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Alternative endpoints to the 5-year overall survival and locoregional control for nasopharyngeal carcinoma: A retrospective analysis of 2,450 patients

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Abstract. The purpose of the present study was to investigate alternative endpoints to the 5-year overall survival (OS) and locoregional control (LRC) for nasopharyngeal carcinoma (NPC). A total of 2,450 NPC patients were enrolled in this study, including 1,842 patients treated with two-dimensional (2D) radiotherapy (RT), 451 treated with 3D conformal RT (CRT) and 157 treated with intensity-modulated RT (IMRT). We sequentially calculated the 1-, 2-, 3- and 4-year survival rates using a life table and compared these with the 5-year survival rate using the McNemar method, with the survival rate of the last indifferent comparison being considered as the alternative endpoint. For 2D RT, stage I patients exhibited similar survival rates at 1 and 5 years (98.9 vs. 94.4%, respectively; P=0.125 for both OS and LRC); stage N3 patients exhibited similar 4-year OS (55.2 vs. 53.5%; P=1.000) and 2-year LRC (78.3 vs. 71.2%; P=0.125) to the 5-year OS and LRC. For IMRT, the 1-, 2-, 3-, 4- and 5-year OS and LRC rates in stage I/II NPC patients were 100, 98, 96, 94 and 94% for OS and 100, 98, 96, 96 and 96% for LRC, respectively. No significant differences were observed for all the comparisons. For stage III/IV NPC patients treated with IMRT, the 1-, 2-, 3-, 4- and 5-year rates were 99.1, 96.3, 92.5, 88.8 and 85.0% for OS and 98.1, 97.2, 95.3, 90.7 and 89.7% for LRC, respectively. Only the 4-year OS and LRC rates were indifferent from those at 5 years (P=0.125 for OS and P=1.00 for LRC). In conclusion, the 1-year OS and LRC for stage I NPC patients treated with 2D RT or stage I/II NPC patients treated with IMRT, the 4-year OS and 2-year LRC for stage N3 NPC patients treated with 2D RT and the 4-year OS and LRC for stage III/IV NPC patients treated with IMRT were determined as the alternative endpoints to the 5-year OS and LRC for NPC patients.

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Key words: alternative endpoints, 5-year, locoregional control, nasopharyngeal carcinoma, overall survival

Introduction

Nasopharyngeal carcinoma (NPC) exhibits an extremely high incidence in Southern China and Southeast Asia, particularly among Cantonese individuals living in Guangdong province, with an incidence of up to 20 per 100,000 individuals (1-4). NPC is highly radiosensitive and radiotherapy (RT) is currently the mainstay of treatment. Previous studies reported that the 5-year survival rate was 66-83% with RT (5-7). For conventional 2-dimensional (2D) RT, the survival rates of stage T1-2/N0-1 NPC patients reached 75-90%; however, the survival rates of stage T3-4/N2-3 patients were decreased to 50-75% (8). With the development of the RT technique, including 3D conformal RT (CRT) and intensity-modulated RT (IMRT), a local control of >90% was achieved in stage I/II NPC patients (9-11). Furthermore, the improvement in the survival of NPC patients may also be attributed to the application of chemotherapy. Concurrent chemoradiotherapy was considered as the standard of care for patients with locally advanced NPC, with 3- and 5-year overall survival (OS) rates of ~87% and ~75%, respectively (12-15).

A long-term cure is the most important outcome for NPC. Over the last few decades, the aim to improve the long-term outcome translated into the use of OS as the primary endpoint for NPC prognostic studies and clinical trials (6-8). Improved local control has been achieved by IMRT treatment and resulted in the use of locoregional control (LRC) as the primary endpoint for NPC treated with IMRT (11,13). Historically, the 5-year survival rate has been the most commonly used measurement for the comparison of the prognosis and the assessment of the success of any particular treatment. The 5-year survival endpoint is simple to measure,

