Abstract: Background. The purpose of this article is to report the overall survival (OS) outcome of patients with nasopharyngeal carcinoma (NPC) with local failure who received salvage treatment and to identify prognostic factors for OS.

Methods. Between January 1996 and December 2000, 2915 patients received primary radiotherapy (RT) with or without chemotherapy for nonmetastatic NPC. At a median follow-up of 3.1 years, 319 patients had developed local failure as the first failure, with or without synchronous regional/distant failure. OS was calculated from the start of primary RT. Univariate and multivariate analyses were performed to identify prognostic factors for OS in patients with isolated local failure.

Results. The T classification distribution of the local failure (rT classification) was as follows: 68 (21%) rT1 to T2a, 92 (29%) rT2b, 82 (26%) rT3, and 77 (24%) rT4. The rT classification was the same as the initial T classification in 82% of patients. Two hundred seventy-five patients (86%) had isolated local failure, and 232 (84%) of them did not have any distant metastasis or regional failure develop during follow-up. Salvage treatment was given to 200 patients (73%) with isolated local failure. One hundred fifty-nine patients (80%) received reirradiation (108 external beam RT [EBRT], 44 brachytherapy, and seven EBRT plus brachytherapy), 22 patients (11%) underwent nasopharyngectomy with or without postoperative RT, and 19 patients (9%) were treated with chemotherapy alone. Four patients died of RT complications, and one died of chemotherapy toxicity in the absence of active NPC. The 3-year actuarial OS for patients with isolated local failure was 74%. On multivariate analysis, advanced initial T classification (hazard ratio [HR], 1.44; \( p = .0006 \)) and the use of salvage treatment (HR, 0.54; \( p = .0038 \)) were independent prognostic factors. For the subgroups of patients who had the same recurrent and initial T classification, salvage treatment was associated with improved OS only in the subgroup with T1 to T2 local failure (\( n = 127 \); HR = 0.53, \( p = .0038 \)), but not in the subgroups with T3 (\( n = 48 \)) or T4 (\( n = 54 \)) disease.

Conclusions. Most patients with first local failure have localized disease. Salvage treatment is feasible in most of the patients who have isolated local failure.
Local failure occurs in 9% to 40% of patients with nasopharyngeal carcinoma (NPC) after primary radiotherapy (RT), with or without chemotherapy, in recent studies based on staging by CT or MRI. A second course of external beam RT (EBRT) is commonly used as salvage treatment. Most of the earlier reports on reirradiation for local failure in patients with NPC did not have the benefit of consistent use of CT or MRI for restaging. When local failure is restaged by CT and treated with EBRT, further 5-year survival rates of 7% to 36% are achieved. High-dose EBRT with or without brachytherapy (total dose ≥60 Gy) gives higher local control and survival rates compared with reirradiation to a lower dose. However, reirradiation for local failure is potentially hazardous because of the proximity of the tumor to critical neural structures and the high radiation dose received during primary RT. Severe late RT complications occur in 20% to 57% of patients who receive EBRT for local failure. Alternative RT techniques have been used as salvage treatment in an attempt to minimize treatment complications and improve tumor control. These include combined EBRT and brachytherapy, brachytherapy alone, stereotactic radiosurgery, and intensity-modulated RT (IMRT). Apart from reirradiation, nasopharyngectomy has been performed for salvage of local failure and patients with local failure too extensive for reirradiation or surgery are often given cisplatin-based chemotherapy.

In view of its potential hazard, it is important to determine whether salvage therapy prolongs survival in NPC patients with local failure. However, there have been only relatively small studies from single institutions on the survival outcome of patients with NPC with local failure in the CT/MRI era. In this retrospective study by the Hong Kong Nasopharyngeal Carcinoma Study Group (HKNPCSG), the data of all patients with NPC who received curative-intent primary RT between January 1996 and December 2000 in all five regional oncology centers under the Hospital Authority in Hong Kong were pooled and analyzed. The aims of the study were to present the outcome of patients with local failure, to describe the overall survival (OS) outcome with the use of salvage therapy, and to identify prognostic factors for OS.

