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ORIGINAL ARTICLE

Locoregional Treatment for *De Novo* Metastatic Nasopharyngeal Carcinoma

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OBJECTIVE

Optimal management of *de novo* metastatic nasopharyngeal carcinoma (NPC) is debatable. The aim of this study is to evaluate the patient characteristics, the impact of locoregional treatment on disease control and overall survival (OS) and to analyze the factors that correlate with the outcome of patients with *de novo* metastatic NPC patients treated between 2000 and 2018.

METHODS

Among 589 NPC patients referred to our clinic in the past 18 years, the cases of 36 *de novo* metastatic NPC patients who received radical locoregional radiotherapy (LR-RT) were analyzed retrospectively. After excluding one patient who had previously received chemotherapy for 12 courses in another clinic, the remaining 35 patients were analyzed in terms of population characteristics, OS, and possible confounding factors.

RESULTS

Seven of 35 patients were under the age of 16. The histology was World Health Organization (WHO) type 2-3 in 94.3%. All but two patients received 3-6 cycles of induction chemotherapy. The median dose of LR RT was 70 Gy. The median follow-up time was 25 months. Two and 4 year OS rate was 51% and 34%, respectively. Univariate analysis showed no significant effects of age (>6, ≤40), gender, oligometastatic disease, the existence of liver metastasis, or RT dose on the OS.

CONCLUSION

De novo metastatic NPC patients had highly prolonged survival with the use of LR-RT and this treatment approach should be validated by further multi-centric clinical studies.

Keywords: *De novo*; distant metastasis; nasopharyngeal carcinoma; outcomes; radiation therapy.

Introduction

Nasopharyngeal carcinoma (NPC) differs from other head and neck carcinomas by its specific geographic and ethnic distribution, its association with Epstein-Barr virus (EBV) infection, and predisposition of distant metastases.[1]

NPC is also chemotherapy and radiotherapy (RT) sensitive disease with distinct demographic, clinical, staging, and treatment options as compared to non-nasopharyngeal head and neck cancer.[2] RT is the fundamental treatment modality and concurrent chemo-RT is recommended for locoregionally advanced NPC according to the National Comprehensive Cancer Network (NCCN) Guidelines.[3] However, distant metastasis remains a key challenge.

Both synchronous and metachronous distant metastases are more common among NPC compared to other

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head and neck cancers.[4-6] For synchronous distant metastasis of NPC, this rate ranges between 6 and 15%.[7,8] Most of the current oncological treatment guidelines suggest chemotherapy as the only treatment option for metastatic disease in NPC.[9,10] This might be seen as a reflection of the old perspective which limits RT role with cancer palliation, mostly for symptom control. Only the NCCN guidelines regard post-chemotherapy locoregional RT (LR-RT) as a treatment option without any suggestion on treatment or follow-up.[3]

In recent years, the interest in LR-RT of primary tumors with distant metastases has increased. The survival benefit of local treatment directed at all metastasis in oligometastatic disease has been demonstrated in an early randomized study.[11] The effectiveness of local therapies to the primary tumor in metastatic disease is evolving for some specific cancer types.

According to the "seed and soil" hypothesis, the soluble growth factors secreted from the primary tumor causes the clustering of hematopoietic progenitor cells and macrophages, creating an environment conducive to the spread of malignant clones and the formation of metastasis.[12,13] This emphasizes the importance of the local tumor stage and the possible contribution of local therapies to survival in patients with distant metastases.[14] In accordance with this thesis, the survival benefit of local therapy in metastatic renal cell cancers and transitional cell bladder cancer has been demonstrated.[14,15] Similarly, the role of radical LR-RT in metastatic NPC has been investigated in several retrospective studies[16-19] and in a very recent a prospective randomized trial.[20] They conclude LRRT infer a positive effect on OS.

Following induction chemotherapy, we deliver radical LR RT in *de novo* metastatic NPC (unless obvious progression under chemotherapy) for more than two decades due to the survival advantage observed in our clinical practice. We aimed to share our retrospectively evaluated data of patients with nasopharyngeal cancer who had distant metastases at the time of diagnosis and were treated with LR RT in terms of clinical features and survival.

