STEREOTACTIC RADIOSURGERY PLUS INTRACAVITARY IRRADIATION IN THE SALVAGE OF NASOPHARYNGEAL CARCINOMA

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Abstract: *Background.* We sought to assess the efficacy and complications of linear accelerator-based stereotactic radiosurgery (SRS) plus intracavitary irradiation (ICI) as salvage treatment for local persistent and recurrent nasopharyngeal carcinoma (NPC) after primary external beam radiotherapy (EBRT).

Methods. Between July 1995 and June 2003, 36 patients (25 men and 11 women; median age, 48 years; range, 22–66 years) with local recurrent NPC confined to the nasopharynx (rT1) or limited extension to the parapharynx and nasal cavity (rT2) were treated with SRS plus ICI. Nineteen patients had rT1 and 17 had rT2 disease. Five patients (13.8%) had persistent disease, and 31 patients (86.1%) had recurrent disease using the definition of >4 months after the primary treatment as recurrent relapse. The median target volume was 36.3 cm^3 (range, 10.3–56.2 cm^3) for the SRS treatment. All patients received 18 Gy to the 90% isodose line followed by two separate ICI 6 Gy each to 0.5 cm from the surface of the endotracheal balloon. Patients were assessed with serial nasoendoscopy and repeat scans (CT or MRI) at 3 months, and suspicious lesions were rebiopsied.

Results. The median follow-up for surviving patients was 4.24 years (range, 0.73–8.81 years). Twenty-two of 36 (61%) patients were alive at the time of reporting. Twenty patients were free of disease, and two patients were alive with disease. Fourteen of 36 (39%) patients had died (five of distant metastases, six of local recurrences, two of both local disease and distant metastases, and one of unrelated cause). Patients with rT1 disease (median survival not reached) fared better that patients with rT2 disease (median survival, 4.6 years). The actuarial 5-year disease-free survival and overall survival (OS) were 57% (rT1 78%, rT2 39%) and 62% (rT1 80%, rT2 48%), respectively. The actuarial 5-year local control was 65% (rT1 82%, rT2 49%). The treatment was well tolerated with no significant acute complications. Sixteen patients (44%) had late complications, including palatal fibrosis in six patients (17%), trismus in seven patients (20%), cranial nerve palsies in seven patients (20%), temporal lobe necrosis in two patients (8%), and osteoradionecrosis of the skull base in six patients (17%). The complication-free survival rates at 2 and 5 years were 70% (95% confidence interval [CI], 56% to 87%) and 31% (95% CI, 17% to 56%), respectively. No patient died as a direct result of the late complication.

Conclusion. Although our series is small, the combination of SRS and ICI seems to be an effective salvage treatment for early-stage recurrent NPC. The OS of 62% at 5 years is very encouraging and favorable compared with reported reirradiation or surgical series. The late complications are considerable but expected because of the high doses of radiation previously delivered. The ideal dose fractionation for SRS and ICI is unknown and remains to be defined. *Head Neck* **28:** 321–329, 2006

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Nasopharyngeal carcinoma (NPC) is the most common head and neck malignancy in Singapore.[1] The disease is endemic in Southeast Asia, southern China, and the Mediterranean basin. It is most prevalent in the Chinese, especially those of Cantonese ethnic origin. The endemic form of NPC is often very radiosensitive, with an overall cure rate of 80% to 90% for stage I–II and 30% to 60% for stage III–IV disease with radiotherapy (RT) alone.[2] Concurrent chemoradiotherapy for stage III/IV NPC has been shown to be superior to RT alone in the Intergroup 0099 randomized trial,[3] with an improvement in overall survival (OS) of 30% at 3 years. The survival benefit of concurrent chemoradiotherapy has also recently been validated in the endemic population in three randomized trials.[4–6] However, despite more aggressive treatment with combination chemoradiotherapy, patients continue to experience treatment failure at the local site.

