·Nasopharyngeal Carcinoma Column·

Prognostic factors of 305 nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy

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[Abstract] Background and Objective: Radiotherapy is effective in treating nasopharyngeal carcinoma (NPC). This study evaluated the treatment efficacy, toxicity, and prognostic factors of intensity-modulated radiotherapy (IMRT) in the treatment NPC. **Methods:** Between September 2003 and September 2006, 305 patients with NPC were treated with IMRT in Fujian Provincial Cancer Hospital. IMRT was delivered as follows: gross tumor volume (GTV) received 66.0–69.8 Gy in 30–33 fractions, high-risk clinical target volume (CTV-1) received 60.0–66.65 Gy, low-risk clinical target volume (CTV-2) and clinical target volume of cervical lymph node regions (CTV-N) received 54.0–55.8 Gy. Patients with stages III or IV disease also received cisplatin-based chemotherapy. All patients were assessed for local-regional control, survival, and toxicity. **Results:** With a median follow-up of 35 months (range, 5–61 months), there were 16, 8, and 39 patients who had developed local, regional, and distant recurrence, respectively. The 3-year rates of local control, regional control, metastasis-free survival, disease-free survival, and overall survival were 94.3%, 97.7%, 86.1%, 80.3%, and 89.1%, respectively. Multivariate analyses revealed that T-classification had no predictive value for local control and survival, whereas N-classification was a significant prognostic factor for overall survival ($P < 0.001$), metastasis-free survival ($P < 0.001$), and disease-free survival ($P = 0.003$). For stages III–IV disease, concurrent and adjuvant chemotherapy did not influence prognosis. The most severe acute toxicities included Grade III mucositis in 14 patients (4.6%), Grade III skin desquamation in 90 (29.5%), and Grades III–IV leucocytopenia in 20 (6.5%). There were 7% patients with Grade II xerostomia after 2 years of IMRT, no Grades 3 or 4 xerostomia was detected. **Conclusions:** IMRT provided favorable locoregional control and survival rates for patients with NPC, even in those with locally advanced disease. The acute and late toxicities were acceptable. N-classification was the main factor of prognosis. Further study is needed on chemotherapy for patients with NPC.

Key words: Nasopharyngeal neoplasm, radiotherapy, intensity-modulated, prognosis, side effect

Nasopharyngeal carcinoma (NPC) is the most common head and neck cancer in Southeast Asia and radiotherapy is the main treatment. Intensity-modulated radiotherapy (IMRT) is increasingly used in the treatment of patients with NPC. Some studies have shown that the treatment of NPC with IMRT can improve the rate of local control and reduce toxicity and side effects[1-3]. However, since IMRT has been used for only a short time, few large-sample studies and long-term efficacy have been reported. In this study, through retrospective analysis of a large sample, efficacy and complications of IMRT in patients with NPC were observed, and prognostic factors were explored.

Patients and Methods

Patients and pre-treatment preparation

Between September 2003 and September 2006, 308 newly diagnosed patients with NPC received full courses of standard IMRT in the Department of Radiotherapy, Fujian Provincial Tumor Hospital[4]. Two patients with doses less than 66 Gy and 1 patient with distant metastasis were excluded, and the data on the remaining 305 patients were analyzed. Disease in all patients was histopathologically confirmed by fiberoptic nasopharyngoscopy before treatment, and each patient received a systemic physical examination, routine blood tests, blood biochemistry tests, chest radiograph, electrocardiogram, bone emission computed

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tomography (ECT), abdominal ultrasound, and computed tomography (CT) or magnetic resonance imaging (MRI) examinations of the nasopharynx and neck (MRI instead of CT after July 2005). There were 230 males (75.4%) and 75 female (24.6%), with a median age of 45 years (range, 11–86 years). Karnofsky performance status (KPS) scores were 90 for 261 patients (85.6%), 80 for 41 patients (13.4%), and 70 for 3 patients (1%). Histologically, 1 patient (0.3%) had World Health Organization (WHO) type I, 3 patients (1%) had type II, and 301 patients (98.7%) had type III. According to the 1992 Fuzhou staging criteria, 1 patient had stage I (0.3%), 44 had stage II (14.4%), 168 had stage III (55.1%), and 92 had stage IVa (30.2%). Detailed T and N distributions are shown in Table 1.