Materials and Methods

589 cases of patients who had biopsy-proven nasopharyngeal cancer referred to our clinic between 2000 and 2018 were assessed and 36 patients who had distant metastases at diagnosis and also received radical dose RT to the head and neck region were identified. After excluding one patient who had previously received chemotherapy for 12 courses in another clinic, the remaining 35 patients were included in the analysis.

Pretreatment Evaluation

All patients received pre-treatment evaluation consisting of a complete history and physical examination, endoscopic examination, complete blood counts, blood chemistries, computed tomography (CT), or magnetic resonance imaging (MRI) of the nasopharynx and neck.

Until 2006, all patients were screened for distant metastases, using chest radiography, Technetium-99m bone scintigraphy, and abdominal ultrasonography (USG). After 2006, (^{18}F-fluorodeoxyglucose positron emission tomography-CT [PET-CT]) superseded these methods. Tumors were staged according to the 7th edition of the American Joint Cancer Committee (AJCC) TNM staging system.

Treatment

De novo metastatic NPC patients eligible for combined modality chemotherapy received 3-6 courses of 33 of the 35 patients. The chemotherapy responses were evaluated by CT or MRI. The metastases were screened by abdominal USG, chest radiography, bone scintigraphy, or PET-CT. The patients with partial/complete chemotherapy response were assessed for RT. A total of 60-74 Gy of RT were administered with daily fractions of 1.8-2 Gy. In patients under the age of 16, the RT dose was reduced (60-63 Gy) and concurrent chemotherapy was not used. For the patients older than 16 years of age, the decisions for the concurrent chemotherapy were made on a patient basis. Side effects during RT were monitored weekly.

Follow-up Evaluations

The periods for follow-up exams were 1 month-3 months for the first 2 years after RT, 4-6 months for the 3rd, 4th, and 5th years and annually thereafter. Complete blood count, blood biochemistry, and endoscopic examination were performed at each control. Head and neck region evaluation was performed annually by CT or MRI. PET-CT evaluation was held 3 months after the end of LR treatment and else when there is clinical indication.

Statistical Analysis

OS was calculated from the date of diagnosis to the day of death for any reason or date of the last follow up. Survival was estimated by the Kaplan-Meier method. Potential prognostic factors for OS, including age, sex, radiation dose, chemotherapy, and site of metastases, number of metastatic disease, and liver metastasis were

evaluated using log-rank comparisons. P<0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26.

Results

The median age of the patients was 49 (9-85 years) and 85.7% (n=30) of them were male. Overwhelming majority of the patients had either undifferentiated carcinoma 65.7% (n=23) or non-keratinized carcinoma 28.6% (n=10) only 2 (5.7%) of the 35 patients and keratinized carcinoma. PET-CT was used in 82.9% (n=29) of the patients at diagnosis. Eight (22.9) patients had a single metastasis. Furthermore, 17.1% of patients were oligometastatic. The remaining 60% was multiple metastatic. Thirteen (37.1%) of the patients had multiple organ metastases. Bone metastasis was present in 71.4% of patients, liver metastasis in 22.9%, and lung metastasis in 20%. Three patients had mediastinal lymph node metastasis, three patients had bone marrow involvement, one patient had axillary lymph nodes, one patient had adrenal, and one patient had para-aortic lymph node metastasis (Table 1).

Except for two patients with insufficient renal function, all patients first received 3-6 cycles of chemotherapy. While the median dose of RT was 7000 cGy (6000-7400), a reduced dose of 6000-63.00 cGy RT was applied to patient's ≤16 years of age for treatment (Table 2). Eighteen patients received RT concurrently with chemotherapy (one patient, carboplatin; 17 patients, cisplatin). Palliative bone irradiation was performed in 19 patients after LR RT, and one patient received radioembolization for liver metastasis (Table 2).

The median follow-up time was 25 months (5-196 months). During the follow-up period, 24 patients died, one surviving patient with active disease continues to be treated with chemotherapy. Ten patients were on follow-up without disease (48-196 months). Six of the ten patients are alive for more than 5 years without disease. 4-year-survival was calculated as 34% (Fig. 1). In univariate analysis, none of the factors (age ≤40 years, gender, oligometastatic disease, presence of liver metastasis, and RT dose) effected survival.