Because of the deep-seated location of the nasopharynx, its proximity to various vital organs, and the high radiation doses given for the primary therapy, retreatment is often very difficult, with many side effects. The choice of treatment for recurrent disease includes reirradiation or nasopharyngectomy. The best salvage therapy remains elusive, and there are proponents of either surgery or reirradiation.

Various techniques of reirradiation have been reported in the literature. High-dose-rate brachytherapy or intracavitary irradiation (ICI) is a well-established RT salvage treatment for recurrent NPC.[7,8] Stereotactic radiosurgery (SRS) is an emerging technique with encouraging early reports in the literature.[9–11] These two modalities can be used alone or in combination with external beam radiotherapy (EBRT), especially in more advanced local recurrences. However, the combination of SRS plus ICI has never been reported as a salvage approach for recurrent NPC. ICI is highly operator dependent. Moreover, larger and deeper lesions are not adequately treated because of the rapid fall-off of the doses with increasing distance in accordance to the inverse square law. SRS is less operator dependent, and the target lesions can be covered with a smaller irradiated volume compared with conventional EBRT. In our experience, significant shrinkage of tumor often takes place 1 week after the 18-Gy single fraction of radiosurgery. Scheduling the first ICI 1 week after the SRS and the second ICI the following week may enhance the optimal effect of the brachytherapy treatment. Recurrent NPC may be different radiobiologically from its original tumor. Patients with these tumors have previously been treated with high-dose fractionated radiotherapy and experienced treatment failure. Although geographic miss may be a reason for some of the local failures, another possibility is the existence of radioresistant cancer cells. The single large dose of SRS may trigger endothelial microvasculature apoptosis, with consequent increase tumor cell kill overcoming this inherent radioresistance.[12,13] We postulate that, by combining SRS with ICI, we might improve the survival and lower the toxicity rate. We have used this approach since 1994 to treat patients with recurrent NPC localized to the nasopharynx (rT1) or minimal extension outside the nasopharynx (rT2). We started treatment using a fixed head-frame technique. The immobilization was subsequently changed to a relocatable modified Gill-Thomas-Cosman (GTC) head frame.[14] This study reports our experience and results.

MATERIALS AND METHODS

From July 1995 to June 2003, 36 patients (25 men and 11 women; median age, 48 years; range, 22–66 years) with local recurrent or persistent NPC confined to the nasopharynx (rT1) or with limited extension to the parapharynx and nasal cavity (rT2) were treated with SRS plus two insertions of ICI. All patients had World Health Organization (WHO) type-3 NPC previously treated with radical EBRT. Four months after the completion of the primary EBRT was taken as the cutoff point to differentiate between persistent or recurrent disease (V4 months, persistent; >4 months, recurrent). Using this definition, five (13.9%) patients had persistent disease, and 31 (86.1%) had local recurrent relapse. All patients had histologically proven disease before the SRS and ICI treatment with negative staging investigations, including at least a chest x-ray, liver ultrasound, and bone scan.

Radiosurgery Technique. SRS was planned using the commercial X-knife system (Radionics, Burlington, MA) and delivered with a modified 6-MV linear accelerator (Siemens KD2 Radionics, Burlington, MA). When we started SRS treatment in 1994, immobilization was initially performed using a Brown-Roberts-Wells (BRW) frame. To cover the nasopharynx adequately, the BRW frame was fixed to the antrum, and thus the ring was low enough to include the nasopharynx down to the level of the C2/C3 junction. However, the

