Fractionated High-Dose–Rate Brachytherapy in Primary Carcinoma of the Nasopharynx

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Purpose: **A growing body of data suggests that local control in nasopharyngeal cancer (NPC) is related to the radiation dose administered. We conducted a single-institution study of high-dose radiotherapy (RT), which incorporated high-dose-rate (HDR) brachytherapy (BT). These results were analyzed together with data obtained from controls who did not receive BT.**

Patients and Methods: **The BT group comprised 42 consecutive patients of whom 29 patients were staged according to the tumor, node, metastasis system as T1 through 3, 13 patients were T4, and 34 patients were N+ disease. BT was administered on an outpatient basis by means of a specially designed flexible nasopharyngeal applicator, and the dose distributions were optimized. Treatment for T1 through 3 tumors comprised 60 Gy of external-beam radiotherapy (ERT) followed by six fractions of 3 Gy BT (two fractions per day). Patients with parapharyngeal tumor extension and/or T4 tumors received 70 Gy ERT and four fractions of 3 Gy BT. The no-BT group consisted of all patients treated from 1965 to 1991 (n = 109), of whom 82 patients had stages T1 through 3, 27 patients had T4, and 80 patients had N+ disease. Multivariate Cox proportional hazards analyses were performed by using the end points time to local failure (TTLF), time to distant failure (TTDF), disease-free survival (DFS), cause-specific survival (CSS), and the prognostic factors age, tumor stage, node stage, and grade. Because the overall treatment time varied substantially in the no-BT group, the dependence of local failure (LF) on the physical dose as well as the biologic effective dose (BED) corrected for the overall treatment time (OTT) ($BEDcor_{10}$) was studied.**

Results: **The BT group had a superior 3-year local relapse-free rate (86% *v* 60%; univariate analysis, *P* = .004). Multivariate analysis showed hazards ratios for BT versus no-BT of 0.24 for TTLF (*P* = .003), 0.35 for TTDF (*P* = .038), 0.31 for DFS (*P* < .001), and 0.44 for CSS (*P* = .01). The best prognostic group consisted of patients with T1 through 3, N0 through 2b tumors treated with BT who attained a 5-year TTLF of 94% and CSS of 91%. In contrast, the worst prognostic group, ie, 5-year TTLF of 47% and CSS of 24%, was composed of patients with T4 and/or N2c through 3 tumors who did not receive BT.**

Conclusion: **High doses of radiation (73 to 95 Gy) can be administered to patients with NPC with minimal morbidity by means of optimized HDR-BT. The use of a BT boost proved to be of significant benefit, particularly in patients with T1 through 3, N0 through 2b disease. The steep dose-effect relationship seen for the physical dose and the $BEDcor_{10}$ indicates that the results are dose related. The analysis has identified a poor prognostic group in whom treatment intensification with chemotherapy (CHT) is indicated.**

J Clin Oncol 16:2213-2220.

NASOPHARYNGEAL CANCER (NPC) shows a predilection for populations in the Far East and North Africa, whereas a low incidence is found among Western populations.[1-4] Some reports have shown age to be an independent prognostic factor, ie, that favors young age.[5,6] The histology of NPC is generally poorly differentiated or undifferentiated carcinoma.[7,8] Whereas there is controversy as to the most appropriate staging system, the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) tumor, node, metastasis staging guidelines are commonly adopted in Western countries,[9-13] and up to 70% to 80% of patients present with stage III to IV disease.

The nasopharynx is a cuboid midline space in direct continuity with critical structures, centered around the base of the skull. Given its location, radiotherapy (RT) represents the standard therapy for this radiosensitive tumor.[1,3,4,14-19] Despite advances in imaging[20-23] and external-beam radiotherapy (ERT) techniques,[24,25] local relapses still represent the commonest cause of failure and range from 30% to 60%.[3,15,26] The most important prognostic factor in local failure (LF) is the extent of the primary tumor at the time of presentation.[4,27,28] Ten-year LF rates range from 15% in stage T1 to 60% in stage T4.[15] There is also evidence to suggest that LF correlates with radiation dose.[15,17,19,29-32]

NPC is associated with a high incidence of systemic metastases, and combined RT and chemotherapy (CHT)

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Submitted June 25, 1997; accepted February 25, 1998.