Table 1 The primary tumor status (T stage) and regional lymph node metastasis (N stage) of the patients with NPC underwent IMRT

T stage	N0	N1	N2	N3	Total
T1	1	2	–	–	3
T2	9	33	61	7	110
T3	11	52	45	8	116
T4	8	42	20	6	76
Total	29	129	126	21	305

The values in this table show the number of patients.

IMRT

Masks were made for all patients in the supine position, followed by a 3-mm thick enhanced CT scanning. The upper bound of the scanning was the top of the head and the lower bound was 2 cm below the scapuloclavicular joint. Before July 2005 CT images were used to delineate the target volume, and thereafter integration software (Oncentra Materplan version 1.5) was used to delineate the target volume on MRI-CT fusion images. Target volume delineation was performed as reported in reference [4]. IMRT was applied to primary tumor and lymph node areas above the lower edge of the hyoid bone, using 7 coplanar radiation fields with intervals of 51 degrees, and the isocenter was set at the geometric center of the gross tumor volume-primary (GTV-P).

The PLATO treatment planning software (RTS version 2.6.4) was used for inverse planning. The prescribed doses of the planning target volume (PTV) were 66.00–69.75 Gy to GTV (GTV-P and the GVT-N), 60.00–66.65 Gy to high-risk clinical target volume (CTV-1), and 54.00–55.8 Gy to both low-risk clinical target volume (CTV-2) and the clinical target volume of cervical lymph nodes (CTV-N). Radiation was delivered in 30–33 fractions. Dose-volume histograms (DVHs) were analyzed, and the volume of PTV with doses more than 105% of the prescribed dose was requested to be less than 20%, less than 93% to be less than 3%, and no region with more than 110% of the prescribed dose existed. Maximum dose (D_{max}) and minimum dose (D_{min}) were calculated at the point dose. Limiting doses to organs at risk (OARs) was set according to the Radiation Therapy Oncology Group (RTOG) 0225 report[5]. Volume with 26 Gy (V_{26Gy}) in the unilateral parotid gland was determined to be less than 50%. Lower cervical lymph nodes were irradiated by conventional tangential irradiation, with a total dose of 50.40 Gy/28 fractions and a reference point at 3-cm deep (positive lymph nodes had a boost by local electron beam irradiation to total dose of about 70 Gy). Radiotherapy was performed by linear accelerator (Eleckta Precise) with 40 pairs of multileaf collimator (MLC).

Combined treatment

A total of 260 patients with stages III–IVa disease received 2 cycles of induction chemotherapy, except for 4 patients because of contraindications or patients' refusal. A total of 40 patients with locally advanced disease received 1 to 3 cycles of concurrent chemotherapy. A total of 55 patients with stage III-IVa disease received 2 to 4 cycles of adjuvant chemotherapy. All chemotherapy regimens were platinum-based. After completing the planned IMRT, 59 patients (including 27 with stage-T4, 22 with stage-T3, and 10 with stage-T2 disease) received a radiation boost of 6–12 Gy due to residual disease observed by imaging or nasopharyngoscope, and 26 patients received a boost of 4.5–10.0 Gy due to lymph nodes with diameters larger than 1 cm as observed by imaging at the end of radiotherapy.

Follow-up

All patients received physical and hematologic examinations every week during radiotherapy. Follow-up was performed every 3 months for the first 2 years and every 6 months thereafter. Follow-up included complete physical and hematologic examinations, chest X-ray, abdominal ultrasound, and fiberoptic nasopharyngoscopy. An MRI of the nasopharynx was examined every 6 months. All local or regional relapse was confirmed by pathology. Toxicity was evaluated by the RTOG criteria[6].

Statistical analysis

Observed indicators included IMRT dose analysis, acute and late toxicities, tumor prognosis, and patient survival. Local-control rate, disease-free survival, overall survival rate, and so on, were analyzed by the Kaplan-Meier method. Survival time was calculated from diagnosis to either death or the last follow-up. Acute and late toxicities were evaluated by the RTOG criteria for radiation injury. Late toxicity was defined as toxicity occurring 3 months after radiotherapy or persisting for longer than 90 days. Different factors of prognosis were analyzed by log-rank test and the Cox proportional hazards model was used for multivariate analysis. $P < 0.05$ indicated statistical significance.