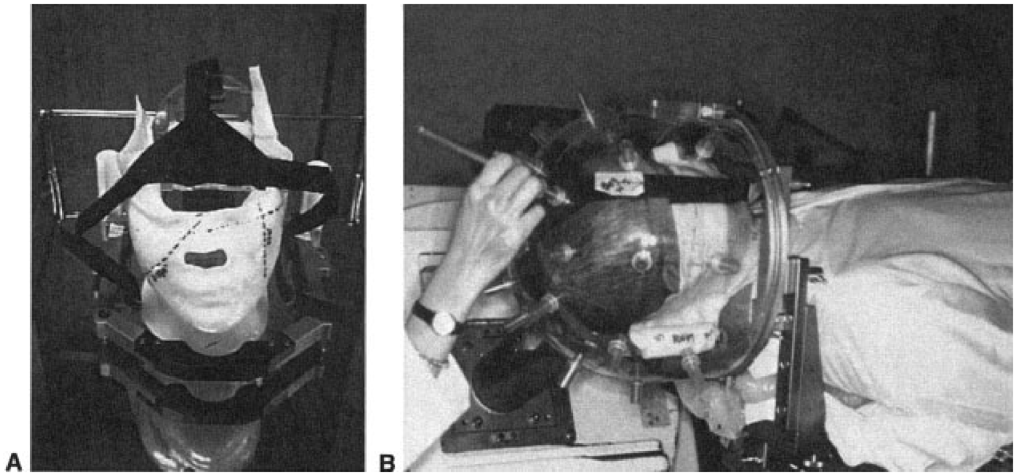

FIGURE 1. **(A)** Modified Gill-Thomas-Cosman head frame with thermoplastic immobilization mask; **(B)** stereotactic radiosurgery setup verification.

issue of sideway movements at the atlanto-occipital and atlanto-axial joints was not addressed. Subsequently, this was changed to a GTC relocatable head frame with dental trays, which was less invasive than the fixed head-frame immobilization. However, many of the patients with NPC had no teeth because of teeth extraction before the primary treatment or the loss of saliva resulting in dental caries and loss of teeth. For this group of patients with dentition problems, the reproducibility accuracy within 1 mm as required for SRS treatment could not be maintained with the GTC frame and dental tray. Moreover, patients with recurrent NPC with lesions as low as C2 or C3 level could not be treated because of the fixed position of the dental tray and the constraint of couch mount adapter limiting patient positioning in the gantry direction. On the basis of our experience with the use of the thermotransformable mask for our patients with NPC on conventional RT, an immobilization mask was developed to replace the dental bite for the relocatable GTC head frame. The original occipital plate that served as the headrest was also modified to provide anchorage of the mask. Figure 1A shows a diagram of the modified GTC head frame with the immobilization thermoplastic mask, and Figure 1B shows the SRS setup verification. An analysis of our patients treated using this modified immobilization head frame showed a reproducibility accuracy of 0.6 ± 0.3 mm^3. Repeat quality assurance CT scan showed no change in the treatment position and confirmed the reproducibility accuracy.[14] All patients in this series were treated using this immobilization technique.

The target volumes were localized with 3-mm CT slices. MRI of similar cuts was performed and CT-MRI fusion done for all patients. The normal anatomes and the target volume were drawn on the fusion images, which included the visible tumor and the surrounding mucosa and soft tissue. The entire nasopharynx was normally included in the target volume. The median target volume was 36.6 mm^3 (range, 10.3–56.2 mm^3). The treatment was delivered using three to four non-coplanar arcs of photon beams with the smallest collimator that covered the target volume; the median collimator size was 4.5 cm (range, 3–4.75 cm). A total of 18 Gy in a single fraction was delivered to the 90% isodose line.

Intracavitary Irradiation. This treatment used two pediatric cuffed size No. 5 endotracheal tubes with an outer diameter of 6.6 to 6.8 mm and inner diameter of 5.0 mm. The endotracheal tube was inserted into the nasopharynx and the endotracheal tube balloon inflated with 5 mL of radiographic contrast. Orthogonal films were taken in the simulator for treatment planning. A total of 12 Gy in two fractions 1 week apart was delivered using a Gammamed 12i high-dose-rate brachytherapy machine (Isotopen-Technik, Dr. Sauerwein, GMBH). The dose was prescribed to 0.5 cm deep from the surface of the endotracheal tube balloon 1 week after the completion of SRS treatment.

Follow-up Assessment and Statistical Analysis. All patients were followed up at regular intervals after therapy by the radiation oncologists and ear,

Table 1. Patient characteristics.