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0732-183X/98/1606-0017$3.00/0

regimens are therefore frequently applied.[33-38] However, the application of high doses of ERT to large volumes, with or without CHT, can result in serious complications that include damage to the salivary glands, optic pathways, brain stem, temporal lobes, ear, spinal cord, pituitary gland, and hypothalamus.[39-42] Because a steep dose falloff can be obtained with brachytherapy (BT), there has been increasing interest in the use of BT[43] for the treatment of persistent local disease and/or recurrent NPC[16,44-47] and also in boosts (small volume) of primary NPC to high cumulative doses.[19,31] Recent advances in BT include computerized high–dose-rate (HDR) afterloaders and three-dimensional computer planning systems with optimization capabilities.[48,49] We have developed a flexible applicator (the Rotterdam Nasopharyngeal Applicator (RNA; Fig 1) that allows for outpatient HDR-BT.[50,51] We used the RNA to escalate doses by means of BT, because such an approach had the potential to limit doses to adjacent critical organs to a greater extent than ERT alone. Because a randomized trial was not feasible in view of the low incidence of NPC in The Netherlands, we directed our efforts during the past 6 years to enroll all patients with nonmetastatic NPC in a standard scheme of ERT followed by fractionated HDR-BT. To determine the efficacy of the addition of HDR-BT, the records of all patients with primary NPC who had been treated at our center from 1965 to 1991 by ERT alone were also analyzed.

PATIENTS AND METHODS

The diagnosis of NPC was established by computer tomography (CT) scanning (available in the Daniel den Hoed Cancer Center, Rotterdam, The Netherlands [DDHCC] as of 1980) or magnetic resonance imaging scans of the head and neck, local biopsy, palpation, and ultrasound fine needle aspiration cytology of the regional lymph nodes. Patients were staged according to the UICC/AJCC classification rules, 1987/1992 editions.[10,11] No BT was used in the treatment of primary NPC before April 1991, but all patients treated between 1991 to 1995 had ERT combined with HDR-BT. To study the influence of dose on local control, records of all patients with primary, nonmetastasized (M0) squamous cell or undifferentiated carcinoma of the nasopharynx treated at our center between 1965 and 1995 were analyzed.

In the no-BT group, only patients treated with curative intent were included (n = 109). Excluded were patients who had been treated to a dose less than 60 Gy (n = 30), patients who had synchronous second primary tumors (n = 7), and one patient who had been treated with CHT only. The no-BT group comprised patients who had been treated with either ERT alone (ERT group, n = 69) or ERT combined with CHT (CHT group; n = 40).

A remote-controlled HDR afterloader (type microSelectron HDR [± 370 GBq source] Nucletron-Oldelft Nucletron, Veenendaal, the Netherlands) was available at the DDHCC from 1991, and fractionated HDR-BT has been implemented on a routine basis in a number of head and neck tumor sites,[49] which included patients with primary NPC. The RNA is made from flexible silicone (silicone, type 625, Wacker Chemie, Krommenie, The Netherlands) and is introduced after topical anesthesia (Cocaine hydrochloride). It is designed to closely conform to the soft tissues of the nasopharyngeal vault and to remain in situ for the duration of the treatment (2 to 6 days) (Fig 1). Treatment planning with optimization (Nucletron Planning System, version 11.30) on dose points depicted on orthogonal radiographs (Fig 2), which represent target and critical normal structures, is then performed.[50] After dose computations, standard afterloading catheters are introduced in the RNA and connected to an HDR afterloading device with a high activity (370 GBq) Ir^{192} stepping source. The BT dose was initially prescribed to a point 1 cm from the source train axis. When it was appreciated that the position of the RNA could vary between patients, we elected to prescribe the dose to a fixed, anatomic landmark (the "NP dose point") located in the bony roof of the nasopharynx. Consequently, when the BT doses were retrospectively derived from the orthogonal radiographs of the early patients treated, some were found to have received a higher dose than the according-to-protocol prescribed dose of 12 or 18 Gy (see below).

