

Radiotherapy for stage IAE non-Hodgkin's lymphoma of the testicle - a case report

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Background. The aim of this report is to present the irradiation technique applied to a patient with primary testicular non-Hodgkin's (NHL) lymphoma stage IEA, histologically CD20 positive NHL - diffuse follicular center cell (FCC) lymphoma grade III. Since primary NHLs of the testis are rather rare, no uniform radiotherapy approach to their treatment has been developed to date. Testicular NHLs are relatively often of aggressive biological characteristics, so that the disease relapse is not uncommon even in patients in an early stage of the disease (stage I and II), who received seemingly optimal therapy (orchietomy of the diseased testicle, polychemotherapy and irradiation).

Case report. In this report the applied radiation treatment field is shown. The disease was diagnosed in June 2001 after the inguinal orchietomy. Afterwards, the patient received 6 courses of polychemotherapy (CHOP) plus intrathecal methotrexate therapy. The irradiation was conducted with one direct 6 megavolt (MV) energy photon beam. The irradiation field encompassed the contralateral testicle (scrotum) and inguino-femoral lymph nodes. The radiotherapy dose was 30 Gy applied in 15 fractions calculated at the depth of 4 cm. The radiotherapy finished in December 2001. The patient has regular check-ups (last in May 2003) and has been in remission since then.

Conclusions. Relapse sites are quite often extranodal, not in the regional lymph nodes. Therefore, considering the radiation treatment fields there are no definitive recommendations.

Key words: testicular neoplasms; lymphoma, non-hodgkin

Received 7 June 2003

Accepted 21 June 2003

Introduction

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Primary lymphoma of the testis is a rather rare disease. It accounts for around 1% of all NHL's, 2% of extranodal lymphoma and less than 10% of all testicular neoplasms. However, in men over 60, it is the most common malignancy of the testis. The prognosis of testicular lymphoma is relatively poor com-

pared to other nodal and extranodal lymphomas. Median survival is 12 to 24 months.¹⁻³

Because this entity is relatively rare, much of the literature includes reports on a limited number of patients (usually between 10 to 30) collected over a span of many years.⁴⁻¹⁷ Accordingly, one can find differences in both lymphoma classifications and treatment approaches. Recently, two publications including a much larger number of patients have also appeared due to the multicentric or international nature of data collection and study.^{15,17} Due to their relatively larger number of patients, these recent publications allow us to better define the specific clinical features at presentation, prognostically important clinical variables, a response to therapy, and patterns of failure.

Most of primary testicular lymphomas are of B-cell origin, and overall diffuse large B-cell lymphomas as well as diffuse small noncleaved cell lymphoma appear to be the most common type. Follicular lymphomas and other histologic subtypes are less frequently represented.¹⁻³ Inguinal orchiectomy is universally recommended as an initial therapy for patients with localized disease. Although the long-term disease-free survival has been described after the orchiectomy alone, the vast majority of the patients relapse, so this cannot be considered an adequate therapy, not even for patients with IE disease. Furthermore, relapse rates exceeding 50% have been observed in the majority of reports in which the adjuvant radiotherapy (RT) was used following the orchiectomy. Relapses often occur in extranodal sites, such as in the central nervous system (CNS), Waldeyer's ring, skin and lung. In field failures were reported in patients who received adjuvant locoregional radiation at doses lower than 30 to 35 Gy. Such clinical course suggests that testicular NHL is usually a systemic disease, even when it initially presents as a localized disease. Accordingly, combined chemotherapy and

radiation therapy have been the accepted treatment modality for stage IE and IIE aggressive nodal lymphomas. The chemotherapy is usually doxorubicin based (for example, CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone) accompanied with concomitant CNS prophylaxis (4-6 injection of methotrexate intrathecally). The radiotherapy, if any, is usually applied in a form of involved-field, encompassing the contralateral testis (scrotum) or scrotal, iliac and possibly para-aortic regions. A routine use of irradiation to the paraaortic lymphnodes is not recommended because of the unpredictable metastatic pathway of the primary NHL lymphomas. The irradiation of the contralateral testis is with a prophylactic intention since the relapse rate in case of nonirradiation, is approximately 8% to 35%.¹⁻³ On the other hand, there are also reports where the irradiation of the contralateral testis was either not performed^{5,7,9,11} or performed only in a portion of patients reported.^{4,12,15,17}

Regarding radiotherapy, these reports surprisingly include very few details about the target volume and techniques.⁴⁻¹⁷ Concerning the radiation dose, they regularly mention the total dose. The target volume and irradiation technique is usually not precisely described. In a sentence or two it is mentioned that the involved field or involved-region irradiation was administered, or that scrotum and pelvic (iliac) lymphnodes ± paraaortic lymphnodes were irradiated. Therefore, we present the irradiation treatment we applied to a patient with stage IEA primary testicular NHL lymphoma.

