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Prognostic Factors and Long-Term Outcomes of Childhood Nasopharyngeal Carcinoma

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Abstract

Background—To study survival and long-term morbidities of children with nasopharyngeal carcinoma (NPC).

Patients and Methods—Retrospective review of children with NPC treated at St. Jude Children's Research Hospital between 1961 and 2004. Prognostic factors and long term effects of therapy were analyzed.

Results—Fifty-nine patients (median age 14.1 years) were identified. Most were male (66.1%) and Black (54.2%) and had lymphoepithelioma (93.2%). Thirty-five (59.3%), 20 (33.9%) and 4 (6.8%) patients were staged IV, III and II respectively. All patients received radiotherapy (RT) to primary tumor, and most received cervical RT (98.3%) and chemotherapy (88.1%). The 15-year survival and event-free survival (EFS) were $67.2\% \pm 7.5\%$ and $63.5\% \pm 7.8\%$, respectively. Five patients (8.5%) developed subsequent malignancies 8.6–27 years after NPC diagnosis. EFS was improved in patients diagnosed after 1980 ($74.8\% \pm 10.0\%$ vs. $45.5\% \pm 10.1\%$, $p=0.031$), patients with stage III compared to stage IV ($79.3\% \pm 9.6\%$ vs. $56.2\% \pm 11.8\%$, $p=0.049$), patients that received cisplatin ($81.0\% \pm 10.7\%$ vs. $45.8\% \pm 9.7\%$, $p=0.013$), and patients treated with $RT \geq 50Gy$ ($71.4\% \pm 9.3\%$ vs. $43.8\% \pm 11.6\%$, $p=0.048$). Whites had higher distant failure than Blacks ($41.7\% \pm 10.4\%$ vs. $15.6\% \pm 6.5\%$, $p=0.045$). The 15-year cumulative incidence (CI) of any morbidity, sensorineural hearing loss (SNHL), primary hypothyroidism, and growth hormone deficiency (GHD) were $83.7\% \pm 5.4\%$, $52.9\% \pm 6.7\%$, $42.7\% \pm 6.6\%$, and $14.1\% \pm 4.7\%$, respectively. There were dose-response relationships between RT dose and primary hypothyroidism and GHD.

Conclusion—Outcome of children with NPC improved over the past 4 decades with cisplatin-based chemotherapy and higher RT doses. However, many survivors had long-term treatment-related morbidities.

Keywords

Nasopharyngeal carcinoma; children; long-term effects

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an uncommon malignancy in children, with an incidence of 0.1–1.5 per million per year in the US.¹ It is classified pathologically into 3 subtypes; type III, or undifferentiated carcinoma (also known as lymphoepithelioma), is the most common subtype in children.² Clinically, the most common presenting symptom of childhood NPC is cervical lymphadenopathy.^{2, 3}

Treatment recommendations for childhood NPC follow guidelines established for adults. Standard of care for patients with loco-regional disease includes radiotherapy (RT) to the nasopharynx and cervical lymph nodes.¹ Because of high incidence of local and systemic failure in locally advanced disease, chemotherapy has been incorporated into the treatment of those patients. In recent years, randomized and non-randomized studies have documented the advantage of concomitant administration of cisplatin-based chemotherapy and RT. The use of adjuvant and neoadjuvant chemotherapy is a matter of much debate; however, available data would suggest an advantage to the use of neoadjuvant therapy.⁴

Several studies have analyzed the clinical characteristics and treatment outcomes of NPC in children and young adults.^{1, 5–29} With combined chemotherapy and radiotherapy, survival rates in excess of 60–70%, and up to 91%, have been reported.^{12, 17} However, morbidities such as endocrinopathies, hearing loss, bone demineralization, and second neoplasms are not uncommon.^{5, 6, 12–18, 20, 27–29} Since most published series are small and have short follow-up, the long-term outcome of children with NPC has not been well characterized. Therefore, we performed a retrospective review of all children with NPC treated at our institution during the past 43 years to investigate the long-term survival and morbidity in different eras, as well as factors associated with those outcomes.

PATIENTS and METHODS

Clinical review

With institutional review board approval, we reviewed the medical records of all NPC patients younger than 20 years treated at St. Jude Children's Research Hospital between 1961 and 2004. The subjects were retrospectively identified in our institutional database. The survivorship program at St. Jude Children's Research Hospital performs active, on site follow-up for 10 years from diagnosis. Afterwards, patients are followed using annual comprehensive questionnaires and phone calls. We extracted data on the presenting features, histopathology, imaging findings, treatment, outcome, and late morbidities. Since staging of NPC has evolved over the past decades, we attempted to re-stage all patients according to the most recent version of the American Joint Committee on Cancer (AJCC) NPC staging classification,³⁰ using the available clinical information and the original radiology reports.