Similar ERT schemes were used for patients in both the BT and no-BT groups. The ERT is delivered by a linear accelerator with a 4 to 8 MV photon beam using a (shrinking) three-field technique, ie, two parallel-opposed laterals and an abutted low-anterior field with shielding of the larynx. The eyes are blocked in the lateral portals; in case of

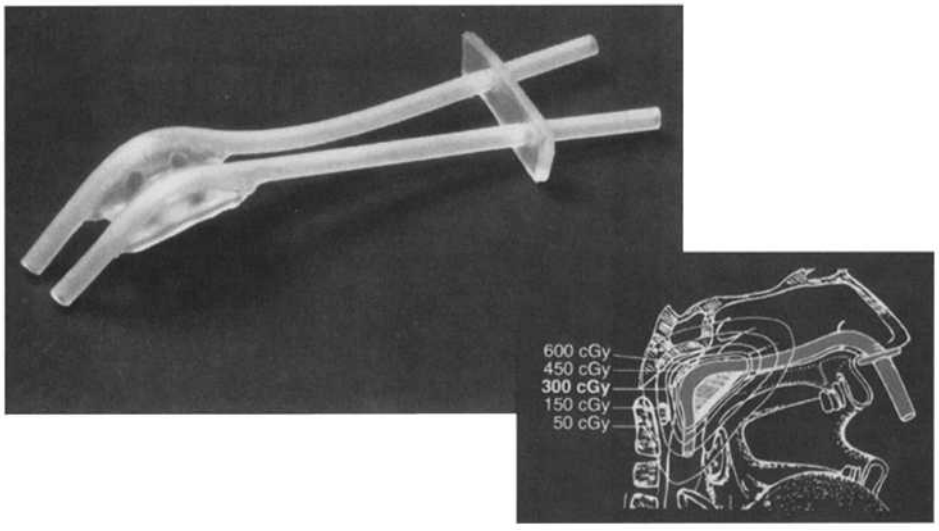

Fig 1. Standard silicone RNA; inset depicts isodoses that show the steep dose falloff with BT when applied by means of an HDR remote-controlled HDR afterloader.

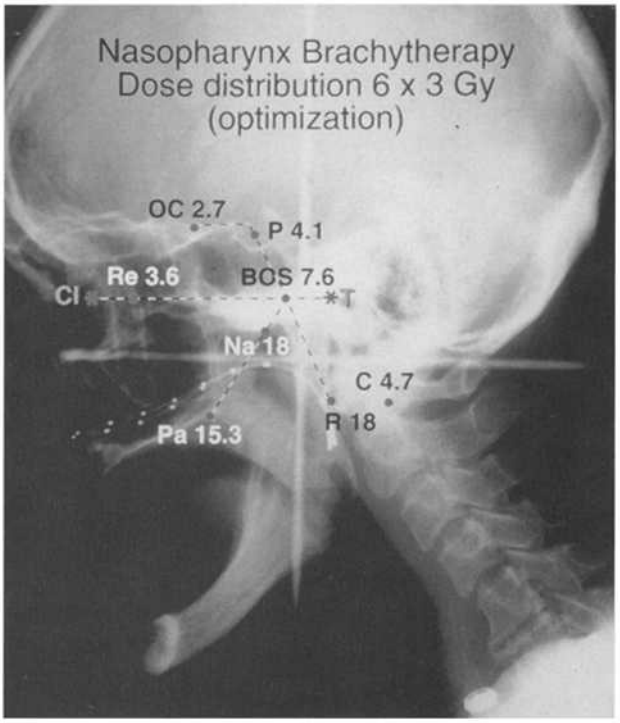

Fig 2. Example of an optimized BT dose distribution in the target (BOS, base of skull; Na, nasopharynx; R, node of Rouviere) and normal tissue points (OC, optic chiasm; P, pituitary gland; Re, retina; Pa, palate; C, spinal cord). The numbers indicate optimized doses in the target and normal tissue points in Gy; the resulting dose distribution has been optimized such that the Na and R dose points receive the reference dose of 18 Gy.[50]