	Median or no. of patients (%)
Demographic data	
Age	48 years
Sex	
Male	25 (69.4)
Female	11 (30.1)
Ethnicity	
Chinese	35 (97.2)
Malay	1 (2.8)
Previous treatment	
EBRT 60 Gy	2 (5.6)
EBRT 62 Gy	1 (2.8)
EBRT 70 Gy	9 (25.0)
EBRT 62 Gy + ICI 10 Gy	18 (50.0)
EBRT 70 Gy + Chemotherapy	1 (2.8)
EBRT 66 Gy + ICI 10 Gy, ICI 5 Gy × 8	1 (2.8)
Not available	4 (11.0)
Late complication	
Palatal fibrosis	6 (16.7)
Trismus < 2 cm	7 (19.4)
Cranial nerve palsies	7 (19.4)
Temporal lobe necrosis	2 (5.6)
Osteoradionecrosis of the skull base	6 (16.7)
Follow-up of the patients who are alive	
Time to last follow-up	4.24 y (0.73–8.81)

Abbreviations: EBRT, external beam radiation therapy; ICI, intracavitary irradiation.

nose, and throat surgeons. Nasoendoscopy was performed at each visit, and an imaging study, either CT or MRI, of the posterior nasal space (PNS) was performed at 3 months, 6 months, and yearly thereafter. A biopsy was taken for any suspicious lesion on nasoendoscopy or imaging studies.

The proportions of OS, local control, and disease-free survival were calculated using the Kaplan–Meier method.[15] The corresponding proportions at 2 and 5 years were reported. Overall survival was defined as time from the start of the radiosurgery to the death or last follow-up for living patients. Local control survival was defined as time from the start of the radiosurgery to the recurrence after the radiosurgery treatment, death, or last follow-up for patients with no recurrence. The disease-free interval was defined as the start of the radiosurgery to the metastasis or local recurrence after the radiosurgery treatment or death or last follow-up.

In this study, the late complication–free survival was defined as the estimate of a patient's likelihood of both being alive and being free of complications calculated by the Kaplan–Meier method. Three patients were not included in this analysis, because they had complications before the start of the radiosurgery. The time to develop the complication was defined as the interval from the start of the radiosurgery to the onset of complication, death, or last follow-up for patients who did not have complications develop during follow-up. The log-rank test was used to test the survival curves between different groups defined by T classification and disease status.

RESULTS

A total of 36 patients were included in this study (Table 1). Thirty-five were Chinese, and one was Malay. There are 25 men and 11 women. The median age in these series was 48 years (range, 22–66 years).

Table 2 summarizes the results of survival analysis in terms of OS, local control, disease-free and late complication using Kaplan–Meier method. In this cohort, 14 patients (40%) had died, five of distant metastases, six of local recurrences, two of both local disease and distant metastases, and one of pulmonary embolism unrelated to the primary disease. The median follow-up for surviving patients was 4.24 years (range, 0.73–8.81 years). Twenty-two of 36 patients (61%) were alive at the time of reporting. Twenty patients were free of disease, and two patients were alive with disease. The actuarial 2-year OS was 86% (rT1 89%, rT2 82%), and the 5-year OS was 62% (rT1 80%, rT2 48%) (Figure 2). The actuarial local control rate was 85% at 2 years (rT1 88%, rT2 80%) and 65% at 5 years (rT1 82%, rT2 49%) (Figure 3). No statistically significant difference between rT1 and rT2 was observed in terms of overall survival ($p = .141$), local control ($p = .162$), and disease-free survival ($p = .147$). The proportions of survival at 2 years and 5 years for patients with rT1 were higher than those for patients with rT2, although the difference was not statistically significant. In patients with rT1, the median survival for OS, local control and disease-free survival were not reached during this study period, and 78% of these subjects remained disease free after 5 years' follow-up.

Kaplan–Meier analysis according to status of relapse showed a better outcome for persistent disease compared with recurrent relapse (Table 2). The 5-year OS was 100% and 53% for persistent and recurrent disease, respectively (Figure 4). Among five patients with persistent disease, one died of pulmonary embolism without any evidence

Table 2. Summaries of survival analysis using the Kaplan–Meier method.