Treatment protocols

Four major treatment protocols were used for NPC in the past 43 years. Patients diagnosed in 1966–1980, 1985–1990 and 1991–2000 were mostly treated using the institutional NPC-77, 85N2, and NPC1 protocols. In some instances, patients were treated outside of those studies but following the same regimens. For purpose of simplification, those patients were analyzed with the corresponding protocol. Patients diagnosed after 2000 were treated with a non-protocol treatment plan using a chemoradiotherapy (NPTP-CRT-PF) regimen that included neoadjuvant and concomitant chemotherapy and RT. Patients diagnosed before 1966, in 1981–1984 and those not eligible for the above treatment protocols were treated with other non-protocol treatment plans involving radiotherapy and different chemotherapy regimens. The treatment regimens are summarized in Table 2. The NPC-77 protocol consisted of radiotherapy to the nasopharynx and cervical lymph nodes, with

cyclophosphamide for 1 year. The 85N2 and NPC1 protocols included RT alone for T1N0 and T2N0 disease, and 4 cycles of neoadjuvant chemotherapy followed by radiotherapy for T3-4 and/or N1-3 disease. The NPTP-CRT-PF regimen consisted of neoadjuvant chemotherapy followed by concurrent chemo-radiotherapy. Fifty-two patients received 2D-irradiation, one patient was treated using 3D-conformal irradiation, and six patients were treated using intensity modulated radiation therapy. Six patients received amifostine given prior to cisplatin administration and prior to daily irradiation.

Statistical Methods

Overall survival (OS) was defined as the time interval from date of diagnosis to date of death from any cause or to date of last contact. Event-free survival (EFS) was defined as the time interval from date of diagnosis to date of first event (relapsed or progressive disease, second malignancy or death from any cause) or to date of last contact for patients without events. OS and EFS were estimated using the Kaplan-Meier method. Standard errors (SE) were calculated using the method of Peto and Pike.³¹ Differences in OS and EFS were examined using the exact log rank test.

Local failure and distant failure were defined as the time intervals from date of diagnosis to date of local disease recurrence/progression (involving either the nasopharynx or cervical lymphatics) and distant disease recurrence/progression, respectively. The cumulative incidences (CI) of local and distant failure were estimated.³² Competing events for local failure included distant failure, second neoplasm or death before local failure. Competing events for distant failure included local failure, second neoplasm or death before distant failure. Patients with simultaneous local and distant failures were considered as having local or distant failure in the respective analysis. Differences in CI were examined using Gray's test.³³

RESULTS

Patient and treatment characteristics (Table 1)

Fifty-nine patients were diagnosed with NPC from December 1961 to March 2004. The median age at diagnosis was 14.1 years (range, 6.1–19.7 years). Most patients were male (66.1%). Blacks were significantly over-represented in NPC compared to other malignancies in the same period of time, as Blacks constituted 54.2% of NPC diagnoses, compared to 20.4% for other malignancies ($p < 0.001$).

Lymphoepithelioma (type III NPC) was the most common histology (93.2%), with the remaining patients having the diagnosis of non-keratinizing squamous cell carcinoma. The majority of patients had advanced T stage, regional lymph node metastases and high AJCC stage (Table 1). All patients received RT to the primary tumor at doses of 30–70Gy (median, 55.1Gy). All but 1 patient received RT to nodal sites at doses 30–66.6Gy (median, 53.9Gy). Seven patients did not receive chemotherapy.

Survival and second neoplasms

Thirty-five patients (59.3%) were alive with a median follow-up of 16.5 years (range, 4.9–41.9 years). First events included relapsed or progressive disease in 18 patients (3 local, 13 distant, 2 simultaneous local/distant), second neoplasm in 4 patients, and death in 5 patients. Of the 5 patients with death as their first event, 2 died in car accidents and 1 died due to aspiration pneumonia. Causes of death were not available for the other 2 patients. Median time to disease progression and death as first events were 7.6 months (range 3.7–15.3 months) and 16.1 years (range 7.6–30.3 years), respectively. OS estimates at 5 and 15 years were $71.2\% \pm 5.9\%$ and $67.2\% \pm 7.5\%$, respectively. The corresponding EFS estimates were

69.5%±6.0% and 63.5%±7.8%, respectively (Figure 1a). Both patients with distant metastatic disease died; one patient with metastases to bone and mediastinum died 19 months from diagnosis, and one patient with metastases to bone and liver died 16 months from diagnosis of NPC. The 15-year CIs of local and distant failure were 8.5%±3.7% and 25.4%±5.7%, respectively. Only 1 of the 18 patients who had relapsed or progressive disease was alive. The 15-year post-relapse survival was 5.6%±3.8%.