tumor extension into the nasal cavity or ethmoids, an anterior high-energy electron field is added. The ERT dose is prescribed according to the International Commission on Radiation Units Report 50 recommendations.[52] After 46 Gy, a first-field reduction is implemented to ensure that the spinal cord dose stays at less than the tolerance level and the ERT continues with a combination of photons and electrons to the primary tumor and lymph nodes. For T1 through 3 tumors, a total dose of 60 Gy is applied by ERT by using a once-daily fraction of 2 Gy, five times per week. After a rest period of 1 to 2 weeks, a boost is administered to the primary site by means of fractionated HDR-BT, using six fractions of 3 Gy, two fractions daily with a 6-hour interval between fractions (cumulative dose of 78 Gy). In case of parapharyngeal extension and/or T4 tumors, the ERT dose is 70 Gy followed by four fractions of 3 Gy by HDR-BT (cumulative dose of 82 Gy). Lymph node metastases are treated to a dose of 70 Gy.

All patients are jointly seen by a radiation oncologist and a head and neck surgeon in follow-up clinics at regular, ie, 3- to 6-month intervals, for up to 10 years. Acute and late side effects are scored with the criteria of the Radiation Therapy Oncology Group scoring system. The Kaplan-Meier method and the log-rank test were used to perform a crude analysis for the end points time to local failure (TTLF), time to distant failure (TTDF), disease-free survival (DFS), and time to death from tumor or cause-specific survival (CSS) for the different treatment groups. Seven factors, ie, age, sex, race, grade, tumor stage, node stage, and HDR-BT, were analyzed in a multivariate Cox proportional hazards model. From stepwise forward and backward analyses, the best fitting model and an optimal categorization of factors was obtained. By excluding nonsignificant factors ($P > .05$), five prognostic variables were selected: age (< 40 $v \geq 40$ years), tumor stage (T1 through 3 v T4), node stage (N0 through 2b v N2c through 3), grade (1 through 3 v 4), and HDR-BT. Initially, a split-course regimen was customary in the DDHCC after a dose of 40 Gy had been applied.[53,54] Radiobiologic and clinical experience indicate that lengthening of the overall treatment time (OTT) leads to a reduction of the biologically effective dose (BED).[53,54] As the OTTs were quite variable, the BED_{10} (biologic effective dose for tumor effects with $\alpha/\beta = 10$) and the BED_{10} corrected for the overall treatment time ($BEDcor_{10}$) were calculated in addition to the physical dose. The BED_{10} is defined as the summation of the $BED_{10\text{-}ERT}$ (for tumor effects by ERT) and $BED_{10\text{-}BT}$ (for tumor effects by fractionated HDR). The $BED_{10\text{-}ERT}$ was calculated by means of the common Linear Quadratic formalism as proposed by Fowler[55] and the $BED_{10\text{-}BT}$ by means of the model suggested by Brenner and Hall.[56] The $BEDcor_{10}$ values for both ERT and BT were calculated from the corresponding BED values by subtracting a repopulating correction term; for these calculations, values for the potential doubling time (Tpot) = 5 days and $\alpha = 0.28\ Gy^{-1}$ have been applied, which results in a repopulation correction term of 0.5 Gy daily.[49] Details of these computations are described elsewhere.[49] The effectiveness of the treatment modality, defined as the probability of occurrence of a local relapse within 2 years after the start of treatment, was studied in dependence of the total physical dose, BED_{10}, and $BEDcor_{10}$. These probabilities were obtained from a univariate Cox proportional hazards model.