**Keywords:** nasopharyngeal carcinoma; local failure; salvage treatment; survival outcome

**Patients and Methods**

**Patients.** Between January 1996 and December 2000, a total of 2915 patients with histologically confirmed nonmetastatic NPC were treated with curative-intent RT, with or without chemotherapy, in the five participant oncology centers of the HKNPCSG. All disease in patients was staged by physical examination, nasopharyngoscopy, chest radiograph, CT and/or MRI of the nasopharyngeal and cervical regions, and serum alkaline phosphatase level. CT of the thorax, ultrasonography of the abdomen, and bone scan were performed to rule out distant metastasis in patients with suspicious clinical features or biochemical abnormalities. The 1997 stage classification of the American Joint Committee on Cancer (AJCC)/Union Internationale Contre le Cancer (UICC) was used. Details of nodal involvement were routinely recorded in purpose-specific diagrams, allowing retrospective determination of nodal stage according to the 1997 AJCC/UICC stage classification if this was not applied initially.

**Primary Radiotherapy.** RT consisted of a basic course, followed by booster treatment in selected patients. In the basic course, RT was delivered with 6 MV photons, and two-dimensional (2D) planning with Ho’s technique or three-dimensional conformal RT (3DCRT) was used. Standard fractionation with 2 Gy per fraction at five daily fractions per week was used in 87% of patients. In 13% of patients, RT was accelerated using six daily fractions per week. The median dose to the primary tumor and upper cervical nodes was 66 Gy. Booster irradiation (10–20 Gy) to parapharyngeal tumor extension was delivered in 51% of patients. In 11% of patients, intracavitary brachytherapy or EBRT to the local site was given for adjuvant dose escalation or for treating persistent disease diagnosed within 16 weeks of the completion of the primary RT course. Neoadjuvant, concurrent, or adjuvant chemotherapy, mostly cisplatin-based, was given to 681 patients (23%) with advanced disease.
Treatment for Local Failure. Local failure was defined as the presence of local disease more than 24 weeks after completion of the primary RT. The definition allows for possible delayed histologic remission\textsuperscript{25} and completion of adjuvant chemotherapy. Diagnosis of local failure was made with histologic proof or by imaging evidence of an abnormal soft tissue mass associated with progressive skull base erosion or highly suspicious clinical features (eg, progressive cranial nerve palsy).\textsuperscript{1,10}

Disease in patients with local failure was restaged with the same investigations as for newly diagnosed patients with NPC. Salvage treatment was offered to patients with nondisseminated disease and satisfactory performance status (Karnofsky performance score \( \geq 70\)). The choice of salvage treatment modality was determined by tumor extent, previous radiation dosimetry, and institutional policy and expertise. For this study, salvage treatment was defined as treatment with curative intent or with the intent to prolong survival and included: (1) reirradiation by EBRT to a dose equivalent to \( \geq 60 \) Gy with standard fractionation\textsuperscript{1,7,9,10}; (2) EBRT to a dose equivalent to 40 to 60 Gy with standard fractionation plus fractionated brachytherapy boost of a total dose of 10 to 41.5 Gy\textsuperscript{7,9,10}; (3) brachytherapy alone to an equivalent dose of 50 to 60 Gy by gold grain implantation, intracavitary mold treatment, or fractionated intracavitary treatment\textsuperscript{7,9,10,12,13}; (4) nasopharyngectomy with or without postoperative RT\textsuperscript{1,16–19}, or (5) chemotherapy alone (mostly cisplatin-based combination regimens) for patients with extensive disease not suitable for nasopharyngectomy or further RT. Additional chemotherapy was used in selected patients together with radical RT or nasopharyngectomy. Synchronous regional failure was treated with radical neck dissection whenever feasible, with or without adjuvant RT; EBRT if surgery was not feasible; or chemotherapy if RT or surgery was not feasible.\textsuperscript{26} Patients who had extensive local failure or poor performance status and those who refused salvage treatment received supportive care only. Patients with synchronous distant metastasis were offered chemotherapy if their condition permitted.

Follow-Up After Salvage Treatment. Fiberoptic nasopharyngoscopy and biopsy of suspicious lesions were performed 6 weeks after the completion of salvage treatment. Patients were subsequently seen every 1 to 3 months in the first year, every 2 to 4 months in the second year, and every 3 to 6 months thereafter. The nasopharynx, neck, and cranial nerves were examined. CT and/or MRI of the nasopharyngeal and cervical regions were performed for suspected recurrence. Biopsy of the nasopharynx or cervical nodes was taken as indicated. Imaging screening for distant metastasis was performed if indicated by suspicious symptoms or signs. Late RT complications were recorded.