Table 1 Patient and treatment characteristic

	n	%
Gender		
Male	30	85.70
Female	5	14.30
Histopathology		
WHO1	2	5.70
WHO2	10	28.60
WHO3	23	65.70
İnitial PET-CT		
Yes	29	82.90
No	6	17.10
T stage		
T1	2	5.70
T2	20	57.10
T3	5	14.30
T4	8	22.90
N stage		
N0	1	2.90
N2	18	51.40
N3	16	45.70
No. of metastatic lesions		
Single	8	22.90
Oligo	6	17.10
Multiple	21	60.00
No. of metastatic organs		
Single	22	62.90
Multiple	13	37.10
Liver metastasis		
Yes	8	22.90
No	27	77.10
Induction chemotherapy		
Yes	33	94.30
No	2	5.70
Concurrent chemotherapy		
Yes	18	51.40
No	17	48.60

WHO: World Health Organization; PET: Positron emission tomography; T stage: Primary tumor staging; N stage: Node staging

Discussion

It has been reported that 6-15% of NPC patients are diagnosed with *de novo* metastatic cancer before any treatment has begun.[7,8] By the development of PET-CT at the end of the 1990s, its sensitivity and specificity in cancer staging have begun to be investigated. In their trial comparing four different staging methods (n=78), Chua et al.[21] found PET-CT superior in the terms of sensitivity, specificity, and accuracy to the conventional methods (chest radiography, abdominal USG, and bone scan) (Also the conventional methods performed poorly in this trial, missing four of six metastases). Ng et al.[22] reported a false positivity rate of 18% with PET-CT for their prospective trial (n=115). Tang et al.[8] (n=583) showed that PET-CT detects more distant metastases than conventional staging in patients with NPC and the largest benefit in terms of cost and patient management was observed in the subgroup