RESULTS

The BT group comprised 42 consecutive NPC patients, stages T1 through 4, N0 through 3, treated between 1991 and 1995 with ERT and HDR-BT. One of these patients (stage T4 N2a) received induction CHT with six weekly courses of cisplatin. Tumor stages are listed in Table 1; 48% had histologic World Health Organization (WHO) grades 1 through 3 and 45% had WHO grade 4. The median follow-up was 2.6 years (range, 0.4 to 5.3 years) and the mean age was 54.8 years (SD, 15.5 years); men outnumbered women (31 v 11) and patients of nonwhite origin comprised 29%. The median applied dose (and 95% interpercentile range) for the BT group was 82 Gy (range, 73 to 95 Gy). In addition to the expected acute and late mucosal and

Table 1. Tumor and Node Stage Distribution of 151 Consecutive Patients With Primary NPC Who Were Treated Between 1965 to 1995

	T1		T2		T3		T4		All Stages	
Node Stage	No-BT	BT	No-BT	BT	No-BT	BT	No-BT	BT	No-BT	BT
0	1	0	15	2	5	4	8	2	29	8
1	3	0	7	1	2	1	5	0	17	2
2a	2	1	5	1	4	3	4	1	15	6
2b	3	2	13	1	2	3	2	1	20	7
2c	1	0	6	3	4	5	6	9	17	17
3	1	0	7	1	1	1	2	0	11	2
All Stages	11	3	53	9	18	17	27	13	109	42

NOTE. No-BT indicates patients treated with ERT ± CHT between 1965-1991. BT indicates patients treated with ERT + BT between 1991-1995.

skin toxicities that occurred with the applied ERT doses, only three patients experienced significant grade 3 late toxicity, ie, synechiae of the nasal mucosal linings because of the addition of BT. This complication, however, was easily correctable with minor surgery in all cases.

The no-BT group comprised patients treated from 1965 to 1991 with either ERT alone (ERT group) or ERT combined with CHT (CHT group). The histologic differentiation grade of the no-BT patients was WHO grades 1 through 3 in 58%, and WHO grade 4 in 38%. The CHT regimens consisted of combinations of vincristine, bleomycin, cyclophosphamide, cisplatin, and/or methotrexate, administered either as induction therapy (18%), in a post-RT adjuvant setting (15%), or as both induction and sandwiched in between split-course ERT (66%).[53,54] The median follow-up of the 40 patients (with 25% nonwhites) in the CHT group was 10.7 years; mean age was 51.2 years (SD, 15 years), and men predominated (29 *v* 11). The median follow-up of the 69 patients treated by ERT alone (with 19% nonwhites) was 7.6 years; mean age was 56.1 years (SD, 15.9 years), men predominated (52 *v* 17). The median applied dose (and 95% interpercentile range) for the CHT group was 64 Gy (range, 60 to 76 Gy), and for the ERT group, 70 Gy (range, 59 to 75 Gy). The toxicity data for the historic no-BT control group is, unfortunately, incomplete.

The impact of dose is shown by the steep dose-response relationships depicted for the parameters physical dose, BED_{10}, and $BEDcor_{10}$ for all 151 patients analyzed (Fig 3). The treatment outcome for the ERT, CHT, and BT groups for the end points TTLF, TTDF, DFS, and CSS (uncorrected for potential prognostic factors) are listed in Table 2. No significant differences were observed between the ERT group and the CHT group. A significant difference was found for the TTLF between the BT versus no-BT patients

