMO, the European Society of Medical Oncology; ASH, the American Society of Hematology; ASCO, the American Society for Clinical Oncology; EHA, the European Hematology Association

of disease in patients with early-stage NHL (Bonnet et al., 2007; Dorth et al., 2012; Miller et al., 1998; Ng et al., 2016). After the chemotherapy and subsequent immunotherapy, however, the complete response rates in the modern treatment era have shown an increase without radiation treatment (Bonnet et al., 2007; Dorth et al., 2012; Miller et al., 1998; Ng et al., 2016). Consequently, the use of radiation treatment added to chemotherapy has been discussed for patients with early-stage NHL that currently have a complete response. In previous studies,

it has been shown that combined multimodality treatment, chemotherapy followed by radiation treatment, has improved the rates of complete response and progression-free survival as well as the local control of the disease in patients with early-stage DLBCL, as compared to chemotherapy or radiotherapy alone (Bonnet et al., 2007; Dorth et al., 2012; Miller et al., 1998; Ng et al., 2016). However, this judgment is not yet clear in patients with advanced stage DLBCL (Ng et al., 2016). In some studies, it has been shown that chemotherapy plus radiation treatment has improved in the local control of the disease and provided nearly 75 to 95% rates for 5-year local control of the disease in patients with DLBCL, evaluated primarily with PET-CT (Bonnet et al., 2007; Dorth et al., 2012; Miller et al., 1998; Ng et al., 2016). The results of some studies have indicated that chemotherapy with consolidative radiation treatment in patients with early-stage NHL has improved the rates of both the complete response and the local control of the disease (Dorth et al., 2012; Horning et al., 2014; Miller et al., 1998; Miller et al., 2001; Ng et al., 2016; Reyes et al., 2015). However, there are not yet any completed randomized clinical trials about consolidative radiation treatment after complete response in NHL patients with both early- and advanced stage that used rituximab, an antiCD20 antibody (Ng et al., 2016). Moreover, consolidation radiotherapy did not make a significant contribution to the overall survival in patients with early- and advanced stage NHL in these studies (Bonnet et al., 2007; Dorth et al., 2012; Held et al., 2013; Held et al., 2014; Horning et al., 2014; Miller et al., 1998; Miller et al., 2001; Ng et al., 2016; Reyes et al., 2015; Vargo et al., 2015). Therefore, given the use as a treatment option of consolidative radiotherapy in patients with DLBCL, it is primarily suggested in some eligible patients, such as those who have a bulky disease (>7.5 cm), those with skeletal involvement, and those with a partial response after immunochemotherapy in a non-bulky disease (Held et al., 2014; Ng et al, 2016). In these conditions, the recommended dose of the radiation is 18–20 Gy (Bonnet et al., 2007; Dorth et al., 2012; Held et al., 2014; Horning et al., 2004; Miller et al., 1998; Ng et al., 2016; Phan et al., 2010; Reyes et al., 2005; Tilly et al., 2015).

In this study, we found that 61% of the participants indicated that there was no consensus in the international guidelines and former studies about consolidation radiotherapy after complete response, proved by PET-CT, followed by chemo- or immune-chemotherapy in patients with DLBCL. Whereas this rate was 57% among medical oncologists, it was 68% among radiation oncologists (P = 0.245). This result may be associated with the relatively low number of medical oncologists.

Because of the high ratios for complete response, radiotherapy was a most important option for the treatment of patients with early-stage disease in the treatment era before chemotherapy for HL (Hoppe et al., 1982). Similar to the results in previous studies associated with NHL, the ratios of complete response and progression-free survival have been improved by chemotherapy alone in patients with early-stage HL (Hoppe et al., 1982). Although more than 75% of the patients have achieved complete response with chemotherapy, unfortunately, it has been indicated that the disease relapses in up to one-third of them during the follow-up period (Hoppe et al., 1982). In subsequent studies, it has been shown that a combined multimodality treatment option, radiotherapy added to chemotherapy, has contributed in ratios of complete response and progression-free survival, in comparison to chemotherapy alone in these patients (Duggan et al., 23003; Eghbali et al., 2005; Engert et al., 2005). Historically, while both radiotherapy alone and consolidative radiotherapy after chemotherapy have been widely adopted as a standard treatment in patients with early-stage HL, this condition is not clear for patients with advanced-stage HL who achieved complete response by chemotherapy (Hoppe et al., 1982). However, in some previous studies and single-center experiences, authors have indicated that consolidation radiation treatment could be suggested in patients who have high risk factors for the recurrence of the disease.