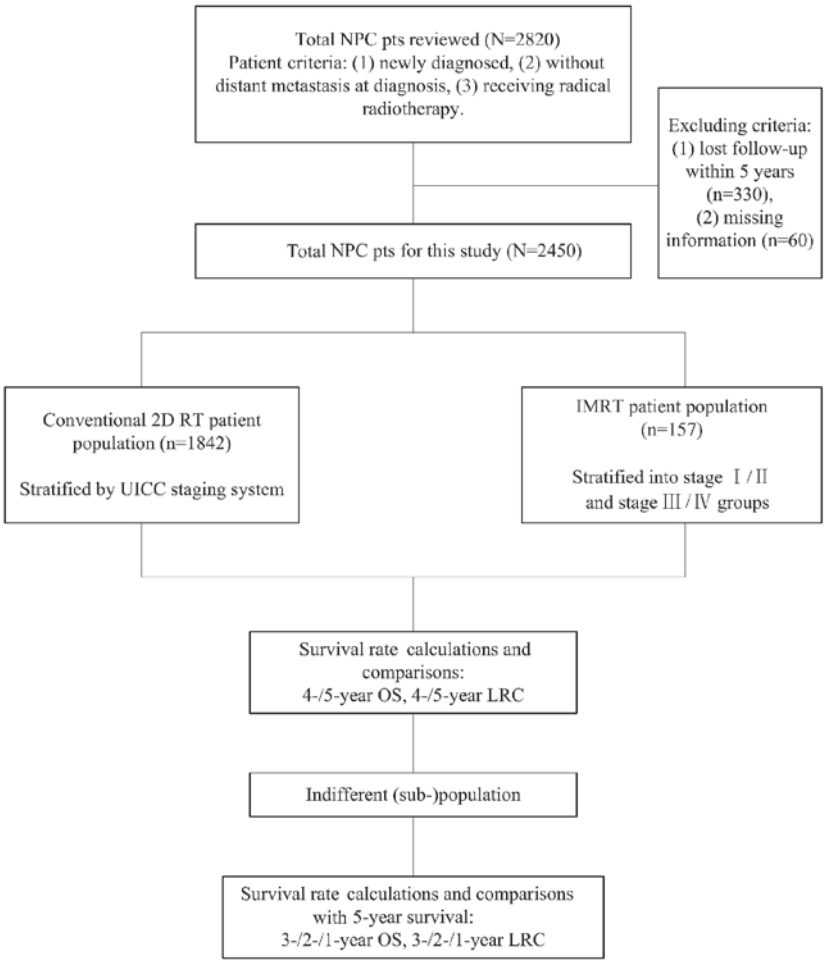

Figure 1. Flowchart of the study design. NPC, nasopharyngeal carcinoma; pts, patients; UICC, Union for International Cancer Control; 2D RT, 2-dimensional radiotherapy; IMRT, intensity-modulated RT; OS, overall survival; LRC, locoregional control.

easy to interpret, clinically meaningful and straightforward to explain; however, it requires extended follow-up. In order to overcome this disadvantage, an endpoint reached in <5 years is required. The new endpoint shares the advantages of the 5-year survival mentioned above, but may also provide answers to the questions posed by the study more rapidly. Therefore, the purpose of our study was to investigate OS and LRC at <5 years as a possible alternative to the 5-year survival endpoint for NPC.

Materials and methods

Patient population. We reviewed the medical records of 2,820 patients who were newly diagnosed with NPC which had been confirmed by biopsy without distant metastasis in the Sun Yat-Sen University Cancer Center (Guangzhou, China), in the period between November, 2000 and December, 2004. An ethical approval was provided by the Sun Yat-set University Cancer Center. The patients with missing information or who were lost to follow-up within 5 years were excluded (n=370). A total of 2,450 patients were finally included in our study. Taking into consideration that the RT technique may alter the survival outcome and affect the results of the study, we further analyzed patients who had received either conventional 2D RT (n=1,842) or IMRT (n=157).

A receiver operating characteristic curve was used to determine the optimal threshold difference value of age, with a cut-off value of 49.5 years (sensitivity, 54.5% and specificity, 65.6%) in this study. Tumor staging was performed according to the Union for International Cancer Control (UICC, 2002) staging system. All patients completed the prescribed radical RT treatment, course with or without chemotherapy.