Results

DVHs

Table 2 shows DVHs of different target volumes. Although the prescribed dose of GTV-P-PTV was 66.00–69.75 Gy, the actual average dose was 72.12 Gy, because volume with dose less than 93% of the prescribed dose was requested to be less than 3%. Since GTV-P was included in CTV-1 and CTV-2, GTV-P-PTV, CTV-1-PTV, and CTV-2-PTV had close maximum doses. DVH results of OARs are shown in Table 3. The average of maximum

Table 2 Dose-volume histogram (DVH) statistics for targets

Item	Average value (range)		
	GTV-P-PTV	CTV-1-PTV	CTV-2-PTV
Volume (cm^3)	34.2 (0.8–135.5)	85.2 (16.6–268.1)	163.7 (93.2–308.7)
D_{max} (Gy)	78.3 (69.2–90.3)	78.0 (69.1–90.3)	77.6 (69.2–90.5)
D_{min} (Gy)	63.6 (51.8–80.4)	56.9 (46.4–64.5)	49.3 (28.8–56.2)
Mean dose (Gy)	72.1 (63.1–78.8)	69.2 (63.2–76.5)	65.8 (60.9–74.1)

GTV-P-PTV, gross tumor volume-primary, planning target volume; CTV-1-PTV, high-risk clinical target volume, planning target volume; CTV-2-PTV, low-risk clinical target volume, planning target volume; D_{max}, maximum dose; D_{min}, minimum dose

Table 3 DVH data for organs at risk (OARs)

Volume	Mean value (range)			
	Brainstem	Spinal cord	Optic nerve-left	Optic nerve-right
1% (Gy)	46.5 (23.2–74.7)	37.2 (12.5–44.5)		
5% (Gy)	42.0 (20.2–66.9)	34.6 (9.3–42.4)	25.4 (2.0–81.4)	27.6 (2.0–83.0)
10% (Gy)	39.1 (18.5–60.1)	33.1 (8.0–40.7)	22.8 (1.8–79.2)	24.9 (1.8–81.4)

dose to optic chiasms was 35.5 Gy (range, 29.3–87.0 Gy), and average volume of dose more than 54 Gy was 10% (range, 0% –100%). The mean doses to the left and right parotid gland was 27.8 Gy (range, 18.4–49.7 Gy) and 29.1 Gy (range, 21.3–42.02 Gy), respectively, and the average V_{26Gy} was 47.6% (range,9.6% –98.3%) and 50.2% (range, 20.6%–96.6%), respectively.

Treatment outcomes

The median follow-up time was 35 months (range, 5–61 months). The 3-year rates of local control, regional control, distant metastasis-free, disease-free survival, and overall survival were 94.3%, 97.7%, 86.1%, 80.3%, and 89.1%, respectively (Figure 1). A total of 27 patients (8.4%) died, among which 19 died of distant metastasis, 8 died of locoregional relapse, 1 died of nasopharyngeal bleeding, 2 died of another cancer, 1 died from a car accident, and 2 died of unknown causes.

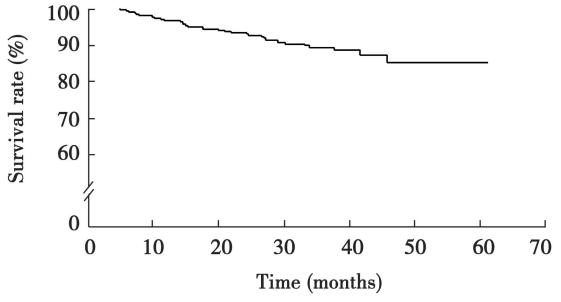

Figure 1 Kaplan-Meier estimates of 3-year overall survival for the 305 patients with NPC underwent IMRT

In the 305 patients, 16 and 8 patients had local and/or regional relapse, among which 4 patients had both local and regional relapse, with a median relapse time of 18 months (range, 5–53 months). Among the 16 patients with local relapse, 14 had relapse in GTV, and the other 2 patients had invasion to CTV. There was no relapse outside CTV-2. All relapsed lesions had received the prescribed dose of IMRT. A total of 39 patients had distant metastasis, with a median time of 15 months (range, 2–31 months), among which 29 had single organ metastasis and 10 had multiple organ metastasis. Metastatic sites were as follows: bone metastasis in 19 patients, lung or mediastinal lymph node metastasis in 16 patients, liver metastasis in 14 patients, and axillary and thoracoepigastric wall metastasis in 1 patient.