Outcomes and Statistical Methods. The primary endpoint of the study was the OS of patients with first local failure. OS was plotted by the Kaplan-Meier method and calculated from the start of primary RT to the date of death or censored at the date of last follow-up. Survival curves were compared by use of the log-rank test. Multivariate analysis using the stepwise Cox regression method was performed to determine independent significant prognostic factors for OS for patients with isolated local failure. The potential prognostic factors studied were patient age at primary diagnosis (<40 years or \( \geq 40 \) years), sex, histologic type (undifferentiated carcinoma [WHO type 3] vs others), UICC T classification and N status of initial disease, primary treatment factors (the use of neoadjuvant, concurrent, or adjuvant chemotherapy, accelerated fractionation RT, and RT boost after 66 Gy), UICC T classification of the local failure, and the use of salvage treatment. All statistical tests were two-sided, and a \( p \) value of <.05 was considered to indicate statistical significance.

The patterns of local failure were studied. Patients were deemed to have synchronous regional failure or distant metastasis if the regional failure or distant metastasis was diagnosed within 2 months of the local failure. This interval was the usual time required to complete the staging investigations. Patients with local failure preceded by regional failure or distant metastasis by more than 2 months were excluded from the analysis.

RESULTS

Patterns of Local Failure. Table 1 summarizes the patient and tumor characteristics at initial diagnosis for the 2915 patients included in the study. At a median follow-up of 3.1 years (range, <0.1–6.6 years), 319 patients (11\%) had local failure develop with or without synchronous regional failure or distant metastasis. The T-classification
distribution of the local failure was as follows: 68 (21%) rT1 to rT2a, 92 (29%) rT2b, 82 (26%) rT3, and 77 (24%) rT4. The recurrent T classification was the same as the initial T classification in 82% of patients (Table 2). Restaging investigations indicated that 275 patients (86%) had isolated local failure; they had a 3-year OS of 74%. On follow-up, 232 (84%) of these patients did not have any distant metastasis or regional failure.

### Table 2. Initial T classification and recurrent T classification in patients with local failure (n = 319).

<table>
<thead>
<tr>
<th>Initial T classification</th>
<th>No. patients by recurrent T classification</th>
<th>Total no. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rT1–rT2a</td>
<td>rT2b</td>
</tr>
<tr>
<td>T1–T2a</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>T2b</td>
<td>5</td>
<td>89</td>
</tr>
<tr>
<td>T3</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>T4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>92</td>
</tr>
</tbody>
</table>

Abbreviations: WHO, World Health Organization; UICC, Union Internationale Contre le Cancer.

### Table 3. Salvage and supportive treatment according to recurrent T classification in patients with clinically isolated local failure (n = 275).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. patients by recurrent T classification</th>
<th>Total no. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rT1–rT2a</td>
<td>rT2b</td>
</tr>
<tr>
<td>EBRT 60–66 Gy</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>EBRT 40–60 Gy + brachytherapy boost</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Nasopharyngectomy +/- postoperative radiotherapy</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>No salvage treatment</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>79</td>
</tr>
</tbody>
</table>

Abbreviation: EBRT, external beam radiotherapy.

#### Overall Survival Outcome of Patients with Isolated Local Failure: Effects of Salvage Treatment and Initial/Recurrent T Classification. Salvage treatment was given to 200 patients (73%) with isolated local failure. Details of salvage treatment according to the extent of local failure are listed in Table 3. One hundred fifty-nine patients (80%) received a second course of radical RT. Twenty-two patients (11%) underwent nasopharyngectomy with or without postoperative radiotherapy. Nineteen patients (9%) were treated with chemotherapy alone.

For the entire group of patients with isolated local failure, those who received salvage treatment had a significantly better OS than those who did not receive salvage treatment (p < .0001; Figure 1). Figure 2 shows the OS of patients with isolated local failure who received radical treatment and those who did not.
RT or nasopharyngectomy as salvage treatment. There was no significant difference in OS between these two groups. Patients treated with chemotherapy alone had significantly lower OS than those treated with either radical RT or nasopharyngectomy ($p < .0001$). The OS of patients with different initial T classifications and recurrent T classifications is shown in Figure 3A and Figure 3B, respectively.

**Prognostic Factors for Isolated Local Failure.** In patients with isolated local failure, the prognostic factors for OS on univariate analysis were advanced initial T classification (hazard ratio
[HR], 1.55; \( p < .0001 \)), the use of neoadjuvant chemotherapy in the primary treatment (HR, 1.91; \( p = .010 \)), advanced recurrent T classification (HR, 1.49; \( p < .0001 \)), and the use of salvage treatment (HR, 0.43; \( p < .0001 \)). On multivariate analysis, advanced initial T classification (HR, 1.44; \( p = .0006 \)) and the use of salvage treatment (HR, 0.54; \( p = .0038 \)) remained independent prognostic factors.