Study design. The flowchart of our study design is presented in Fig. 1. We calculated and compared the survival rates of the three patient populations at 4 and 5 years. Tumor stage was found to significantly affect survival outcome; therefore, we repeated the analysis in patients stratified by the UICC staging system in the three populations. If a population or sub-population exhibited no significant difference between the 4- and 5-year survival, we further calculated the 3-, 2- and 1-year survival rates and compared these to the 5-year survival rate. The survival rate of the last indifferent comparison was considered as the alternative endpoint to the 5-year survival.

Treatment. RT alone was administered to stage I/II NPC patients and RT combined with chemotherapy was administered to stage III/IV NPC patients. RT was a conventional fractionation with a high-energy 6-8 MV X-ray from a linear accelerator. Facial-cervical field isocenter radiation with a low-melting point lead block was used; the irradiation

field included the skull base, nasopharynx and neck. The facial-cervical and lower cervical anterior tangent fields were used first, with the addition of the anterior nasal field in cases with invasion of the nasal cavity, to a dose of 36 Gy, followed by the bilateral preauricular fields plus the anterior tangent field, to a total dose of 60-78 Gy. Chemotherapy included induction, concomitant and adjuvant chemotherapy. The chemotherapeutic regimen was mainly cisplatin plus 5-fluorouracil for 1-3 cycles.

Follow-up. The patients were followed up by phone and/or in the outpatient clinic. The follow-up items included survival status, LRC failure and distant metastasis. All the events were confirmed by pathological examination and/or imaging. The last date of follow-up was February, 2011.

Endpoints and statistical analysis. Two endpoints were selected, OS and LRC. OS was defined as time from diagnosis to death from any cause. LRC was defined as time from diagnosis to the first occurrence of tumor growth at the primary site or regional lymph nodes.

The survival rates were calculated using a life table. Survival curves were drawn using the Kaplan-Meier method with the two-sided log-rank test. Survival rate comparisons were performed with the McNemar's test. All the tests were two-tailed and P<0.05 was considered to indicate a statistically significant difference. The statistical analyses were performed with Statistical Product and Service Solutions software, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographics. The baseline characteristics of the patients are summarized in Table I. The most common pathological type was non-keratinizing undifferentiated carcinoma, accounting for 86.7% of the cases.

Survival rate comparisons in the entire patient population. The 4- and 5-year OS and LRC rates are presented in Table II. The differences between the rates were found to be statistically significant (P<0.001).

We further stratified patients according to the UICC staging system. The corresponding survival rates are presented in Table II. Survival rate comparisons were performed for each stage (P-values shown in Table II). The OS and LRC curves by UICC clinical stage are presented in Fig. 2A and B. All the comparisons exhibited statistically significant differences, except between patients with UICC clinical stages I and N3. Further comparison of the 3-, 2- and 1-year survival rates to the 5-year survival rate for stages I and N3 (Table III) revealed that, for patients with UICC clinical stage I, the 3-year OS may be selected as an alternative endpoint to the 5-year OS (P=0.063) and for patients with UICC stage N3 the 3-year LRC may be selected as an alternative endpoint to the 5-year LRC (P=0.063).

Survival rate comparisons in patients treated with 2D RT. The 4- and 5-year OS and LRC rates are presented in Table II. The differences between the rates were found to be statistically significant (P<0.001).

Table I. Baseline characteristics of the entire patient population (n=2,450).

Characteristics	No.	Percentage
Age (years)		
≤49	1502	61.3
>50	948	38.7
Gender		
Female	585	23.9
Male	1865	76.1
UICC clinical stage		
I	127	5.2
II	864	35.3
III	986	40.2
IV	473	19.3
UICC T stage		
T1	396	16.2
T2	1032	42.1
T3	626	25.5
T4	396	16.2
UICC N stage		
N0	641	26.2
N1	981	40.0
N2	738	30.1
N3	90	3.7
Treatment		
RT	1095	44.7
Chemoradiotherapy	1355	55.3
RT modality		
Conventional 2D RT	1842	75.2
3D CRT	451	18.4
IMRT	157	6.4

UICC, Union for International Cancer Control; RT, radiotherapy; 2D, 2-dimensional; 3D CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated RT.