Five patients (8.5%) (3 Whites, 2 Blacks) developed subsequent neoplasms. One patient had a basal cell carcinoma 27 years after his diagnosis of NPC. Twenty-two months later he developed mucoepidermoid carcinoma in the parotid gland and died 8.8 years later. Another patient with a germline *TP53* mutation developed colorectal adenocarcinoma with liver metastasis 8.6 years after his diagnosis of NPC. He developed subsequent malignancies (right maxillary squamous cell carcinoma, esophageal adenocarcinoma, adenocarcinoma of minor salivary gland of lip) and died 15.2 years after the diagnosis of colorectal adenocarcinoma. Three patients were alive 17.7, 22.7, and 8.8 years after diagnosis of a brainstem tumor, thyroid adenoma, and basal cell carcinoma of the neck, respectively. The latency of these second neoplasms was quite long (24.3, 15.7, and 23.4 years).

Predictors of outcome (Table 3)

Males and White patients appeared to have worse outcome, but the differences were not statistically significant (Table 3). Patients diagnosed after 1980 had improved EFS (15-year estimates: 74.8%±10.0% vs. 45.5%±10.1%, $p=0.031$) (Figure 1b). There was also a significant difference in EFS between AJCC stage III and IV patients (79.3%±9.6% vs. 56.2%±11.8%, $p=0.049$) (Figure 1c). Outcome distributions among the 5 major treatment groups were not significantly different (Table 3). However, patients who received cisplatin had improved EFS (81.0%±10.7% vs. 45.8%±9.7%, $p=0.013$). Nevertheless, the use of cisplatin was highly correlated with treatment era ($p<0.001$); all patients who received cisplatin were diagnosed after 1980, while 22 of 24 patients who did not receive cisplatin were diagnosed before 1980. Patients who received RT≥50Gy to the primary tumor had improved OS (73.8%±8.9% vs. 50.0%±11.8%, $p=0.044$) and EFS (71.4%±9.3% vs. 43.8%±11.6%, $p=0.048$). Similarly, patients who received RT≥50Gy to the nodal sites had better OS (78.2%±8.6% vs. 47.6%±11.5%, $p=0.018$) and EFS (78.2%±8.6% vs. 38.1%±11.3%, $p=0.054$). We further investigated the use of cisplatin in conjunction with primary tumor RT dose. Patients who received cisplatin and RT≥50Gy had the highest 15-year OS and EFS (81.0%±10.7%). Patients who did not receive cisplatin but received RT≥50Gy had intermediate OS (60.0%±13.4%) and EFS (53.3%±13.8%). Patients who did not receive cisplatin and received RT<50Gy had the lowest OS (50.0%±11.8%) and EFS (43.8%±11.6%) (Figure 1d).

We did not examine predictors of local failure due to the small number of patients with this event. We did examine potential predictors of distant failure. White patients had significantly higher CI of distant failure compared to Black patients (15-year estimates: 41.7%±10.4% vs. 15.6%±6.5%, $p=0.045$). Tumor and nodal staging did not correlate with distant failure. However, treatment-related parameters strongly correlated with distant relapse. The CI of distant failure was lower in patients who received cisplatin (14.3%±6.7% vs. 37.5%±10.2%, $p=0.047$) and patients who received RT≥50Gy to the primary tumor (18.6%±6.0% vs. 43.8%±13.0%, $p=0.041$) or nodal sites (13.2%±5.6% vs. 47.6%±11.3%, $p=0.003$). The 15-year CI of distant failure was lowest in patients who received cisplatin and RT≥50Gy (14.3%±6.77%), intermediate in patients who had no cisplatin but received RT≥50Gy (26.7%±11.9%), and highest in patients who had no cisplatin and received RT<50Gy (43.8%±13.0%).