Characteristic	Events	Censored	Proportion, 2 y	Proportion, 5 y	Median, y	*p* value
Overall survival	14	22	86	62	6.50	
T classification						
rT1	4	15	89	80	—	.141
rT2	10	7	82	48	4.60	
Disease						
Persistent	1	4	100	100	8.26	.072
Recurrent	13	18	83	53	5.51	
Local control	10	26	85	65	—	
T classification						
rT1	3	16	88	82	—	.162
rT2	7	10	80	49	4.18	
Disease						
Persistent	0	5	100	100	—	.099
Recurrent	10	21	82	57	—	
Disease-free survival	15	21	77	57	—	
T classification						
rT1	5	14	84	78	—	.147
rT2	10	7	71	39	3.59	
Disease						
Persistent	0	5	100	100	—	.039
Recurrent	15	16	74	48	4.18	

of disease recurrence. The disease-free survival of these five patients differs significantly from that of patients with recurrence ($p = .039$).

The treatment was well tolerated with no significant acute complications. However, 16 patients (44%) had late toxicity, including palatal fibrosis in six patients (17%), trismus <2 cm in seven patients (20%), cranial nerve palsies in seven patients (20%), temporal lobe necrosis in two patients (8%), and osteoradionecrosis of the skull base in six patients (17%). A total of 33 patients were included in late complication–free survival analysis. Twenty of these 33 patients were alive at the time of reporting, and 11 of 20 (55%) were free of any late complications. The complication-free survival rates at 2 years and 5 years were 70% (95% confidence interval [CI], 56% to 87%) and 31% (95% CI, 17% to 56%), respectively (Figure 5). No patient died as a direct result of the late complication.

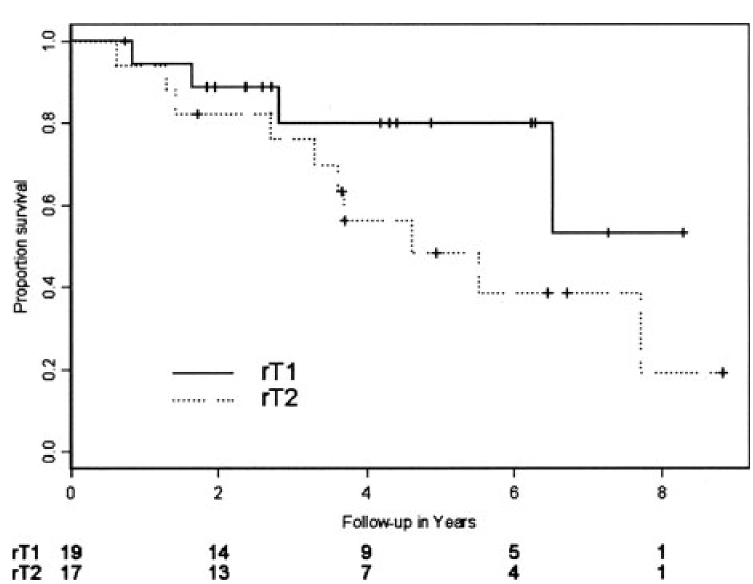

FIGURE 2. Overall survival by T classification.