Table 2 Summary of clinical characteristics and treatments of 35 patients

Patient	Age/ Gender	Histo-pathology	T stage	N stage	Metastatic areas	No. of metastatic lesions	No. of metastatic organs	Liver metastasis	Induction chemotherapy	LR RT	Concomitant CT	Survival time (months)	Last status
1	25/E	WHO 2	3	3	Bone	Multiple	Single	No	3 PE	7000	No	9	Ex
2	22/E	WHO 3	2	3	Bone, liver	Multiple	Multiple	Yes	6 PE	7000	No	196	NED
3	69/E	WHO 3	2	2	Bone	Single	Single	No	3 PE	7040	No	20	Ex
4	55/K	WHO 3	4	3	Bone	Multiple	Single	No	3 TP	7000	Cisplatin	5	Ex
5	55/E	WHO 3	2	2	Bone, liver	Multiple	Multiple	Yes	3 carboplatin+ docetaxel	7000	No	18	Ex
6	49/E	WHO 1	4	2	bone	Multiple	single	No	3 TP	7000	Cisplatin	43	Ex
7	13/K	WHO 3	2	3	Bone	Single	Single	No	3 BEP	6300	No	161	NED
8	23/K	WHO 3	4	3	Bone marrow	Multiple	Single	No	3 TP	7000	No	6	Ex
9	59/E	WHO 3	1	3	Bone, mediastinum	Multiple	Multiple	No	3 TP	7000	No	11	Ex
10	53/E	WHO 2	2	2	Bone	Single	Single	No	No	7000	No	15	Ex
11	54/E	WHO 3	3	2	Bone, liver	Multiple	Multiple	Yes	6 TP	7000	No	12	Ex
12	40/E	WHO 2	2	3	Bone	Multiple	Single	No	6 TP	7000	No	6	Ex
13	68/E	WHO 3	4	3	Bone	Multiple	Single	No	6 TP	7000	Cisplatin	12	Ex
14	65/E	WHO 3	1	2	Lung, mediastinum	Multiple	Multiple	No	6 TP	7000	Cisplatin	93	NED
15	50/E	WHO 2	2	2	Bone	Oligometastasis	Single	No	3 TP	7000	Cisplatin	9	Ex
16	9/E	WHO 3	2	2	Bone, lung	Multiple	Multiple	No	3 PE	6300	No	22	Ex
17	85/E	WHO 3	3	2	Lung	Multiple	Single	No	No	7000	No	9	Ex
18	12/E	WHO 3	3	3	Bone, bone marrow	Multiple	Multiple	No	3 TP	7000	No	44	Ex
19	38/E	WHO 2	2	2	Liver, paraaortic lymph nodes	Oligometastasis	Multiple	Yes	3 TP	7000	Cisplatin	83	NED
20	59/K	WHO 3	2	2	Liver, surrenal	Oligometastasis	Multiple	Yes	3 TP	7000	Cisplatin	7	Ex
21	13/E	WHO 3	2	2	Liver	Single	Single	Yes	3 PE	6300	No	77	NED
22	16/E	WHO 3	2	3	Bone marrow, axilla lymph nodes	Multiple	Multiple	No	3 BEP	6300	No	67	NED
23	34/E	WHO 3	2	2	Bone, mediastinum	Multiple	Multiple	No	3 TP	7000	Cisplatin	48	Ex
24	57/E	WHO 3	2	2	Bone	Single	Single	No	3 TP	7000	Carboplatin	25	Ex
25	34/E	WHO 3	2	3	Bone, liver	Multiple	Multiple	Yes	6 TP	7000	Cisplatin	35	Ex
26	28/E	WHO 2	4	0	Lung	Multiple	Single	No	3 DCX	7400	Cisplatin	57	NED
27	60/E	WHO 3	2	3	Lung	Multiple	Single	No	3 TP	7000	Cisplatin	49	Ex
28	13/E	WHO 1	2	3	Bone	Single	Single	No	3 EP	6000	No	54	NED
29	52/E	WHO 2	2	3	Bone	Single	Single	No	3 TP	7000	Cisplatin	10	Ex
30	49/E	WHO 3	4	3	Bone	Multiple	Single	No	3 TP	7000	Cisplatin	49	NED
31	66/E	WHO 2	4	2	Bone, lung, liver	Multiple	Multiple	Yes	3 TP	7000	Cisplatin	41	Ex
32	45/E	WHO 3	4	2	Bone	Oligometastasis	Single	No	3 DCX	7000	Cisplatin	48	NED
33	64/E	WHO 2	2	2	Bone	Oligometastasis	Single	No	3 DCX	7000	Cisplatin	44	Active disease
34	10/K	WHO 2	2	2	Lung	Single	Single	No	3 EP	6000	No	15	Ex
35	34/E	WHO 3	3	3	Bone	Oligometastasis	Single	No	3 DCX	7000	Cisplatin	8	Ex

T stage: Primary tumor staging; N stage: Nodal staging; LR RT : Locoregional radiotherapy dose; CT: Chemotherapy; WHO: World Health Organization; PE: Cisplatin+epirubicin; TP: Docetaxel+cisplatin; BEP: Bleomicin+epirubicin+cisplatin; DCX: Docetaxel+cisplatin+capecitabine; NED: No evidence of disease; Ex: Exitus

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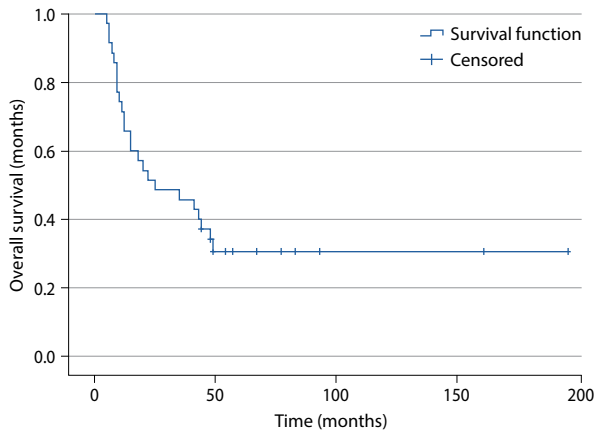

Fig. 1. Overall survival of all patients.

with N2-3 disease and EBV DNA ≥4000 copies/mL. In our clinic, we have been staging the NPC patients using PET-CT, irrespective of their local stage since 2006. Six of the patients (17%) analyzed in this study were staged previously with conventional methods. All patients in the study were stage N2-3 in regional staging, except one patient with T4N0 disease.