Morbidities

The evaluation of long-term morbidities must be considered in the context of the limitations imposed by the retrospective nature of the study. The CI of various screened morbidities is shown in Table 4. The CI of primary hypothyroidism was much higher in the modern treatment era (after 1980) (15-year estimates: $65.6\% \pm 8.3\%$ vs. $4.6\% \pm 4.6\%$, $p < 0.001$), and a similar phenomenon was observed for growth hormone deficiency (GHD) ($19.5\% \pm 6.8\%$ vs. $4.6\% \pm 4.6\%$, $p = 0.041$), and osteopenia ($17.1\% \pm 6.6\%$ vs. $0.0\% \pm 0.0\%$, $p = 0.044$). The CI of any degree of sensorineural hearing loss (SNHL) appeared higher in patients who received cisplatin ($68.4\% \pm 9.3\%$ vs. $37.5\% \pm 10.2\%$, $p = 0.052$). There was also a dose-response relationship between RT dose and development of SNHL or severe SNHL (grade 3 or higher) (Table 5). Patients who received $RT \geq 50Gy$ had significantly higher CI of SNHL ($65.9\% \pm 7.6\%$ vs. $18.8\% \pm 10.1\%$, $p = 0.002$); and patients who received $RT > 65Gy$ had significantly higher CI of severe SNHL ($25.0\% \pm 10.0\%$ vs. $2.7\% \pm 2.7\%$, $p = 0.012$). The 15-year CI of SNHL was higher in patients who received cisplatin and $RT \geq 50Gy$ ($68.4\% \pm 9.3\%$), and in patients who did not receive cisplatin but received $RT \geq 50Gy$ ($61.1\% \pm 13.7\%$), than in patients who neither received cisplatin nor $RT \geq 50Gy$ ($18.8\% \pm 10.1\%$) (Figure 2a).

There was also a dose-response relationship between cervical RT dose and CI of primary hypothyroidism ($p < 0.001$). The highest 15-year CI of hypothyroidism occurred in patients who received $RT \geq 60Gy$ ($77.2\% \pm 11.7\%$), followed by $50-60Gy$ ($47.4\% \pm 12.0\%$) and $< 50Gy$ ($9.5\% \pm 6.6\%$) (Figure 2b). Patients who received $RT \geq 50Gy$ to the primary tumor also had higher CI of GHD ($19.6\% \pm 6.4\%$ vs. 0.0% , $p = 0.015$).

DISCUSSION

Epidemiology

We observed that Blacks were over-represented in our cohort of NPC patients compared to other malignancies. The higher incidence of NPC in Blacks has been described but the underlying reason for this racial disparity is uncertain.³⁴ This is in contrast with other EBV-related malignancies where the incidence of Blacks is the same or lower than Whites.³⁵ The racial disparity in NPC appears to be more pronounced in children compared to adults.³⁴ Taken together, these data suggest that different pathways of EBV tumorigenesis according to ethnicity and age may be involved.

Survival and Event-free Survival

The 5-year OS ($71.2\% \pm 5.9\%$) and EFS ($69.5\% \pm 6.0\%$) of our cohort are comparable to previous reports. The more relevant prognostic factors for outcome were related to locoregional stage and treatment administered. Patients with AJCC stage IV had significantly lower EFS. Likewise, the presence of progressive or recurrent disease resulted in dismal outcomes despite salvage treatments. As observed previously, most recurrences were distant rather than loco-regional.^{5, 15, 18, 21, 27, 36} An important finding of our study was the association of race with outcome; Black patients tended to have better EFS with significantly lower incidence of distant failure compared to White patients. The reason for the difference was not apparent and requires further investigation.

Long-term outcome of childhood NPC has been seldom reported; the 10-year survival has been reported to be 36–58%.^{1, 14, 20, 21} Uzel reported a 15-year survival of 62.4% in 32 patients with a median follow-up of 8.9 years.¹⁶ We estimated the OS and EFS to be $67.2\% \pm 7.5\%$ and $63.5\% \pm 7.8\%$, and $64.3\% \pm 8.8\%$ and $57.6\% \pm 9.4\%$, respectively, at 15 and 20 years. A longer follow-up will be required to document whether the disease-related outcome estimates continue to decrease. EFS estimates increased from 46% to 75% after 1980.

