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Hodgkin lymphoma

Doses to head and neck normal tissues for early stage Hodgkin lymphoma after involved node radiotherapy

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ABSTRACT

Purpose: To evaluate dose plans for head and neck organs at risk (OARs) for classical Hodgkin lymphoma (HL) patients using involved node radiotherapy (INRT) delivered as 3D conformal radiotherapy (3DCRT), volumetric modulated arc therapy (VMAT), and intensity modulated proton therapy (PT), in comparison to the past mantle field (MF).

Materials and methods: Data from 37 patients with cervical lymph node involvement were used. All patients originally received chemotherapy followed by 3DCRT–INRT (30.6 Gy). A VMAT–INRT, PT–INRT (both 30.6 Gy), and a MF plan (36 Gy) were simulated. Doses to head and neck OARs were compared with cumulative DVHs and repeated measures ANOVA.

Results: The estimated median mean doses were 15.3, 19.3, 15.4, and 37.3 Gy (thyroid), 10.9, 12.0, 7.9, and 34.5 Gy (neck muscles), 2.3, 11.1, 1.8, and 37.1 Gy (larynx), 1.7, 5.1, 1.3, and 23.8 Gy (pharynx), 0.5, 0.8, 0.01, and 32.3 Gy (ipsilateral parotid), and 2.4, 3.8, 0.7, and 34.7 Gy (ipsilateral submandibular) with 3DCRT, VMAT, PT, and MF (all $p < 0.0001$), respectively.

Conclusion: The use of INRT significantly lowered the estimated radiation dose to the head and neck OARs. VMAT appeared suboptimal compared to 3DCRT and PT, and for some patients, PT offered an additional gain.

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The majority of early stage Hodgkin lymphoma (HL) patients become long-term survivors with combined modality treatment [1,2], and therefore, it is important to minimize the risk of treatment-induced late effects. However, due to the long follow-up required to detect the excess morbidity and mortality, the majority of studies report on patients who were treated with extended field radiotherapy (RT) and/or outdated chemotherapy regimens.

RT for HL has changed considerably over the last two decades: The irradiated volume has been reduced as field size has evolved from extended field RT to involved field RT and, recently, further to Involved Node RT (INRT) [3,4]. Similarly, radiation dose has been reduced to 20–30 Gy as treatment regimens are stratified according to extent of clinical disease and prognostic factors [1,2]. Also, there has been great advancement of RT techniques, such as 3D conformal RT (3DCRT), different intensity modulated RT (IMRT)-techniques such as volumetric modulated arc therapy (VMAT), and intensity modulated proton therapy (PT).

Several studies have investigated the possible dosimetric advantages and limitations with an emphasis on the major thoracic organs at risk (i.e., the heart, lungs and breasts) for patients with mediastinal HL [5–10]. However, many patients with supradiaphragmatic HL present with cervical lymph node involvement, alone or in combination with mediastinal disease, and for these patients, head and neck normal tissues will invariably be irradiated.

In this study, the dosimetric data on the thyroid, neck muscles, pharynx, larynx, and salivary glands of INRT delivered as 3DCRT, VMAT, and intensity modulated PT, respectively, are evaluated for HL patients with cervical lymph node involvement. We compare these techniques with the previously applied extended mantle field (MF) technique and the dose level used for this treatment.

Materials and methods

Patients

We included data from patients ⩾15 years treated with INRT for clinical stage I–II classical HL from 2006 till 2010 at our institution. Only patients with cervical involvement were selected (see Supplementary material for flowchart of patient selection). Extensive details on initial treatment have been reported

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Table 1
Baseline and treatment characteristics of 37 early stage HL patients with cervical lymph node involvement.

Characteristic	*n*	(%)
No. of patients	37	
Men	18	(48.7)
Age		
Years, median (range)	33	(15–76)
Clinical stage		
IA	1	(2.7)
IIA	23	(62.2)
IIAE	1	(2.7)
IIB	12	(32.4)
Histology		
Nodular sclerosis	26	(70.3)
Mixed cellularity	9	(24.3)
Classical, NOS	2	(5.4)
EORTC prognostic group		
Favorable	12	(32.4)
Unfavorable	25	(67.6)
Involved side		
Right side involvement	12	(32.4)
Left side involvement	10	(27.0)
Bilateral involvement	15	(40.5)
Chemotherapy		
ABVD	34	(91.9)
ABVD/BEACOPP	2	(5.4)
ChlVPP	1	(2.7)
Clinical target volume		
cm^3, median (range)	174	(20–1565)
Radiotherapy		
AP–PA technique	35	(94.6)
IMRT technique[†]	2	(5.4)

Abbreviations: NOS, not otherwise specified; EORTC, European Organization for Research and Treatment of Cancer; ABVD, adriamycin, bleomycin, vinblastine, darcabazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; CTV, clinical target volume; AP–PA, anteroposterior–posteroanterior, IMRT, intensity modulated radiotherapy.
[†] 2 patients received IMRT to reduce the dose to the lungs.

previously [9,11]. In summary, all patients were treated with combined modality treatment with ABVD (adriamycin, bleomycin, vincristine, dacarbazine)-chemotherapy followed by INRT delivered as 3DCRT with a prescribed dose of 30.6 Gy in 1.8 Gy fractions, 5 fractions/week (F/W) to initially involved lymph nodes.