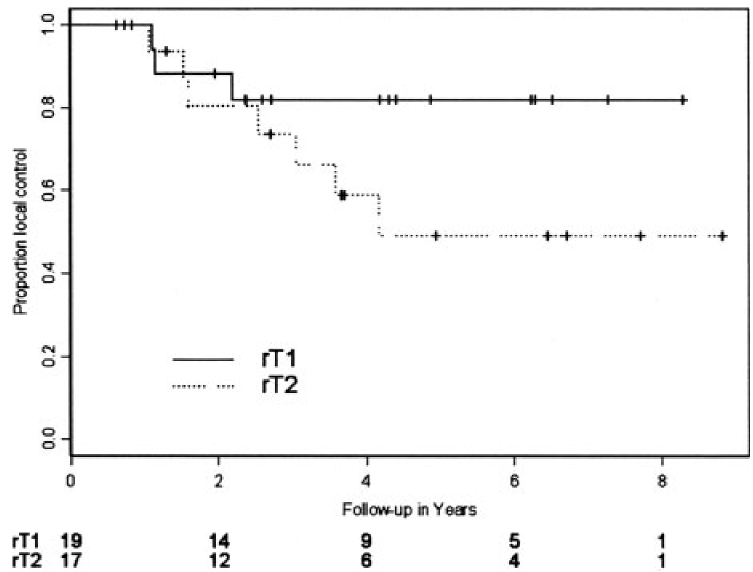

FIGURE 3. Local control by T classification.

DISCUSSION

NPC is the most common head and neck malignancy in Singapore.[1] RT is the mainstay of treatment. The outcome of the management of NPC has improved over the years, with advancement in RT planning technology and discovery of newer chemotherapy with better tumor response rate and radiosensitizing properties. However, despite the recent advancement, local failure remains a significant cause of morbidity and mortality in NPC. The best approach for the treatment of local relapse is unknown. Both nasopharyngectomy and reirradiation have their merits and advocates.

Reirradiation using EBRT requires high doses (>60 Gy)[16,17] to be effective, and, hence, the risk of late complications to the surrounding normal tissues is very high. Anne Lee et al[16] reported a series of 706 patients with local recurrent NPC reirradiated with EBRT with/without brachytherapy. Two hundred eighty of 706 patients had rT1 disease and 145 of 706 patients had rT2 disease. The 5-year OS was 27% and 17% for rT1 and rT2, respectively. The cumulative late toxicity was 24% in this study, with a treatment mortality of 1.8%. Teo et al[18] reported a series of 123 patients treated with reirradiation to $\geq$60 Gy (n = 103) and

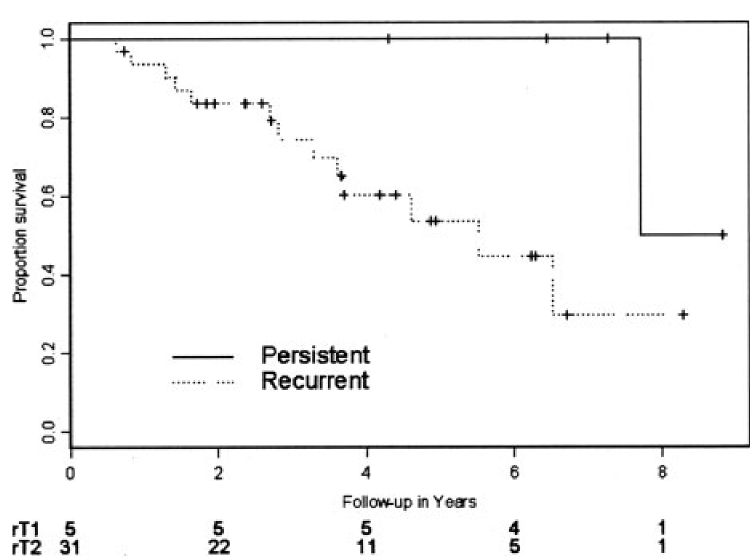

FIGURE 4. Overall survival by disease status.

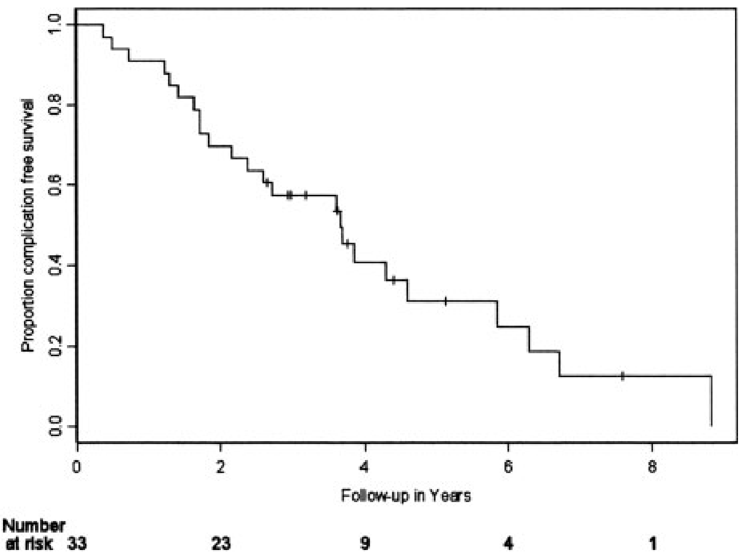

FIGURE 5. Late complication–free survival.