Improvements in radiation planning and delivery, chemotherapy, and supportive care likely contributed to this trend. Higher RT doses were used in the recent era, and RT \geq 50Gy to primary tumor or nodal sites was associated with lower distant failure and better EFS. Similar association between RT dose and survival has been previously reported.^{5, 13, 14, 21, 23} The switch from cyclophosphamide-based to cisplatin-based chemotherapy in the most recent era might also contribute to improved outcome; patients who received cisplatin had lower incidence of distant failure and better EFS, consistent with the recent report by Kupeli.²⁰ We further demonstrated that cisplatin and higher RT doses might have additive or synergistic beneficial effect; patients treated with cisplatin and RT \geq 50Gy had superior EFS compared to patients treated without cisplatin and those treated without cisplatin and RT $<$ 50Gy had the worst outcome. Data from adult NPC studies suggest that concurrent cisplatin and RT is superior to RT alone.^{4, 37} Likewise, there appears to be an added benefit to the incorporation of neoadjuvant chemotherapy.⁴ Whether the same benefit of concurrent chemo-radiotherapy applies to children is currently uncertain; this issue is currently being studied by the ongoing COG ARAR331 trial.

Morbidities—The incidence of long-term morbidities in survivors of childhood NPC has not been well reported. With a median follow-up of 16.5 years and up to almost 42 years, we attempted to estimate the CI of long-term morbidities. Most morbidities started early, within 5 years from diagnosis. Some complications tended to cluster within the first 2 years, including trismus, chronic or recurrent sinusitis or otitis media, and pulmonary fibrosis. In contrast, the frequency of some endocrinopathies, such as growth hormone deficiency, gonadotropin deficiency and primary hypothyroidism, increased with time and some cases were diagnosed after 30 years.

Xerostomia and dental problems, well-known unavoidable adverse effects of RT to the salivary glands, occurred in most patients, consistent with previous reports.^{6, 15–17, 19} Intensity modulated RT (IMRT) can potentially ameliorate mucosal damage and xerostomia in NPC patients.^{38, 39} The administration of amifostine may also be beneficial in patients receiving radiotherapy to the head and neck area. In a report by Brizel,⁴⁰ adult patients with head and neck cancer receiving radiotherapy were randomized to receive amifostine, given daily before radiotherapy. Moderate to severe chronic xerostomia was significantly less prevalent with the use of amifostine. Importantly, the long-term outcome was similar for both groups of patients, demonstrating that the use of amifostine does not influence the antitumor efficacy of the treatment.⁴⁰ Nevertheless, there is significant controversy on the role of this radioprotectant in patients receiving treatment for NPC.⁴¹ The currently open COG ARAR0331 is exploring this question.

SNHL is a debilitating complication of cisplatin and radiotherapy to the head and neck region. However, there is no data documenting the CI of SNHL in childhood NPC. SNHL affected over half of the patients by 15 years. Most patients had grade 2 SNHL, but in nearly one-fifth of patients SNHL was \geq grade 3 requiring hearing aids. We noted a higher incidence of SNHL in patients treated with cisplatin and RT \geq 50Gy, and a dose-response relationship with RT doses. Whether concurrent chemo-radiotherapy increases the risk of SNHL remains to be known.

We observed a relatively high incidence of primary hypothyroidism. Hypopituitarism was also common, especially growth hormone and gonadotropin deficiencies. The endocrinopathies were probably secondary to RT, which was supported by dose-response relationships between RT dose and primary hypothyroidism and GHD. However, the observation might represent detection bias as we performed screening of endocrinopathies more stringently in the more recent era. It has been suggested that reduction of RT dose based on the response to neoadjuvant chemotherapy may not compromise survival.⁴²

Therefore, response-adapted RT is worth further evaluation to minimize endocrine morbidities. Of note, four of the six patients treated with IMRT developed neuroendocrine deficits.

Pulmonary fibrosis occurred in 5 patients in our cohort, probably secondary to bleomycin. Two patients died subsequently and the pulmonary fibrosis was a contributory cause of death. One patient had symptomatic restrictive lung disease and two patients were asymptomatic. Visual impairment occurred infrequently, was usually mild, and mostly secondary to radiation-induced cataracts, retinopathy or optic atrophy. Although not major health issues, these problems may compromise the quality of life of the affected patients. Osteopenia was observed in some patients as we started screening for bone density with DEXA scan and quantitative computed tomography recently. Therefore, the incidence of osteopenia is likely underestimated.