We further stratified patients according to the UICC staging system. The corresponding survival rates and P-values of the comparisons for each stage are presented in Table II. The OS and LRC curves by UICC clinical stage are presented in Fig. 2C and D. All comparisons exhibited statistically significant differences, except between patients with UICC clinical stages I and N3. Further comparison of the 3-, 2- and 1-year survival rates to the 5-year survival rate for stages I and N3 (Table III) revealed that, for patients with UICC stage I, the 1-year OS and LRC may be used as an alternative endpoint to the 5-year OS and LRC (P=0.125), whereas for patients with UICC stage N3, the 2-year LRC may be used instead of the 5-year LRC (P=0.125).

Survival rate comparisons in patients treated with IMRT. The 4- and 5-year OS and LRC rates are presented in Table II.The differences between the 4- and 5-year rates were not found to

Table II. Survival rates at 4 and 5 years and their comparisons.

	OS (%)		LRC (%)		P-value	
Stratification	4-year	5-year	4-year	5-year	4- vs. 5-year OS	4- vs. 5-year LRC
Total patients	78.8	74.6	83.3	80.5	<0.001	<0.001
UICC clinical stage						
I	95.0	93.0	97.6	93.7	0.063	0.063
II	83.0	79.0	87.3	84.1	<0.001	<0.001
III	76.0	72.0	82.2	79.8	<0.001	<0.001
IV	64.0	59.0	74.8	71.7	<0.001	<0.001
UICC T stage						
T1	86.0	83.0	89.4	86.9	<0.001	0.002
T2	78.0	74.0	84.1	81.0	<0.001	<0.001
T3	76.0	73.0	83.4	81.3	<0.001	<0.001
T4	66.0	60.0	75.3	71.5	<0.001	<0.001
UICC N stage						
N0	88.0	84.0	90.3	86.6	<0.001	<0.001
N1	76.0	72.0	83.1	80.4	<0.001	<0.001
N2	71.0	67.0	78.7	76.2	<0.001	<0.001
N3	55.0	55.0	74.4	73.3	0.500	1.000
2D RT patients	76.4	72.0	81.8	78.7	<0.001	<0.001
UICC clinical stage						
I	98.9	94.4	98.9	94.4	0.125	0.125
II	82.5	77.9	86.1	82.8	<0.001	<0.001
III	74.1	70.2	80.2	77.8	<0.001	<0.001
IV	63	57.7	71.8	68	<0.001	<0.001
UICC T stage						
T1	85	80.9	88.1	85	<0.001	0.004
T2	77.8	73.4	82.9	79.8	<0.001	<0.001
T3	75.7	72.3	81.7	79.6	<0.001	0.004
T4	65.1	59	72.5	68.1	<0.001	<0.001
UICC N stage						
N0	88.7	83.3	89.1	84.6	<0.001	<0.001
N1	75.2	70.9	81.1	78.3	<0.001	<0.001
N2	69.4	65.3	77.2	74.8	<0.001	<0.001
N3	55.2	53.5	72.9	71.2	1.000	1.000
IMRT patients	90.4	87.9	92.4	91.7	0.125	1.000
UICC clinical stage						
I	100	100	100	100	1.000	1.000
II	91.2	91.2	94.1	94.1	1.000	1.000
III	88.9	87.5	91.7	90.3	1.000	1.000
IV	88.6	80	88.6	88.6	0.250	1.000
UICC T stage						
T1	97.1	94.1	97.1	97.1	1.000	1.000
T2	90.2	90.2	92.7	92.7	1.000	1.000
T3	85.2	83.3	90.7	88.9	1.000	1.000
T4	92.9	85.7	89.3	89.3	0.500	1.000
UICC N stage						
N0	92.9	90.5	92.9	92.9	1.000	1.000
N1	90.7	90.7	96.3	96.3	1.000	1.000
N2	90.7	87	88.9	87	0.500	1.000
N3	71.4	57.1	85.7	85.7	1.000	1.000

OS, overall survival; LRC, locoregional control; UICC, Union for International Cancer Control; 2D RT, 2-dimensional radiotherapy; IMRT, intensity-modulated RT.