Contouring

Head and neck organs at risk (OARs) were defined as the thyroid, neck muscles, pharynx, larynx, submandibular and parotid glands: The thyroid, submandibular and parotid glands were contoured based on the extent of the glandular tissue. The neck muscles were contoured from the base of skull to the lower border of vertebra C7 as one structure comprising the scalenus, the prevertebral, and the sternocleidomastoid muscles as well as the deep and superficial muscles of the back. The oropharynx and the hypopharynx were contoured as one pharyngeal structure with the soft palate as the cranial border, vertebrae C1–C6 as posterior border, the lower edge of the cricoid cartilage as inferior border, and anteriorly including the soft palate, base of tongue, epiglottis, post-cricoid area, and the piriform sinuses. The larynx was defined as the structures contained within the thyroid cartilage, including the cricoid and arytenoid cartilages but excluding the epiglottis, and with the hyoid bone as the superior border and the lower edge of the cricoid cartilage as inferior border. For all patients, the OARs were contoured on the individual planning computed tomography (CT) scan. For patients with mediastinal involvement, the heart, lungs, and breasts were also contoured for plan optimization.

RT planning

The clinical 3DCRT plans were delivered as either opposed or angled fields based on the target configuration with a direct CTV-to-field-edge margin, according to the institutional clinical practice at the time. Treatment plans for VMAT, PT, and MF were simulated in Eclipse™ v 8.9 (Varian Medical Systems) for each patient, as described in detail elsewhere [9,12]. For VMAT and PT plans, the prescribed dose was 30.6 Gy or GyE (radiobiologically equivalent dose to high-energy photons, corrected with a factor of 1.1) in 1.8 Gy fractions, 5 F/W (planning objectives are presented as Supplementary material), and for MF plans, 36 Gy in 1.8 Gy fractions, 5 F/W.

Plan evaluation

Quantitative plan evaluation was performed by means of cumulative dose–volume histograms (cDVHs), for dose–volume objectives see Supplementary material. A heterogeneity index (HI) to evaluate dose heterogeneity inside the planning target volume (PTV) and a conformity index (CI) to assess treatment plan conformity, was used:

$$\mathrm{HI} = D_{\max 2\%\text{ in PTV}}/D_{\text{prescription}} \quad (1)$$

where $D_{\max 2\%\text{ in PTV}}$ is the maximum dose to at least 2% of the planning target volume (PTV) [13] and $D_{\text{prescription}}$ is the prescribed dose, and

$$\mathrm{CI} = V_{95\%}/V_{\text{PTV}} \quad (2)$$

where $V_{95\%}$ is the volume receiving at least 95% of the prescribed dose, and V_{PTV} is the PTV. The $V_{95\%}$, the volume receiving 107% of dose ($V_{107\%}$) and the conformity function at 20 Gy ($\mathrm{CF}_{20\,\mathrm{Gy}}$) and 5 Gy ($\mathrm{CF}_{5\,\mathrm{Gy}}$) were used to investigate the spatial coherence between target volume and irradiated tissue at different dose levels:

$$\mathrm{CF}_{x\,\mathrm{Gy}} = V_{\text{outside PTV},x\,\mathrm{Gy}}/V_{\text{PTV}} \quad (3)$$

where $V_{\text{outside PTV},\,x\,\mathrm{Gy}}$ is the volume outside the PTV receiving x Gy or more. For HI and CI the ideal value is one and for CF_x zero. The target coverage parameters were only used in the evaluation of VMAT and PT plans as quantitative comparisons of PTV coverage were inappropriate for 3DCRT and MF plans, since no PTV was generated for these plans.

Statistical analyses

Repeated measures analyses of variance (rANOVA) were performed for global differences between the mean dose to OARs (dependent variables) with 3DCRT, VMAT, PT, and MF treatment (categorical variables) with a two-tailed significance level of 0.05. The Greenhouse–Geisser correction was applied when sphericity was violated. *Post hoc* pair-wise comparison analyses were applied to compare the results among the categorical variables. For plan evaluation parameters the Wilcoxon signed rank test were used. All statistical analyses were performed in SAS v 9.3.

Results

Patients

We identified 37 patients eligible for the analyses; baseline and treatment characteristics are presented in Table 1. An example of the treatment plans for a young male patient with clinical stage I