**Effect of Salvage Treatment on Overall Survival for Subgroups in Which Recurrent T Classification Was the Same as Initial T Classification.** For the subgroups of patients with isolated local failure in whom recurrent T classification was the same as initial T classification, salvage treatment was associated with improved OS only in the subgroup with T1 to T2 local failure (\( n = 127; p = .0446 \); Figure 4A). There was no significant difference in OS between patients treated with radical RT or nasopharyngectomy. In the subgroups with T3 (\( n = 48 \); Figure 4B) or T4 (\( n = 54 \); Figure 4C) disease, salvage treatment was not associated with improved OS.

**Disease Status at Last Follow-Up.** The disease status at last follow-up of the 275 patients with isolated local failure is summarized in Table 4. Eighty patients died of NPC. Another two patients were lost to follow-up and were considered to have died of disease. Four patients died of RT complications, and one patient died of chemotherapy toxicity in the absence of active NPC. Among the 200 patients with isolated local failure who received salvage therapy, 30 were diagnosed with further local failure. The median interval from first local failure to second local failure was 0.92 years (range, 0–3.9 years). Seventy-one patients survived without evidence of active NPC.

**DISCUSSION**

To our knowledge, this study is the largest contemporary series on local failure in patients with NPC who received primary RT based on CT or MRI staging. OS was chosen as the primary endpoint of this study because of its paramount clinical significance and the accuracy with which it could be determined in a retrospective study. Many local failures of NPC are deep seated, and approximately one third of recurrent tumors are not visible endoscopically.9 Frequent imaging and repeated biopsies of the nasopharynx during follow-up would be expected to facilitate early detection of local failure, but these approaches would not be feasible in practice. To avoid bias in the computation of OS because of delay in the diagnosis of local failure, OS was calculated from the start of primary RT. This is different from previous studies in which OS was measured from the date of diagnosis of local failure or start of the salvage treatment.8,11

In this series, although 50% of all local failures were advanced (rT3 and rT4), 73% of all patients with local failure (representing 84% of patients with clinically isolated local failure) did not have distant metastasis or regional failure on follow-up. Initial T classification was an independent prognostic factor for OS in our patients with isolated local failure. In a previous report, initial T classification was shown to affect local salvage rate, but there were no data on its impact on OS.7 Recurrent T classification was the same as initial T classification in 82% of our patients. Although recurrent T classification was a prognostic factor on univariate analysis, it did not remain a significant prognostic factor on multivariate analysis. Many previous studies emphasized the prognostic significance of recurrent T classification but did not include initial T classification in their multivariate analyses.1,9,10 The prognostic significance of initial T classification in both newly diagnosed NPC27 and local failure underscores the importance of efforts to develop more effective primary treatment for locally advanced NPC3,4,28,29 to prevent tumor recurrence and avoid complications of salvage treatment.

It was our policy to offer salvage treatment to patients with isolated local failure with the intent to prolong survival if it was technically feasible and if patients accepted its risks. Radical RT,
nasopharyngectomy, or chemotherapy was given to 80% of patients with isolated rT1 to rT3 local failure and to 50% of patients with isolated rT4 disease. Fewer patients with advanced recurrent T classification disease received salvage treatment because of the anticipated excessive risk of severe late complications of reirradiation caused by larger target volumes, unresectability, or sub-optimal performance status due to complications from the primary RT or the recurrent tumor. Because the use of salvage therapy was linked to an earlier stage of recurrent disease and better performance status, it is not surprising that it was associated with better OS in the univariate analysis. However, it is worth noting that it remained an independent prognostic factor on multivariate analysis. We did not have complete data on patient performance status at local failure. It should be noted that performance status at local failure had been factored into the decision process for recommending salvage treatment. The difference in outcome between patients who received salvage treatment and those who did not could partly be due to selection bias. Although this bias might be important in the subgroup of patients with rT3 to rT4 local failure, it was unlikely to be important in the subgroup of patients with rT1 to rT2 local failure because, in our experience, most of these patients had good performance status. Of interest, a previous study has shown that the use of salvage treatment is a significant prognostic factor for survival, even after adjusting for baseline performance status.