nasopharyngectomy (n = 20). Forty-five of 103 patients treated with RT had rT1 or rT2 disease; 15 of 20 patients treated with surgery had rT1 or rT2 disease. The 5-year OS was 26% for rT1 and 8% for rT2 in patients treated with reirradiation. This study reported temporal lobe necrosis in 24%, trismus in 70%, and hearing loss in 56% of all patients. The study showed that patients treated with nasopharyngectomy had a better outcome than those who received RT ($p = .015$). However, 70% of those treated with surgery received postoperative RT because of uncertain or positive margins. As argued by Lee,[19] the 70% of patients who received postoperative RT may be considered to have surgical failures, and the improvement in survival may not be due to surgery but to reirradiation or to both modalities. In the series reported by Chua et al,[20] there was no difference in survival between surgically treated patients compared with those treated with RT, despite a favorable selection of patients for surgery. In this study, a total of 140 patients with recurrent NPC (30% had rT1 or rT2) were treated with reirradiation (n = 94) or nasopharyngectomy (n = 12). The 5-year OS was 57% for patients with rT1 or rT2 disease treated with reirradiation. Thirty-four percent of patients had late neurologic complications, and 30% had trismus. The outcome was very encouraging, but, unfortunately, the authors did not differentiate between persistent or recurrent disease. It is well documented that patients with persistent tumors have a better outcome than those with true recurrences.[8,9,21] Kwong et al[21] reported a 5-year OS of 71.9% and 53.6% in persistent and first recurrent disease, respectively, using gold-grain implants. The reported late complications in this series include headache in 28.3%, palatal fistula in 18.9%, mucosal necrosis in 16%, and neurologic complications in 11.7%. However, gold-grain implants are only suitable for very early lesions and require a surgical dissection (most commonly a transpalatal approach). The treatment is also technically demanding and is only available in highly specialized centers.

Nasopharyngectomy has been shown to be an effective salvage therapy for recurrent NPC. King et al[22] reported a series of 31 patients (29 had rT1 or rT2 tumors) treated with nasopharyngectomy with/without postoperative RT. The 5-year OS was reported as 47%. More than 70% of patients received postoperative RT, and the study showed a significant improvement in survival for those who received postoperative RT compared with those who did not ($p = .024$). The reported complications included palatal defect in 54.8%, trismus in 48.4%, otitis media in 64.5%, dysphagia in 38.7%, and nasal regurgitation in 25.8% of patients. Fee et al[23] reported a series of 37 patients treated with nasopharyngectomy with/without postoperative RT. Twenty-seven patients had rT1 or rT2 tumors, and the reported actuarial 5-year OS was 73% for rT1 and 40% for rT2 disease. This is the best outcome of a surgical series reported to date in the literature. In this report, 20 patients (54%) had surgical complications, including one death from an intraoperative carotid artery injury and a pharyngeal plexus paral-