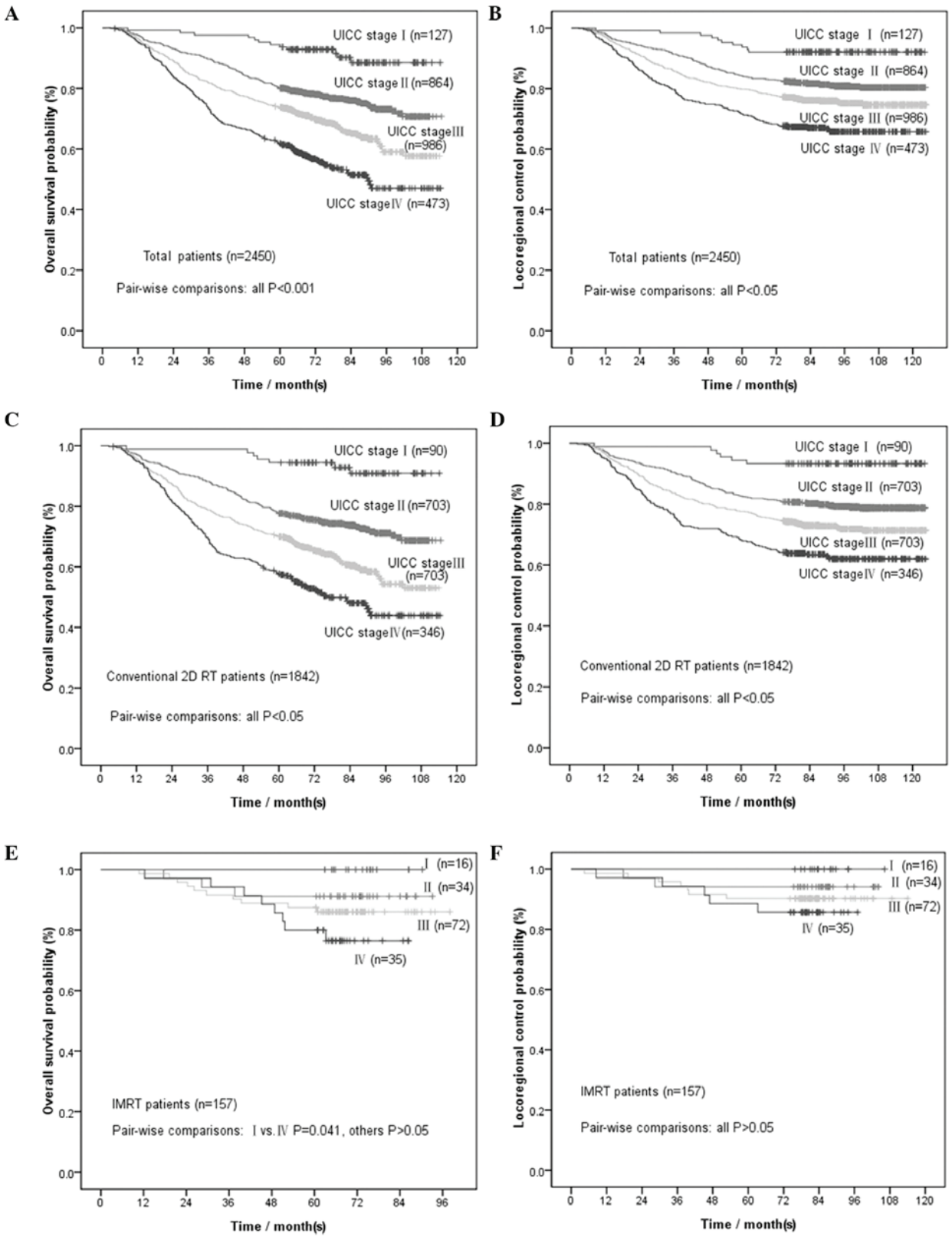

Figure 2. Survival curves stratified by the UICC clinical stages of three populations. OS and LRC curves of the (A and B) population; (C and D) 2D RT population; and the (E and F) IMRT population. Corresponding population size and P-values were presented. P<0.05 was considered to indicate a statistically significant difference. UICC, Union for International Cancer Control; OS, overall survival; LRC, loco-regional control; 2D RT, 2-dimensional radiotherapy; IMRT, intensity-modulated RT.