Case report

The presented patient was born in 1937. Due to the enlargement of the left testis he was examined at the Department of Urology, Clinical Hospital »Merkur«, Zagreb, Croatia. A diagnostic examination, which included al-

so the computerized tomography (CT) of the abdomen and pelvis, did not reveal or indicate a disease spreadout outside of the left testicle. In June 2001, the patient underwent the left inguinal orchiectomy. The pathologic diagnosis was »CD20 positive NHL - diffuse follicular center cell (FCC) lymphoma grade III« (Diffuse large B-cell lymphoma according to the revised European-American classification of lymphoid neoplasms (REAL) - World Health Organization (WHO) classification).³

The patient was thereafter referred to a hematologist at another hospital (Department of Hematology, Clinical Hospital »Dubrava«, Zagreb). There he underwent an additional extended staging procedure that also included CT of the head and neck, thorax and abdomen and pelvis again as well as the bone marrow examination. These examinations did not show any evidence of the disseminated disease and/or regional lymph node involvement. Accordingly, the patient was diagnosed with primary NHL of the testicle, stage IAE. Moreover, according to the International Prognostic Index (IPI), he could be classified among low risk patients. His age was a risk factor (>60), while other four parameters did not indicate the elevated risk (serum lactate dehydrogenase was within normal limits, performance status - ECOG score = 0, stage of the disease I, one extranodal site involved).^{3,18}

He was treated thereafter with six cycles of CHOP polychemotherapy (cyclophosphamide, 750 mg/m² i.v. on day 1; doxorubicin, 50 mg/m² i.v. on day 1; vincristine, 1,4 mg/m² i.v. on day 1; prednisone, 40 mg/m² p.o. on days 1 to 5) and intrathecally with methotrexate (15 mg on the first day of each CHOP chemotherapy cycle). Cycles of CHOP polychemotherapy were administered at 3-week intervals.

When the patient completed the chemotherapy treatment he had a control examination. No signs which could indicate the disease relapse or the development of distant

metastasis were found. After that, he was referred to radiation oncologists at the University Hospital for Tumors in Zagreb for the further radiotherapy treatment. Taking into account patient's previous treatments, the possible clinical course of the disease and the patient's overall good condition (ECOG score 0), it was decided that he should receive the consolidation radiotherapy, to be applied to the contralateral testis (scrotum) and the neighboring inguino-femoral lymph nodes and subcutaneous lymph-vessels (»involved-field«). The total tumor dose was 30 Gy in 15 fractions.^{1,2,19}

Radiation details

Since the scrotum and the inguino-femoral lymphnodes are located superficially, the radiotherapy was performed by a single »direct« beam. Moreover, the region was encompassed by a single radiation field. The radiation was planned as nonisocentral, using a single 6 MV photon beam from the linear accelerator, having a focus to skin distance (FSD) of 100 cm, with the gantry angle of 0 degree (antero-posterior direction), respectively. The radiation field was determined during the simulation process by using a treatment-planning simulator. The patient was placed supine on the simulator table with his arms crossed over his chest (Figure 1). Consequently, for the radiotherapy the patient was always identically positioned. By means of simulator x-rays, the radiation field was tailored so to encompass the scrotum and inguino-femoral lymph nodes (Figure 1). The size of the treatment radiation field was 25 x 17.5 cm (Figure 1). After the appropriate subtractions of the shielded surfaces, the size of the radiation field approximated 18 x 18 cm. At the central axis the patient's antero-posterior diameter was 21.5 cm. The total tumor dose of 30 Gy, or single irradiation fractions of 2 Gy were calculated at the 4 cm depth. The isodose plan is shown in Figure 2. To obtain a comparably homogenous dose