The current study is one of the largest studies in childhood NPC and adds important information regarding treatment and outcomes. A limitation of our study is its retrospective nature. Monitoring for long-term morbidities was heterogeneous and the incidence of various morbidities was likely underestimated. Also, since patients were treated on different regimens over a 40-year period, it is difficult to determine whether differences in outcome were truly related to treatment or to changes over time.

In conclusion, survival of children with NPC has improved over the past 4 decades with improved radiotherapy and chemotherapy. However, life expectancy is reduced by second neoplasms and quality of life may be impaired by long-term morbidities. Better treatments are needed to improve the cure of advanced or recurrent disease and to reduce long-term morbidities. New chemotherapeutic agents, such as taxanes, along with improved radiation techniques, as well as the use of EBV-directed cytotoxic T lymphocytes will likely provide further advance in the management of these patients, while more efforts will have to be placed in minimizing acute and late effects, with the incorporation of chemo- and radiation-protectants and imaging-guided and risk-adapted radiation.

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Figure 1a

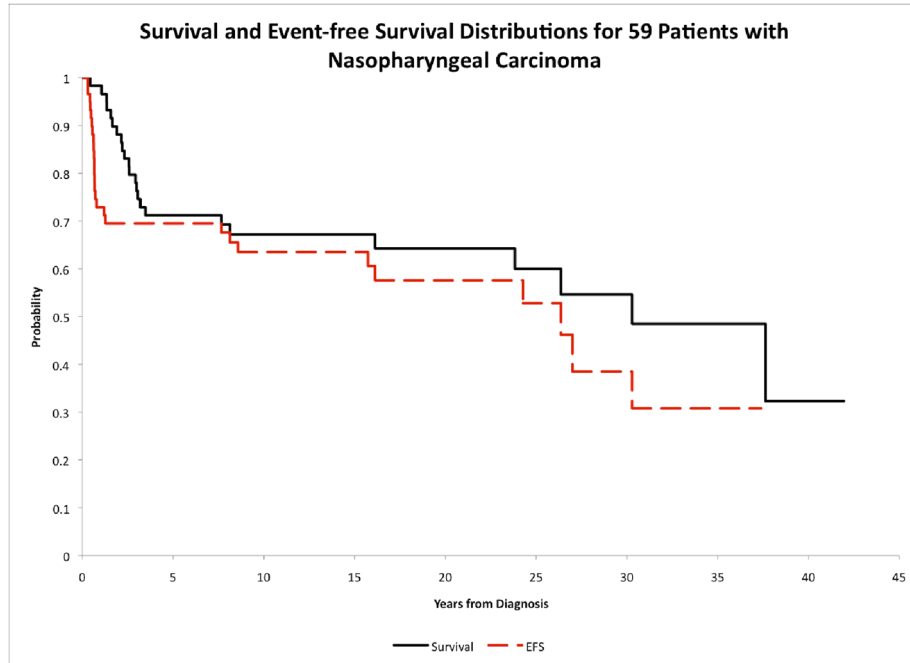


Figure 1b

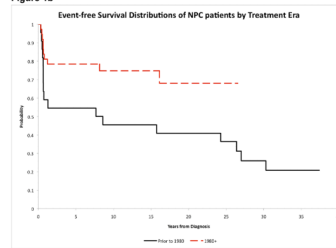


Figure 1c

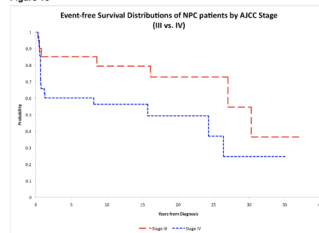


Figure 1d

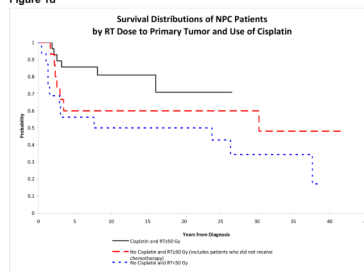


Figure 1.