Decisions on salvage treatment for local failure are traditionally based on the recurrent T classification, but it is the initial T classification that carries independent prognostic significance. Thus, we analyzed subgroups of patients in whom recurrent T classification was the same as initial T classification. As noted previously, the analysis was applicable to 82% of patients overall. We found that salvage treatment was associated with improved OS only in the subgroup with T1 to T2 disease. There was no significant difference in OS between patients treated with radical RT and those treated with nasopharyngectomy. In the subgroups with T3 or T4 disease, salvage treatment was not associated with improved OS. The lack of survival benefit of salvage treatment, mainly reirradiation, in patients with advanced initial and recurrent local tumors may be due to failure to eradicate the extensive local failure, mortality associated with the complications of primary RT and reirradiation, or both. Our findings highlight the need for future studies to determine whether there is any survival benefit with salvage treatment in different stages of locally recurrent NPC. Improvements in treatment techniques are required to reduce treatment toxicity and to enhance tumor control and patient survival.

The optimal salvage treatment for local failure of NPC remains unclear. Currently, available options include reirradiation (2DEBRT, 1, 7–11 3DCRT/stereotactic radiosurgery, 14,31 IMRT, 15 and various brachytherapy techniques, 2,12,13), nasopharyngectomy, 16–20 and chemotherapy. 21,32,33 Advances in RT technology, in the form of stereotactic radiosurgery and IMRT, enable delivery of high radiation doses to the tumor with maximal sparing of adjacent critical normal structures. Stereotactic radiosurgery with or without 3DCRT has resulted in a 2- to 5-year further OS of 49% to 86% with few severe complications. 14,31 Early outcomes of IMRT for patients with recurrent NPC have been encouraging, with favorable dose distribution to the tumor and adjacent critical structures, a 100% loco-regional control rate, and acceptable acute toxicity. 15 However, long-term results in more patients are required to confirm any improvement in therapeutic ratio for stereotactic radiosurgery and IMRT. In early recurrent disease, nasopharyngectomy with or without postoperative RT results in further 5-year OS rates of 40% to 70%. 16,20 Surgical resection has the additional advantage of removing radioresistant disease.

The efficacy of chemotherapy for local failure has not been fully evaluated, 9,21,33 and the apparent disappointing results in some reports may be biased because of selection of patients with extensive disease for chemotherapy. In one series, combination chemotherapy with cisplatin and 5-fluorouracil gave similar OS, although worse progression-free survival in locoregionally recurrent NPC compared with concurrent chemoradiotherapy. 33 At present, chemotherapy should be reserved for patients not suitable for radical RT or nasopharyngectomy. Serum Epstein-Barr virus DNA, a tumor marker with high sensitivity for detection of distant metastasis in NPC, may be useful in selecting patients for salvage chemotherapy. 34 New chemotherapy regimens should be evaluated in prospective studies. Concurrent chemoradiotherapy has yielded promising survival results and warrants further investigation. 33 Treatment toxicity is a crucial consideration in the decision on salvage treatment for local failure of NPC. In this study, treatment-related death
was taken as the most important indicator of treatment toxicity. Consistent with previous single-institutional reports, the mortality rate because of salvage treatment was 2% in the current multicenter study. 7,10,16,20 The typical complications of various treatment modalities have been addressed in previous publications. 1,7–13,16,21,30,33

The most commonly reported salvage treatment for local failure has been reirradiation by conventional technique with or without brachytherapy. It carries a 48% to 73% 5-year actuarial rate of symptomatic late complications and has a treatment mortality rate of 2% to 4%. 7,10 Symptomatic temporal lobe necrosis occurs in approximately 12% of patients and is the most morbidity complication, with a mortality rate of 65%. 1,7,9 The risk of late complication after reirradiation is predominantly affected by the dose of the first course of RT.

In conclusion, this study has shown that most patients with first local failure have localized disease. Salvage treatment is feasible in most of the patients with clinically isolated local failure. Patients who had early initial T classification have a more favorable prognosis. Subgroup analysis suggests that current salvage therapy only prolongs survival in patients with T1 to T2 recurrent disease. Salvage treatment needs to be optimized to improve therapeutic ratio, and its survival, morbidity, and quality of life outcomes should be addressed in future studies.

Acknowledgment. We thank Frankie Mo for data management and statistical analysis and Drs. W. H. Lau, Peter Choi, Peter Teo, and W. H. Kwan, and other members of the Hong Kong Nasopharyngeal Carcinoma Study Group for their contribution in data collection and treatment of the patients.

REFERENCES