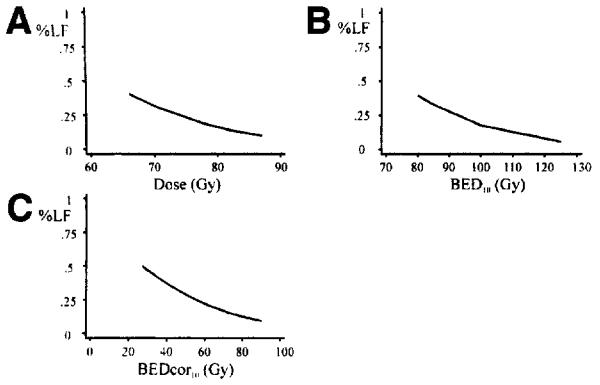

Fig 3. Tumor dose-response relationships for 151 primary NPC patients; dose-effect relations were computed for (A) the physical dose, (B) BED_{10}, and (C) $BEDcor_{10}$. Percentage of patients without LF within 2 years from start of treatment.

with 3-year local control rates of 86% versus 60%, respectively ($P = .004$). Similarly, a significant difference in 3-year DFS was seen between the BT and no-BT groups, with rates of 71% versus 52% ($P = .005$). Multivariate Cox proportional hazards analyses showed age, tumor stage, node stage, and HDR-BT to be strong prognostic variables for the different end points TTLF, DFS, and CSS (Tables 3-5). When all 151 patients were considered, the best prognostic group comprised patients staged T1 through 3, N0 through 2c who were administered BT; ie, 5-year TTLF rate of 94% and CSS of 91%. Similarly, the group with the worst prognosis comprised patients staged T4, N2c through 3 who were not treated with BT (5-year TTLF of 47% and CSS of 24%).

DISCUSSION

After radical RT in NPC, LF and DF rates were 30% and 35% to 45%, respectively.[3] The majority (> 90%) of failures in both categories manifest within 3 years of RT.[57] Local-regional failure is an independent prognostic indicator of distant metastases.[58] Other factors that indicate a high risk for distant metastases are T4 tumor stage, parapharyngeal tumor extension, and advanced nodal metastases.[4,58] Improvements in survival will require improved local control and also the effective treatment of systemic micrometastases in high-risk groups.[26] A growing body of data suggests that tumor control is related to the radiation dose.[17,26,30-32]

Since 1991, we have used a high-dose scheme that consists of ERT and fractionated HDR-BT for primary NPC; the BT dose is optimized with reference to the target (nasopharynx) and surrounding normal critical tissue structures. A significant radiation dose-effect relationship was found for the physical dose, the BED_{10}, and the dose corrected for the OTT ($BEDcor_{10}$). Extended OTTs and/or split-course regimens are now known to reduce the biologic efficacy of RT, and this is reflected in our finding that the steepest slope in dose-effect was seen for the $BEDcor_{10}$. Our data suggest that, on average, a 15% decrease in LF rate can be obtained with every additional 10 Gy $BEDcor_{10}$ in excess of 60 Gy. Our data showed that the crude local control rate for the BT group was significantly better than for the no-BT group, ie, 86% versus 60% ($P = .004$) at 3 years for all stages combined, and similar to the best reported figures in the literature. In spite of the high radiation doses (range, 73 to 95 Gy) used, we saw no severe side effects related to the HDR-BT boost. To minimize synechiae, we now introduce paraffin-impregnated gauze into the nasal cavity after removal of the applicator and the gauze remains in situ for approximately 1 week.

Other groups have also found evidence for improved local control with BT. Wang[19] treated T1 through 3 tumors by

Table 2. End Points TTLF, TTDF, DFS, and CSS Not Adjusted for Prognostic Factors

Variable	No. of Patients	TTLF, Median Years	LC, 3-Year (%)	TTDF, Median Years	DMF, 3-Year (%)	DFS, Median Years	DF, 3-Year (%)	CSS, Median Years	CSS, 3-Year (%)
ERT group	69	NR	64	NR	79	3.2	50	9.9	62
CHT group	40	NR	54	NR	65	1.6	36	3.6	53
No-BT group	109	NR	60	NR	74	2.2	45	4.1	59
BT group	42	NR	86	NR	87	NR	71	NR	70
All patients	151	NR	67	NR	78	3.7	52	5.3	62
P for ERT *v* CHT		.62		.10		.21		.14	
P for no-BT *v* BT		.004		.18		.005		.11	

Abbreviations: LC, local control; DMF, distant metastasis-free; DF, disease free; NR, not reached.