In the last 18 years, 589 NPC patients have been referred to our clinic, 6.1% of them had distant metastases at the time of diagnosis. In this current study of 35 *de novo* metastatic NPC patients with a median follow-up time of 25 months, the 4-year-survival was 34% and no significant prognostic factor on survival could be identified.

Local therapy has been used for metastatic disease with the intent of reducing primary tumor burden, relieving symptoms, or propagation of metastases. Some cancer studies have demonstrated that intensive local therapy could prolong overall survival (OS) in untreated *de novo* metastatic cancer patients.[14,15,23,24] This concept of LR treatment is supported by a randomized clinical trial reporting the OS benefit of high dose RT to the primary tumor (STAMPEDE).[25] The number of clinical studies researching the effect of LR RT in *de novo* metastatic NPC is limited. It should, however, be cleared since treatment of *de novo* metastatic NPC patients must consider the control of primary tumors, which is different from metastatic NPC after treatment. Several retrospective analyses suggested that additional LR RT could improve survival of these patients in addition to palliative chemotherapy.[16-19] In accordance with these emerging data, the NCCN Guidelines recommend concurrent chemoradiation as an option in *de novo* metastatic NPC.

NPC usually metastasize to bones, lungs, and liver.[2,26] Among them, the primary metastasis site is the bones. The solitary bone metastasis is alleged to be related to a better prognosis than the others.[26] The liver, the third common metastasis site after the lungs, has the worst survival rates according to Zou et al. study.[19] They separated the M stage into three subgroups, according to the number of metastatic lesions and the existence of liver metastasis in their classification. While the oligometastatic disease subgroup had the best survival rates, the subgroup with the liver metastasis, which was named M1c, had the worst. In their study using five different prognostic factors (age, N stage, number of metastases, organ involvement, and EBV DNA levels), Sun et al.[27] found the existence of multiple metastases and liver involvements, negative prognostic factors. In our serial, there were eight patients with liver metastases (one patient under 16 years of age, one single-metastatic-patient, and two oligometastatic-patients) and three of them are alive with no evidence of disease for 77, 83 and 196 months.

In their retrospective data Lin et al.[16] evaluated 105 patients with *de novo* metastatic NPC and stated better survival rates for single metastatic patients treated with RT doses higher than 65 Gy. Among the eight single-metastatic-patients in our serial, three of them are alive, continuing their life disease-free.

In 2020, You et al.[20] published a two-armed, Phase III randomized trial, investigating the effectiveness of LR RT in *de novo* metastatic NPC patients with partial or complete response to three cycles of cisplatin, and 5-fluorouracil (PF) treatment. While the control group (who had only taken chemo) had a 2-year-survival rate of 54%, and the 2-year-survival rate of the CT+RT group was 76% (p=0.004). In this trial, 30.9% of patients had one or two metastases, and this group had longer OS. It is the first and sole Phase III trial showing the contribution of LRRT in *de novo* metastatic NPC patients with good response to PF chemotherapy. The exclusion of the unresponsive patients to PF chemotherapy limits the generalizability of the results, the results are still important since they point out the value of LR RT in *de novo* metastatic NPC treatment. In this trial, the RT dose following PF was 7000 cGy and the irradiated RT volumes were designated according to pre-chemotherapy imaging. In the same issue with article invited commentators suggested limiting irradiation with post-chemotherapy volumes and the dose of 60 Gy in the patients with complete response.[28] However, yet there is no convincing proof for the dose decrement in this group with a long survival (You et al., 2-year-survival

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>50%). In our clinical practice, we use pre-chemotherapy imaging and apply 70 Gy for adult patients.

Limitations of the Study

This is a retrospective study with a limited sample size. Although it reflects the two decades of experience of a single center in *de novo* metastatic disease treated with a considerably homogenous program the patient group consisted of various age groups (9-85), had different chemotherapy regimens, their number and sites of metastases varied. This complicates the investigation of survival related factors.

Conclusion

The LR treatment in *de novo* metastatic diseases is gaining prominence since the related patient group can have long survival depending on the count of their metastases and organ involvement. *De novo* metastatic NPC patients had highly prolonged survival with the use of LR RT and this treatment approach should be validated by further multi-centric clinical studies. In our clinic, post-chemotherapy LR RT constitutes the primary treatment option for *de novo* metastatic NPC.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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