	No. of patients	No. of T1 and T2	Overall survival at 5 y, %	Median follow-up, y	Proportion complications, %
RT series					
Wang[17]	51	32	38	—	—
Pryzant et al.[24]	53	27 (confined to NP) 26 (outside NP)	32 (confined to NP)	5	17 (overall)
Lee et al[16]	706	425	27 (T1), 17 (T2)	—	24 (overall), 17 (trismus), 2.6 (TLN), 2.7 (CN palsy)
Teo et al[18]	166	45	26 (T1), 8 (T2)	1.7	20.4 (TLN), 69.9 (trismus), 56.3 (hearing loss)
Chua et al[20]	140	33	57	1.5	30 (trismus), 34 (neurologic)
Kwong et al.[21]	106	45 (persistent) 53 (1st recurrence) 8 (2nd recurrence)	79.1 53.6 42.9	3.6	28.3 (headache), 18.9 (palatal fistula) 16 (mucosal necrosis), 11.7 (neurologic)
Surgical series					
King et al[22]	31	29	47	2.4	54.8 (palatal defect), 48.4 (trismus), 64.5 (otitis media), 38.7 (dysphagia), 25.8 (nasal regurgitation)
Fee et al[23]	37	29	73 (T1), 40 (T2)	5.2	54 (5% major)
Wei et al[25]	18	16	36*	1.3	12.5 (internal carotid artery bleeding)

Table 3. Outcome of selected surgical and reirradiation series.

Abbreviations: RT, radiation therapy; NP, nasopharynx; TLN, temporal lobe necrosis; CN, cranial nerve.
**Proportion survival at 3.5 years.*

ysis resulting in permanent dysphagia. Unlike the series by King et al,[22] postoperative RT did not improve the outcome in this report. Surgery may negate the late complications of RT but has its own set of toxicities (palatal defects, trismus, otitis media with effusion, dysphagia from pharyngeal plexus injury, nasal regurgitation). It is often difficult to operate on a previously heavily irradiated site, and the healing and postoperative recovery could be severely compromised in this group of patients. Moreover, the surgery is technically challenging, and many centers do not have sufficient experience. If postoperative RT is required for positive or uncertain margins, the toxicity may be compounded and aggravated.

Our series showed a 5-year OS of 62% (rT1 80%, rT2 48%). These results are favorable compared with to the best surgical or reirradiation series (Table 3). Our results are consistent with the acknowledged fact that persistent disease has a better outcome than recurrent tumors.[8,9,21] The 5-year OS was 100% for patients with persistent disease and 53% for those with recurrent tumors; 86.1% of our series consisted of patients with locally recurrent disease. The treatment was well tolerated with no significant acute complications. Sixteen patients (44%) had late toxicity develop. The complication-free survival rates at 2 and 5 years were 70% (95% CI, 56% to 87%) and 31% (95% CI, 17% to 56%), respectively. Trismus and cranial nerve palsies were the most common complications. Seven patients (20%) had trismus develop, two of which were severe enough to require a permanent percutaneous gastrostomy tube. Seven patients (20%) had cranial nerve palsies, three of which were acquired before the salvage reirradiation. Six patients (17%) had osteoradionecrosis of the skull base develop, two of which had persistent pain and recurrent infections, whereas the other four remained asymptomatic. Two patients (8%) had radiologic evidence of temporal lobe necrosis but were clinically asymptomatic. The risk of radiation-induced late complications was high, and the trend of the complication-free survival curve (Figure 5) seems to indicate almost all patients will have a complication with time. We acknowledge that the ideal dose and frequency of the combination of SRS and ICI remains unknown, and the doses given may, indeed, be too high. However, only two of seven patients with trismus required a permanent gastrostomy tube for feeding, and two of six patients with osteoradionecrosis of the skull base had persistent pain and infection requiring antibiotics and analgesia. Only two patients (8%) had temporal lobe necrosis develop, and both were asymptomatic. The use of localized irradiation with SRS and ICI decreases the total irradiated volume compared with EBRT and may be the reason for the lower rate of temporal lobe necrosis. Local recurrence was the major cause of mortality, followed by distant metastases to the liver and lungs. A total of seven patients (20%) in our series died of distant metastases. This figure might be further improved with the addition of chemotherapy to perhaps target distant disease.

CONCLUSION

Although our series is small, SRS plus ICI seems to be an effective salvage therapy for early recurrent NPC. The outcome is very encouraging and favorable compared with the best surgical or reirradiation series reported in the literature. This approach is currently the treatment of choice in our center for early recurrent NPC. However, the ideal dose fractionations and frequency of SRS and ICI remain to be defined.

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