Acute and late toxicity

In all 305 patients, the treatment was well tolerated and completed as planned. The most common acute toxicities were skin reactions (grade I in 60.3%, grade II in 35.1%, and grade III in 4.6%), oral mucositis (grade I in 19.4%, grade II in 51.1%, and grade III in 29.5%), and leukopenia caused by bone marrow suppression (grade I in 33.1%, grade II in 44. 6%, grade III in 6.2%, and grade IV in 0.3%). One patient with grade-IV myelosuppression and other patients with grade-III adverse reactions were not affected from treatment after symptomatic therapy.

Late toxicity observed during the follow-up time included: neck fibrosis (grade I in 30.5%, grades II–III in 1%), hearing loss (grade I in 15.4%, grades II-III in 0.7%), and trismus (grade I in 4.3%, grades II–III in 1%). A total of 8 patients had cranial nerve injury, among whom 3 had injuries of group VI, 2 had injuries of group XII, 1 had injuries of group V, 1 had combined injuries of groups V and VI, and 1 had combined injuries of groups X and XI. Three patients had radiation encephalopathy. Dry mouth was the most common late toxicity, with grades I and II accounting for 5% and 95%, respectively, 3 months after radiotherapy; grades 0, I, and II accounting for 7.6%, 85.4%, and 7%, respectively, 24

months after radiotherapy; and grades 0, I, and II accounting for 18.1% , 78.4% , and 3.4% , respectively, 36 months after radiotherapy. Grade IV late toxicity was not observed in the whole group.

Prognostic factors

The effects of age, sex, stage, KPS score, and chemotherapy on prognosis was analyzed. Among the 8 patients with regional relapse, 4 had stage N1 and 4 had stage N2, but further analysis of the prognostic factors could not be carried out because of the small number. The results of univariate analysis are shown in Table 4. Multivariate analysis showed N stage (P = 0.000, χ^2 = 19.58, HR = 2.966, 95% CI = 1.832-4.801) and age (P = 0.048, χ^2 = 3.903, HR = 2.432, 95% CI = 1.007–5.828) were independent prognostic factors affecting overall survival. N stage was also an independent prognostic factor affecting distant metastasis-free survival (P = 0.000, χ^2 = 10.299, HR = 2.819, 95% CI = 1.618–4.914) and disease-free survival (P = 0.003, χ^2 = 8.724, HR = 1.951, 95% CI = 1.252–3.041).

Table 4 Univariate analyses of predictive factors for the patients with NPC received IMRT

Factors	Item	3-year overall suivival (%)	χ^2	P	3-year local control (%)	χ^2	P	3-year metastasis-free survival (%)	χ^2	P	3-year disease-free survival (%)	χ^2	P
Age (years)	≤ 60	91.6	5.92	0.02	94.7	0.81	0.37	86.2	0.13	0.72	81.0	1.18	0.28
	> 60	75.8			92.5			85.6			77.0		
Gender	Male	88.2	1.81	0.19	92.8	3.48	0.06	84.7	1.08	0.3	78.2	2.31	0.13
	Female	92.4			98.6			90.2			86.9		
KPS score	70	66.7	2.59	0.27	66.7	7.4	0.02	100.0	2.64	0.27	66.7	1.13	0.57
	80	81.5			92.5			95.2			87.7		
	90	90.4			95.1			84.7			79.6		
T stage	T1	100.0	0.67	0.88	100.0	6.03	0.11	100.0	3.44	0.33	100.0	4.69	0.2
	T2	90.0			98.0			90.0			86.1		
	T3	88.1			93.5			84.8			78.2		
	T4	89.6			89.7			82.1			74.1		
N stage	N0	96.3	22.1	0.00	96.6	1.6	0.66	95.7	21	0.00	92.4	13.4	0.00
	N1	92.8			93.2			93.9			86.1		
	N2	84.7			94.9			78.7			74.2		
	N3	64.3			93.3			71.4			66.3		
Clinical stage	I	100.0	5.16	0.16	100.0	2.41	0.49	100.0	10.6	0.01	100.0	9.29	0.03
	II	94.1			97.7			100.0			94.9		
	III	90.3			95.7			85.9			81.1		
	IV	84.6			89.9			79.5			71.8		
Boost	Yes	84.7	1.81	0.14	89.5	2.26	0.13	81.0	1.83	0.18	76.1	1.05	0.31
	No	89.9			95.7			87.5			81.5		
Neoadjuvant chemotherapy	Yes	90.1	0.8	0.37	93.8	0.61	0.43	84.5	1.98	0.16	78.7	0.73	0.39
	No	85.4			96.3			93.1			87.4		
Concomitant chemotherapy	Yes	89.7	0.01	0.92	97.3	0.31	0.58	87.3	0.25	0.62	84.9	0.61	0.43
	No	89.2			94.0			85.7			79.6		
Adjuvant chemotherapy	Yes	92.4	0.8	0.37	91.6	0.45	0.5	77.6	4.71	0.03	71.4	3.81	0.06
	No	88.5			94.5			88			82.3		