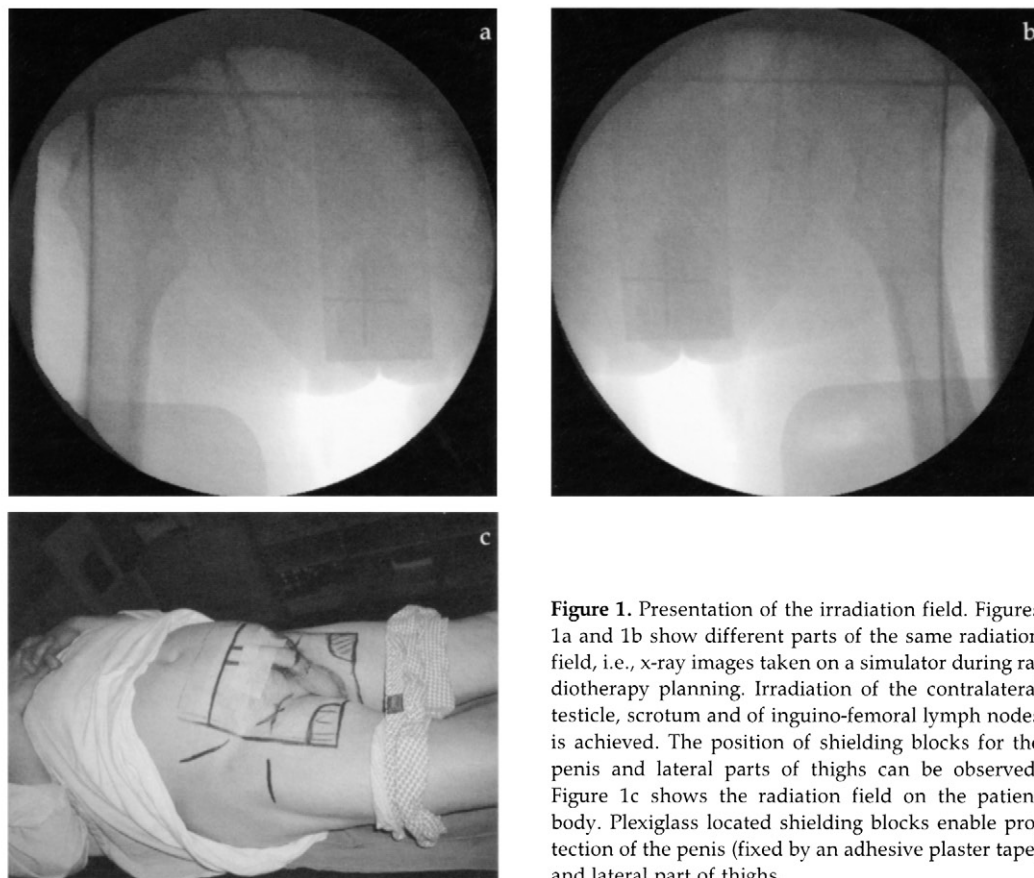


Figure 1. Presentation of the irradiation field. Figures 1a and 1b show different parts of the same radiation field, i.e., x-ray images taken on a simulator during radiotherapy planning. Irradiation of the contralateral testicle, scrotum and of inguino-femoral lymph nodes is achieved. The position of shielding blocks for the penis and lateral parts of thighs can be observed. Figure 1c shows the radiation field on the patient body. Plexiglass located shielding blocks enable protection of the penis (fixed by an adhesive plaster tape) and lateral part of thighs.

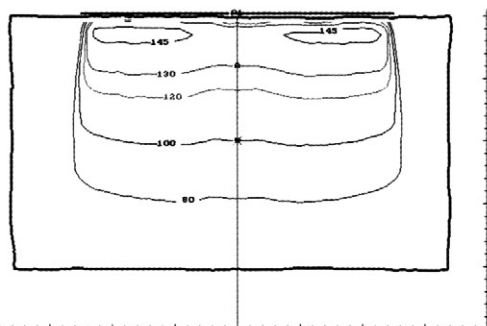


Figure 2. Two-dimensional presentation of the dose distribution ratio by depth delivered by 6 MV photons. (isodose curves, i.e., isodose plan). Centimeter scale is shown on the left and at the bottom. Point «A» in the isodose plan denotes the depth of 4 cm - a dose of 2 Gy per fraction.

distribution within the depth of the first 4 cm, tissue bolus in equivalency of 6 mm of water is used during the irradiation. Finally, after having all calculations done, reviewed and approved, irradiation was carried out. The radiotherapy was conducted in December 2001.

Discussion

This case report is aimed at pointing out the difficulty a radiation oncologist may encounter in planning the radiotherapy for a disease with primary tumors being surgically removed and a propensity for primarily distant metastasis, the disease with no strict recommendations for the radiotherapy due to its

rarity. For example, in the publication from Zucca *et al*¹⁷ which includes 373 patients, the authors admit that among the patients receiving radiotherapy (n=196, as primary or as combined with chemotherapy) there is a wide range of radiotherapy doses (from 18 to 50 Gy) and fields (from only scrotal to a variety of extended fields with or without inclusion of the contralateral testis).