Figure 1a. Overall survival and event-free survival of NPC patients

Figure 1b. Event-free survival of NPC patients by treatment era

Figure 1c. Event-free survival of NPC patients by AJCC stage

Figure 1d. Survival of NPC patients by RT dose to primary tumor and cisplatin

Figure 2a

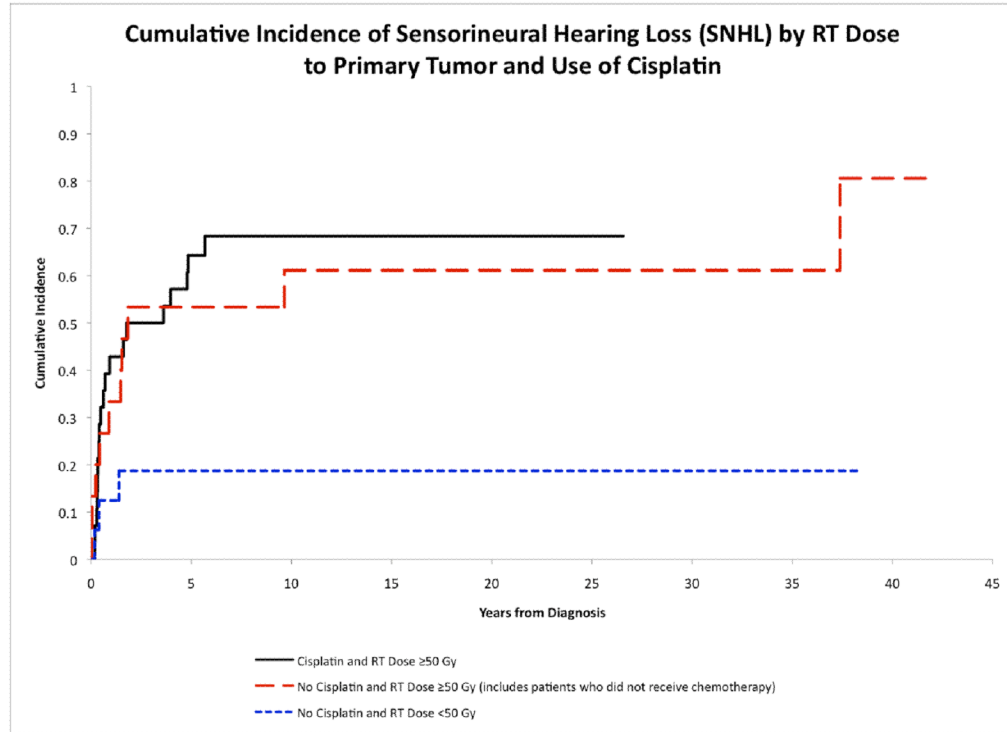


Figure 2b

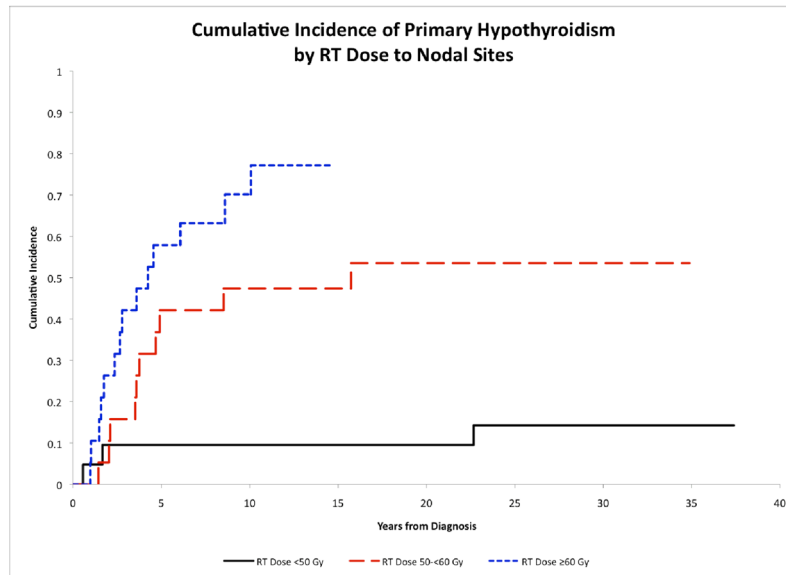


Figure 2.
 Figure 2a. Cumulative incidence of sensorineural hearing loss by RT dose to primary tumor and cisplatin
 Figure 2b. Cumulative incidence of primary hypothyroidism by RT dose to nodal sites

Table 1

Patient Demographics and Clinical Features (n=59)

	N (%) ¹
Gender	
Male	39 (66.1)
Female	20 (33.9)
Race	
Black	32 (54.2)
White	24 (40.7)
Hispanic	2 (3.4)
American Indian	1 (1.7)
Histology	
Lymphoepithelioma	55 (93.2)
Non-keratinizing squamous cell carcinoma	4 (6.8)
T stage	
T1	2 (3.4)
T2	6 (10.2)
T2a	3 (5.1)
T2b	6 (10.2)
T3	20 (33.9)
T4	22 (37.3)
N stage	
N0	5 (8.5)
N1	7 (11.9)
N2	27 (45.8)
N3	2 (3.4)
N3a	12 (20.3)
N3b	6 (10.2)
M stage	
M0	57 (96.6)
M1	2 (3.4)
AJCC combined stage	
IIA	2 (3.4)
IIB	2 (3.4)
III	20 (33.9)
IVA	15 (25.4)
IVB	18 (30.5)
IVC	2 (3.4)

¹ Percentages may not sum to 100% due to rounding.