The effects of concurrent chemotherapy, adjuvant chemotherapy, and boost to residual disease on the prognosis of patients with locally advanced disease (III–IVa) were also analyzed. It was found that for those with boost to residual disease and those without residual disease, the 3-year local-control rate was 87.6% and 96.5% respectively, with significant differences between them (P = 0.03). Concurrent chemotherapy had no effect on 3-year overall survival, local-control rate, distant metastasis-free survival, or disease-free survival (P values were 0.93, 0.59, 0.49, and 0.47; 0.32, 0.34, 0.08, and 0.08, respectively). Since only 4 patients with locally advanced disease had no induction chemotherapy, the impact of induction chemotherapy on these patients was not analyzed.

Discussion

Studies have shown that IMRT can achieve ideal target dose distributions while protecting normal tissue compared with two-dimensional conventional radiotherapy[6-8]. Patients treated with IMRT can obtain a better local control rate and reduced toxicity[1-3,9]. Lee *et al.*[2] reported a retrospective analysis of 67 patients, and found that the 4-year progression-free survival

(PFS) and overall survival were 97% and 88% , respectively. Wolden *et al.*[10] reported the results of 74 patients treated with IMRT, and the 3-year local-control rate was 91% . Kam *et al.*[3] from Hong Kong also reported similar results. Recently in China, Yi *et al.*[11] reported on 147 patients with NPC treated by IMRT, and the results showed that the 3-year local control, overall survival, disease-free survival, and distant metastasis-free survival rate were 93.2% , 93.5% , 72.6% , and 74.4% , respectively. We analyzed 305 patients with a follow-up of 35 months and found that the 3-year local control, regional control, distant metastasis-free, disease-free survival, and overall survival rat were 94.3%, 97.7%, 86.1%, 80.3%, and 89.1%, respectively. All above small sample results confirm that IMRT can get a better effect for patients with NPC.

There are various large sample studies reporting prognostic factors for patients with NPC who were treated by conventional radiotherapy. Recently, Gao *et al.*[12] reported a retrospective analysis of 1837 patients with NPC treated by conventional radiotherapy, and found T and N stage were independent prognostic factors affecting the overall survival and distant metastasis-free rates, and T stage also affected the local-control rate. Compared with conventional radiotherapy, IMRT has qualitative changes in treatment mode, and prognostic factors in NPC may also change. Since current reports on treating patients with NPC by IMRT have small sample sizes and short follow-up times, few prognostic factors were analyzed. This study analyzed the prognostic factors for patients with NPC treated by IMRT, and found that T stage neither affect the local-control rate nor the overall survival rate, while N stage was an independent prognostic factor affecting the distant metastasis-free, disease-free survival, and overall survival rates. Although Yi *et al.* [11] reported that after a median follow-up of 15 months for NPC patients treated with IMRT, the univariate analysis showed that T stage had an effect on the local-control and the overall survival rates, and N stage had an effect on overall survival, disease-free survival, and distant metastasis-free rates, but these prognostic factors had no significance in multivariate analysis. Compared with conventional radiotherapy, T stage is no longer a prognostic factor for overall survival or even local control in IMRT, which may be due to IMRT overcoming the defects of conventional dose distribution and improving doses to locally advanced disease, so tumors receive enough radiation while normal tissue is protected, and the prognosis for these patients is improved. The exact cause has yet to be confirmed by further studies.