be statistically significant (P=0.125 for OS and P=1.000 for LRC, Table II), whereas there were statistically significant differences between the 3- and 5-year rates (P=0.004 for OS and P=0.031 for LRC). We further stratified patients according to the UICC staging system. The comparisons of the 4- and 5-year rates for each stage are presented in Table II. All

Table III. Survival rates at 1, 2 and 3 years and comparisons with 5-year survival rates.

	OS% (P-value)			LRC% (P-value)		
Stratification	1-year	2-year	3-year	1-year	2-year	3-year
Total patients						
UICC clinical stage I	99.2 (0.016)	99.2 (0.016)	97.6 (0.063)	99.2 (0.016)	99.2 (0.016)	98.4 (0.031)
UICC N3 stage	94.4 (<0.001)	75.3 (<0.001)	66.3 (0.002)	94.4 (<0.001)	82.2 (0.008)	78.9 (0.063)
2D RT patients						
UICC clinical stage I	98.9 (0.125)	98.9 (0.125)	98.9 (0.125)	98.9 (0.125)	98.9 (0.125)	98.9 (0.125)
UICC N3 stage	93.3 (<0.001)	69.5 (0.002)	62.8 (0.031)	93.3 (<0.001)	78.3 (0.125)	76.7 (0.250)
IMRT patients						
Stage I/II	100 (0.250)	98.0 (0.500)	96.0 (1.000)	100 (0.500)	98.0 (1.000)	96.0 (1.000)
Stage III/IV	99.1 (<0.001)	96.3 (<0.001)	92.5 (0.008)	98.1 (0.004)	97.2 (0.008)	95.3 (0.031)

OS, overall survival; LRC, locoregional control; UICC, Union for International Cancer Control; 2D RT, 2-dimensional radiotherapy; IMRT, intensity-modulated RT.

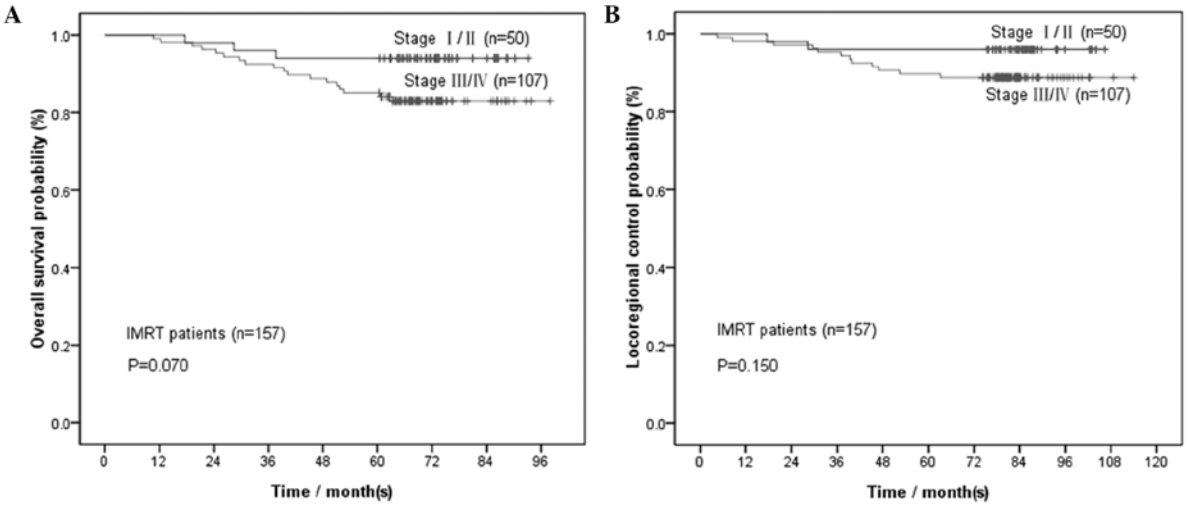

Figure 3. (A) Overall survival and (B) locoregional control curves stratified by stages I/II and III/IV. Corresponding population size and P-values are presented. P<0.05 was considered to indicate a statistically significant difference. IMRT, intensity-modulated radiotherapy.

comparisons were found to be of no statistical significance. The OS and LRC curves according to UICC clinical stage are presented in Fig. 2E and F.