ERT and low-dose-rate BT and observed a local relapse-free survival (LRFS) of 91% at 5 years, as opposed to only 60% for those treated by ERT alone. Chang et al[31] treated patients with ERT and a fractionated HDR-BT boost and suggested that an optimal dose for NPC was between 72.5 to 75 Gy because substantial toxicity, such as perforation of the palate and/or sphenoid sinus floor, occurred with doses that exceeded 75 Gy. This pattern of toxicity contrasts markedly with our experience and a number of findings may explain this. First, we used a smaller fraction size of 3 Gy versus the 5 to 5.5 Gy fractions used by Chang et al.[31] Second, we used a customized applicator, which ensured a more consistent and reproducible dose distribution between patients. Furthermore, Chang et al[31] prescribed the dose at 2 cm from the source axis, which thereby resulted in much higher doses at the surface of the applicator than is the case with our method of prescribing to a fixed anatomic (NP) point, which is generally closer ($\leq$ 1 cm) to the source axis. Our system of routinely optimizing dose distributions with respect to a large number of dose points that depict critical surrounding normal tissues (Fig 2) may also have reduced the likelihood of toxicity.[50] Teo et al[45] administered BT to 71 patients who had persistent local tumor after an ERT dose of 62.5 Gy. A HDR-BT boost of 24 Gy (three fractions in 15 days, prescribed at 1 cm from source plane), was used and a 5-year freedom from LF rate of 74% was achieved. This group observed no benefit for BT in locally advanced cases. In contrast, our data suggest a limited benefit for BT in locally advanced tumors and theoretic modeling suggests that nonhomogeneous dose distributions, a situation typified by BT in locally extensive NPC, may still improve tumor control.[59] Nevertheless, a recent report that described promising local control for a linear accelerator–based stereotactic boost in NPC suggests that this, and not BT, may be a more appropriate method for boosting bulky T4 tumors.[60]

NPC is also a chemosensitive disease,[33,34] and effective systemic CHT may have an important role in patients with high risk for metastases, ie, T4 tumors and/or (bulky) N2c through 3 neck nodal disease. The results of three randomized clinical trials that addressed the benefits of adding CHT to ERT have recently been reported[35,36,61] Chan et al[36] found no differences in the local-regional relapse rate or the distant

Table 3. Univariate and Multivariate Cox Regression Analyses of TTLF for 151 Patients Using Prognostic Factors Age, Tumor and Node Stage, Grade, and HDR-BT

	Univariate		Multivariate	
Variable	Hazard Ratio	*P*	Hazard Ratio	*P*
Age, years				
< 40	1		1	
≥ 40	2.78	.05	2.93	.04
Tumor stage				
T1-3	1		1	
T4	3.25	< .001	3.40	< .001
Node stage				
N0-2b	1		1	
N2c-3	0.98	.95	1.31	.44
Tumor grade				
1, 2, 3	1		1	
4	0.47	.03	0.51	.04
HDR-BT				
No	1		1	
Yes	0.28	.008	0.24	.003

Table 4. Univariate and Multivariate Cox Regression Analyses of DFS of 151 Patients Using Prognostic Factors Age, Tumor and Node Stage, Grade, and BT

	Univariate		Multivariate	
Variable	Hazard Ratio	*P*	Hazard Ratio	*P*
Age, years				
< 40	1		1	
≥ 40	3.00	.01	3.28	.006
Tumor stage				
T1-3	1		1	
T4	2.11	.002	1.98	.006
Node stage				
N0-2b	1		1	
N2c-3	1.94	.006	2.48	< .001
Tumor grade				
1, 2, 3	1		1	
4	0.86	.54	0.77	.28
BT				
No	1		1	
Yes	0.41	.007	0.31	< .001