In recent years, chemotherapy combined with radiotherapy is increasingly used in the treatment of patients with locally advanced NPC. Meta-analysis shows that, compared with radiotherapy alone, concurrent chemotherapy and radiotherapy can extend the survival time of patients with locally advanced NPC, and platinum-based chemotherapy has the most significant effects, but the role of induction and adjuvant chemotherapies are uncertain[13,14]. In this group, patients with locally advanced NPC received comprehensive treatment with IMRT and chemotherapy, and the results showed that induction, concurrent, and adjuvant chemotherapies were not prognostic factors. This may be because patients with concurrent chemotherapy in this group had a small sample size and chemotherapy cycles that affected the outcome. But the main reason is still that IMRT failed on distant metastasis in patients with NPC, indicating such patients require further study of rational and effective comprehensive treatments.

Among the 305 patients in this group, 59 patients with residual disease as observed by imaging or nasopharyngoscope after radiotherapy received a boost of 6–12 Gy by IMRT or three-dimensional conformal radiation therapy (3D-CRT). In patients with locally advanced disease, those with boost to residual disease had significantly lower 3-year local-control rates than those without residual disease (P = 0.03). Yi *et al.*[15] reported 905 patients with conventional radiotherapy and found that in patients with stage-III and -IVa disease, those with boost to residual disease after radiotherapy (DT > 80 Gy) had poor outcomes compared with those without residual disease, and the 5-year overall survival rates were 67.1% and 74.9%, respectively, with a P value of 0.06, which was close to statistical significance and consistent with the results of this group. The findings suggest that after irradiation, there are enough residual cancer stem cells relatively resistant to radiation that cannot be well controlled even if the radiation dose is increased. Currently the criterion whether residual disease observed by clinical imaging or nasopharyngoscope is pathologic is not yet consistent, and individual reports have varied results. Ma *et al.*[16] reported a prospective study and found that the diagnosis of NPC residual disease by CT had a sensitivity and specificity of 0.67 and 0.32, respectively, at 4 months after radiotherapy. Therefore, we need an effective criterion for NPC residual disease and give higher doses or combine other treatment to improve efficacy, which remains to be studied.

In this study, age was also an independent prognostic factor affecting overall survival, and the 3-year overall survival rates for those aged less than 60 years and those aged more than 60 years were 91.6% and 75.8%, respectively, (P = 0.048), which was consistent with the result of our former report on 1706 patients with NPC treated by conventional radiotherapy[17].

IMRT could be tolerated in this group, and grade-III oral mucositis was the most common severe acute toxicity (90 patients accounting for 29.5%), but treatment was not affected by acute toxicity after symptomatic treatment. Grade-II dry mouth accounted for only 7% at 24 months after treatment and 3.4% at 36 months after treatment, and dry mouth gradually improved with time, which was similar with the published research. Lee *et al.*[2] reported dry mouth and found that grades 0, 1, and 2 accounted for 8% , 28% , and 64% , respectively, 3 months after radiotherapy, and 66% , 32% , and 2.4% , respectively, 2 years after radiotherapy. Yi *et al.*[11] also reported similar results. Although in this group 1 patient died of nasopharyngeal bleeding 6 months after radiotherapy, there was no specific high-dose point in the target volume, and it was considered due to tumor specificity, such as locally advanced disease and so on. Although long-term effects require further follow-up, our median follow-up time was 35 months, which could meet the basic research need for local-control rates, since recurrence of NPC mainly occurs in the first 24 months after radiotherapy[18]. In addition, treatment failure was mainly due to distant metastasis, and patients with

advanced N stage had worse outcomes, so effective chemotherapy or targeted therapy would be required to cope with IMRT for patients with advanced NPC.

Conclusion

IMRT for NPC has ideal efficacy and mild acute and late toxicities. T stage is no longer a prognostic factor, while N stage is the main prognostic factor. Concurrent and adjuvant chemotherapy for patients with locally advanced disease has uncertain effects. Distant metastasis is still the main reason for treatment failure. Chemotherapy needs to be further studied and more effective chemotherapy drugs, targeted drugs, and more rational combined treatments need to be explored to reduce the rate of distant metastasis and improve efficacy. Further research still needs prospective analysis with large sample sizes.

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