Considering the limited sample size for each clinical stage in IMRT-treated patients (16 stage I, 34 stage II, 72 stage III and 35 stage IV patients), we divided the IMRT patients into stage I/II and III/IV groups for further analysis. For the 50 patients with stage I/II NPC, the 1-, 2-, 3-, 4- and 5-year OS rates were 100, 98, 96, 94 and 94%, whereas the LRC rates were 100, 98, 96, 96 and 96%, respectively. Comparisons were performed between the 4- and 5-year rates (P=1.00 for OS and P=1.00 for LRC); between the 3- and 5-year rates (P=1.00 for OS and P=1.00 for LRC); between the 2- and 5-year rates (P=0.50 for OS and P=1.00 for LRC); and between the 1- and 5-year rates (P=0.25 for OS and P=0.50 for LRC) (Table III).

For the 107 patients with stage III/IV NPC, the 1-, 2-, 3-, 4- and 5-year OS rates were 99.1, 96.3, 92.5, 88.8 and 85.0%, whereas the LRC rates were 98.1, 97.2, 95.3, 90.7 and 89.7%, respectively. Comparisons were performed between the 4- and 5-year rates (P=0.125 for OS and P=1.00 for LRC); between the 3- and 5-year rates (P=0.008 for OS and P=0.031 for LRC); between the 2- and 5-year rates (P<0.001 for OS and P=0.008 for LRC); and between the 1- and 5-year rates (P<0.001 for OS and P=0.004 for LRC) (Table III). Only the 4-year survival rates were not significantly different from the 5-year rates.

Discussion

The present study was conducted to investigate whether the OS or LRC at <5 years are possible alternative endpoints to the 5-year OS or LRC for NPC. The confirmation of such a finding may enable clinical trials to be completed more quickly with shorter alternative endpoints, meta-analyses may involve a larger number of trials and potential novel

therapeutic agents or treatment modalities may be made available to patients more rapidly. In the present study, we confirmed that OS and LRC at <5 years may indeed be considered as alternative endpoints to the 5-year OS and LRC for NPC.

Our results indicated that the 3-year OS and the 4-year LRC may be used as alternative endpoints for patients with UICC clinical stage I. In addition, the 4-year OS and the 3-year LRC may be used as alternative endpoints for patients with UICC stage N3, regardless of the treatment technique. For patients treated with 2D RT, the 1-year OS and LRC may be used as alternative endpoints for stage I NPC patients, whereas the 4-year OS and the 2-year LRC may be used as alternative endpoints for N3 stage patients. For patients treated with IMRT, the 1-year OS and LRC may be used as alternative endpoints for stage I/II patients, whereas the 4-year OS and LRC may be used as alternative endpoints for stage III/IV patients. Shorter endpoints were not established by our study.

For patients treated with 2D RT, only those with UICC clinical stages I and N3 exhibited alternative endpoints at <5 years, which is associated with the survival trend in each UICC stage. As shown in Fig. 2C and D, the survival curve for stage I was smooth prior to 5 years, whereas the other curves exhibited a downward trend until 7 or 8 years. Similarly, N3 stage also presented a smooth curve prior to 5 years. The same phenomenon was also observed for 1- to 5-year survival rates (Tables II and III). Therefore, we investigated the possibility of alternative endpoints for UICC stages I and N3.