Table 5. Univariate and Multivariate Cox Regression Analyses of Death From Tumor or CSS of 151 Patients Using Prognostic Factors Age, Tumor and Node Stage, Grade, and BT

	Univariate		Multivariate	
Variable	Hazard Ratio	P	Hazard Ratio	P
Age, years				
< 40	1		1	
≥ 40	3.80	.004	4.16	.002
Tumor stage				
T1-3	1		1	
T4	2.82	< .001	2.70	< .001
Node stage				
N0-2b	1		1	
N2c-3	2.55	< .001	3.16	< .001
Tumor grade				
1, 2, 3	1		1	
4	0.83	.46	0.65	.09
BT				
No	1		1	
Yes	0.60	.11	0.44	.01

metastasis rate in 82 patients with locally advanced NPC who were randomized to either high-dose RT that included HDR-BT or a similar RT scheme with cisplatin-based CHT before and after RT.[36] As suggested by an accompanying editorial, Chan et al[36] used a high-dose RT scheme in a patient group without a uniformly high risk for metastases, and this could have minimized the benefits of CHT.[38] The initial results of an International Nasopharyngeal Study Group trial in 339 patients (of whom 22% had T4 tumors and 40% N2c through 3 disease) who were randomized to either 70-Gy ERT or the same ERT preceded by three cycles of bleomycin, epirubicin, and cisplatin suggested an improved DFS for the CHT arm.[35] However, an excess of treatment-related deaths occurred in the combined modality arm (8% *v* 1%). Significantly, no difference in local control was observed between the treatment arms, a finding that supports the view that optimal local treatment will continue to have an important role in the treatment of NPC. In the Intergroup trial, patients with advanced NPC received either 70-Gy ERT or the same dose of ERT combined with cisplatin on days 1, 22, and 43 during radiation, followed by cisplatin and fluorouracil for three courses post-radiotherapy.[61] The preliminary results suggest a superior survival for the CHT arm with comparable side effects, although details of local tumor control rates were not reported.

Future trials in poor-risk NPC will have to evaluate optimal, high-dose RT combined with CHT, but normal tissue toxicity will continue to be of major concern. Our data suggest the existence of a radiation dose-response up to 95 Gy, a dose that is close to the limits of normal tissue tolerance. Concomitant chemoradiotherapy in other head and neck sites has been associated with greater toxicity than RT alone but we are not aware of any published data that evaluate concomitant CHT with BT in NPC. A similar approach in esophageal cancer resulted in a 12% incidence of tracheoesophageal fistulae and an 8% incidence of fatal toxicity, despite the use of only modest doses of radiation (ERT dose of 50 Gy, BT dose of 3 × 5 Gy).[62] At the present time, we would not advocate combining our high-dose NPC scheme with concomitant CHT.

In summary, our own data provide evidence for a radiation dose-response for up to 95 Gy and we have shown that such doses can be delivered safely with minimal toxicity by means of optimized HDR-BT. In this nonrandomized study, it is not possible to determine if a boost administered by means of BT is necessarily superior to that by ERT alone. However, BT delivered in this manner allows for a better sparing of normal tissues. Because local-regional relapse is an independent prognostic indicator of distant metastases in NPC,[58] high-dose RT alone will be sufficient to improve survival in limited disease (T1 through 3, N0 through 2b). With a view to maximize local control and limit toxicity, we have therefore chosen to treat all our patients with the highest risks for distant metastases (T4, N2c through 3) with cisplatin-based induction CHT, followed by the combined ERT and HDR-BT protocol stated above.[63-65]

ACKNOWLEDGMENT

We acknowledge the continuous support of the members of the Rotterdam Head and Neck Group in patient care and appreciate the secretarial work of Inge Dijkstra.

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