In this study, we found similar results with NHL among all of the participants. Forty percent of the participants indicated that there was consensus in the international guidelines and former studies about consolidation radiotherapy after complete response was proved by PET-CT after chemotherapy in patients with HL. Whereas this rate was 31% among medical oncologists, it was 47% among radiation oncologists. In conclusion, the opinion that there is no consensus associated with this issue was dominant among medical oncologists as compared with radiation oncologists (P = 0.031). This result may be related to the relatively low number of medical oncologists.

Previous studies reported the applied dose of the radiation treatment after the induction of chemotherapy as 40–45 Gy in patients with both HL and early- and advanced stage NHL (Bonnet et al., 2007; Duggan et al., 2003; Eghbali et al., 2005; Engert et al., 2005; Gobbi et al., 2005; Held et al., 2014; Hoppe et al., 1982; Horning et al., 2002; Miller et al., 1998; Ng et al., 2016; Reyes et al., 2005; Vargo et al., 2015); this has been discussed in current studies. Some studies on this issue have also shown that similar results on the local control of the disease have been obtained with lower doses, such as 20 and 30 Gy (Hoppe et al., 1982; Ng et al., 2016). Likewise, the recommended dose for consolidative radiotherapy is not clear in the international guidelines and most authors suggest that 30 Gy would be safe and effective as an administered dose (Ng et al., 2016).

This survey study has shown that answers about the administered dose of consolidation radiation treatment are heterogeneous and do not include any consensus. Most of the physicians (49%) answered 40 Gy for the administered optimal dose of the consolidative radiation treatment in patients with HL and NHL. While only 30% of the radiation oncologists answered 40 Gy to this question, 72% of the medical oncologists indicated that it was an optimal dose of the consolidative radiation treatment (P = 0.035). However, 67% of the radiation oncologists suggested that the administered dose was 30 Gy in these patients and this result was a different answer from that of the medical oncologists (4%) (P = 0.021). In conclusion,

the survey study showed that there was not any consensus among the medical and the radiation oncologists regarding the dose of consolidation radiotherapy in patients with complete response after induction chemotherapy.

The most common long-term adverse effects of the radiotherapy are pulmonary and cardiac toxicity and the development of secondary malignancies (Ng et al., 2016, Tilly et al., 2015). Previous studies have shown that radiation therapy itself could induce some toxicity, such as coronary heart disease, restrictive cardiomyopathy due to myocardial fibrosis, valvular damage, and cardiac autonomic dysfunction in patients with lymphomas (Gotti et al., 2013; Ng et al., 2016). Similarly, in the English literature, the incidence of pulmonary toxicity related to radiation treatment has been declared as 10 to 25%. It has been also reported that radiotherapy could lead to secondary malignancies with an 18-fold increased risk in patients with lymphomas (Gotti et al., 2013). In the study, we found that the causes of hesitation of radiation oncologists for radiotherapy was an increased risk for the development of secondary malignancies (54%), the absence of international consensus about it (47%), the lack of national consensus on consolidative radiotherapy (41%), the risk of cardiotoxicity (Horning et al., 2002) and unclear administered dose (14%). However, there was not a significant difference between the radiation and the medical oncologists regarding consolidative radiotherapy ($P = 0.198$).

This study had the following limitations: a small number of participants, a general lack of interest in survey studies among physicians is probably due to the physicians not treating lymphoma, a busy life, and their perspectives regarding survey studies. Medical oncologists may be less interested in lymphoma treatment than the hematologists in their workplaces.

In conclusion, current national consensus regarding consolidative radiotherapy in patients with complete response after the induction of chemotherapy in lymphoma may be necessary for an increase in interest among medical oncologists; this is in addition to training physicians regarding updates on current approaches by international guidelines in this issue. Therefore, we can suggest that medical oncologists should be encouraged for the treatment of lymphomas.

*Conflicts of interest*

We certify that all affiliations, with or without financial involvement, within the past 5 years and the foreseeable future and any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, and royalties).

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