When considering the total tumor dose and the target volume we took into account the possible pattern of relapse, patient's stage of the disease, previous treatments, and his overall good condition. Moreover, the radiosensitivity of the testicular NHL cells, possible existence of microscopic residual NHL cells in both the contralateral testis and inguino-femoral lymph nodes, normal tissue tolerance and possible side effects of irradiation to normal tissues were also taken into account.^{1-3,19} The irradiation could be performed also by a photon beam from a cobalt-60 machine, but due to the fact that the patient was obese with a substantial slope difference between the upper and lower field portions, 6 MV photons were given advantage. We have also been considering the usage of 20 MeV electrons, but the field size was a problem, as well as the patient's contour slope and especially the construction of a penis-shielding block. Megavolt electron beams show the advantage in the deeper body structures receiving much less of the radiation energy. If the irradiation has to be applied only to the scrotum, then the megavolt electrons are satisfactory. At the total tumor dose of 30 Gy in 15 fractions one does not expect an intensive painful skin reaction (irradiation dermatitis) of the scrotum by using megavolt electrons.

The radiation therapy was well tolerated by the patient. The standard routine control examination was 6 weeks after the irradiation had been completed. The patient was well and felt well in the postirradiation period. No skin reaction (irradiation dermatitis) was ob-

served. At examination, his locoregional status was in order. Standard laboratory test results were also normal. Since then, the patient has regular check-ups every three to four months (last in May 2003.) and is in remission since then.

Considering the treatment strategy for non-Hodgkin's lymphoma (NHL) it is largely determined by the histologic sub-type, stage at diagnosis and by the patient's overall condition.^{1-3,20} The treatment of localized (stages I, IE, non-bulky II and IIE) aggressive histologies of non-Hodgkin's lymphoma has been evolving over the past 20 years. These diseases could be locally controlled with the radiotherapy, but systemic relapses and deaths are common. Cure rates for the intermediate- and high-grade localized NHL improved dramatically with the addition of doxorubicin-containing chemotherapy. In the 1990s, two large randomized, prospective trials demonstrate that initial chemotherapy followed by the radiation therapy (combined modality therapy) gives the best results; so, such combined treatment might be considered as the best available current treatment strategy.^{18,21}

Within the group of aggressive NHLs the prognosis of testicular lymphoma is relatively poor compared to other nodal and extranodal aggressive lymphomas^{1-3,8,15,17,22}. The surgery, i.e. orchiectomy, has an important role in the diagnosis, but its usefulness, unless the disease is really limited to the testis, is restricted. As mentioned, available data suggest that in the majority of stage IE patients systemic occult metastases are already present. Accordingly, the radiotherapy usually has also a limited role. The goal of RT in the treatment of localized aggressive NHL is to deliver an adequate dose to the disease site and margin. The radiation is generally given after the initial chemotherapy treatment. Factors determining the dose of radiation, aside from normal tissue tolerance, include bulk of disease and performance status. In case of testicular lymphoma, the affected organ has usu-

ally been already removed by orchiectomy. Due to an unpredictable metastatic pattern of the testicular NHL, the question is what to irradiate. The irradiation is applied on the assumption that the probable site of the initial relapse will be in the pelvic or para-aortic lymph nodes or in the contralateral testis. Distant extranodal failures, especially in the CNS, remain a major problem, even in patients who receive a full course of doxorubicin-based chemotherapy accompanied with the intrathecal CNS prophylaxis with methotrexate alone or combined with cytarabine.^{16,17} In the cases of CNS relapses it may be important to distinguish intraparenchymal failures from the leptomeningeal ones since for the prevention of intraparenchymal failures more effective CNS prophylaxis, such as low-dose whole-brain irradiation or high-dose methotrexate must be prospectively explored.^{11,16} The recent multicentric prospective studies with a relatively high number of patients indicate that, because of the poor prognosis, an aggressive treatment approach, if possible, is warranted.^{16,17} For example, the results from the Zucca's study¹⁷ indicate that among the prognostic factors that were statistically significant at the multivariate analysis, IPI, B symptoms, anthracycline-containing chemotherapy, and prophylactic scrotal irradiation retained statistical significance with the overall survival (OS), cause-specific survival and progression-free survival. Patients receiving radiotherapy have a significantly longer OS, but most of them have a favorable IPI score. Among patients receiving radiotherapy locoregional to the primary testicular site of involvement, the OS was longer for those receiving an irradiation dose of at least 30 Gy. On the other hand, testicular lymphoma is predominantly a disease of older men who often have limited ability to tolerate aggressive treatment. The rarity of the disease makes randomized trials virtually impossible. Hence, an international collaboration is crucial to properly address the management of

testicular lymphoma. The improved understanding of the genetic and molecular characteristics of testicular lymphoma may help identify patients at risk of CNS failure and apply a patient-tailored treatment in the future.^{15,17}

Acknowledgement

This work was partially supported by the Ministry of Science and Technology of the Republic of Croatia (grant no. 0074004 to AJ).

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