Although alternative endpoints were identified for stages I and N3, they were the two extremes of survival. The alternative endpoint for stage I represented stable and good curative effects and that for stage N3 represented stable but poor curative effects. The two stages quickly reached a plateau. This finding was closely associated with the treatment technique. Previous studies reported that control of stage I NPC with conventional 2D RT is usually successful, but the response of locoregionally advanced NPC, such as stage N3 NPC, remains poor (5,7,16-19). In our study, conventional 2D RT alone was successful in increasing OS and LRC in >90% of stage I patients during the 5-year follow-up. Patients with stage I NPC had a significantly low risk of mortality and LRC failure. However, for stage N3 patients, the rates of OS and LRC were decreased from 90% in the 1st year to 60-70% in the 2nd year, indicating that the patients were at high risk, particularly short-term risk, of mortality, LRC failure and, potentially, distant metastasis. Although the alternative endpoint for stage I appears to be encouraging, as regards the OS and LRC for stage N3 cases, there is still room for improvement.

As regards patients treated with IMRT, we identified alternative endpoints for all the patients at <5 years, due to the improvement in survival. IMRT has the advantage of dose conformity, delivering high-radiation dose to the primary tumor, while sparing critical organ/tissues at risk, which results in enhancing the therapeutic ratio (20-24). A number of previous studies reported encouraging results with >90% LRC in patients treated with IMRT (9,25-29). In our study, patients treated with IMRT also exhibited higher OS and LRC rates compared to conventional 2D RT techniques (>85% for OS and >90% for LRC). As shown in Fig. 3A and B, the OS and LRC curves for stages I/II were almost smooth from 1 to 5 years, whereas those of stages III/IV started to become smooth from the 4th year onwards. The same trends were also indicated by the 1- to 5-year survival rates of patients treated with IMRT (Tables II and III).

The 1-year OS and LRC as alternative endpoints for stage I/II NPC patients treated with IMRT indicated that these patients suffered from few tumor-related events, such as mortality and locoregional control failure; thus, good and stable curative effects were achieved. However, no shorter endpoint, other than the 4-year OS and LRC, was confirmed for stage III/IV patients treated with IMRT, possibly due to the fact that stage III/IV NPC patients are more prone to develop distant metastases compared to those with stage I/II disease, due to either T3/T4 or N2/N3 involvement. Although excellent local control was achieved with IMRT, patients still exhibited distant failure (13,25-28).

The alternative endpoints of IMRT were superior to those of 2D RT, regarding universality and stabilization. In patients treated with IMRT, the alternative endpoints of 4-year OS and LRC were extended to all the patients and were even shortened to 1-year OS and LRC for stage I/II patients, which indicated that a significant improvement in OS and LRC was achieved by IMRT.

Over the last few years, an increasing number of studies have focused on IMRT in NPC, either for stages I/II or III/IV. However, a number of those studies only calculated OS and LRC within a 2- to 4-year follow-up period (9,11,12,25-28,30-32), giving rise to the question whether these OS and LRC rates were the same as the 5-year OS and LRC rates. The results of our study indicated that the rates were indeed comparable. Therefore, some of those studies may be included in meta-analyses of 5-year endpoints.

Our study had the following advantages and clinical significance: first, we reviewed a large patient sample (n=2,450) using different types of RT techniques, including conventional 2D RT, 3D CRT and IMRT; second, the follow-up of our study was ≥7 years; third, to the best of our knowledge, our study was the first to focus on investigating OS or LRC at <5 years as possible alternative endpoints to the 5-year endpoint for NPC; and finally, our study indicated that it may be feasible to use OS and LRC at <5 years as the primary endpoints in NPC clinical trials and shorten the trial period.

The main limitation of our study was its retrospective nature. The majority of the patients in our study were treated by 2D RT; thus, the results obtained from the entire patient cohort were biased and closer to the results of 2D RT. Furthermore, the number of patients treated with IMRT was limited and they were only divided into stage I/II and III/IV groups, rather than being stratified by the UICC staging system.

In conclusion, our study provided sound evidence supporting the use of OS and LRC endpoints at <5 years as an alternative to the 5-year endpoint for NPC; however, our results require further confirmation. Even shorter endpoints may be expected in the future with the improvements in NPC patient survival.

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