Table 2

Chemotherapy regimens

Protocol	Years	N	Radiotherapy *	Chemotherapy
NPC-77	1966–1980	18	45–70 Gy	CYC 200 mg/m ² /week x 6 weeks CYC 300 mg/m ² every other week x 12 months
85N2	1985–1990	5	45–70 Gy	<u>Neoadjuvant (4 cycles)</u> MTX 120 mg/m ² d 1 CDDP 100 mg/m ² d 2 5-FU 1000 mg/m ² /d d 1–5 LV 25 mg/m ² q6h x 6 d 2–4
NPC-1	1991–2000	12	45–70 Gy	<u>Neoadjuvant (4 cycles)</u> MTX 120 mg/m ² d 1 CDDP 100 mg/m ² d 2 5-FU 1000 mg/m ² /d d 1–5 LV 25 mg/m ² q6h x 6 d 2–4
NPTP-CRT-PF	2000–2004	6	45–70 Gy	<u>Neoadjuvant (3 cycles)</u> CDDP 80 mg/m ² d 1 5-FU 1000 mg/m ² d 1–4 <u>Concurrent chemoradiation (3 cycles)</u> CDDP 100 mg/m ² d 1
Other regimens		12	45–70 Gy	VCR/BLE/CDDP VCR/DNR/CDDP BLE/MTX/CDDP CYC/MTX CYC/MTX/5FU VCR/CYC VCR/CYC/MTX
No chemotherapy		6	45–70 Gy	-

Abbreviations: CYC: Cyclophosphamide; MTX: Methotrexate; CDDP: Cisplatin; 5-FU: 5-Fluorouracil; LV: Leucovorin; VCR: Vincristine; BLE: Bleomycin; DNR: Daunorubicin

* Radiotherapy to primary tumor and nodal areas was individualized.

Table 3
Potential prognostic factors for overall survival (OS) and event-free survival (EFS) at 15 years for NPC Patients

Factor	n	OS ± 1 SE (%)	P ¹	EFS ± 1 SE (%)	P ¹
Age at Diagnosis					
≤14 years	28	71.4 ± 10.2	0.525	67.9 ± 10.7	0.737
>14 years	31	63.7 ± 10.6		59.9 ± 11.0	
Gender					
Female	20	79.3 ± 10.9	0.088	79.3 ± 10.9	0.101
Male	39	61.2 ± 9.5		55.4 ± 9.9	
Race					
White	24	58.3 ± 10.9	0.130	50.0 ± 11.2	0.141
Black	32	70.3 ± 9.9		70.3 ± 9.9	
Treatment Era					
Before 1980	22	54.5 ± 10.2	0.145	45.5 ± 10.1	0.031
After 1980	37	74.8 ± 10.0		74.8 ± 10.0	
T Stage					
T1/T2	17	76.5 ± 11.2	0.772	70.1 ± 12.1	0.409
T3	20	70.0 ± 11.1		65.0 ± 11.6	
T4	22	57.3 ± 16.7		57.3 ± 16.7	
N Stage					
N0/N1/N2	39	76.4 ± 8.3	0.112	70.6 ± 9.0	0.103
N3	20	49.5 ± 13.3		49.5 ± 13.3	
AJCC Stage					
IIA/IIB	4	50.0 ± 25.0	0.102 ²	50.0 ± 25.0	0.049 ²
III	20	90.0 ± 7.1		79.3 ± 9.6	
IVA/IVB/IVC	35	56.2 ± 11.8		56.2 ± 11.8	
Use of Cisplatin					
Yes ³	28	81.0 ± 10.7	0.070	81.0 ± 10.7	0.013
No ⁴	24	54.2 ± 9.8		45.8 ± 9.7	

Factor	n	OS ± 1 SE (%)	P ¹	EFS ± 1 SE (%)	P ¹
Protocol/Treatment					
NPC-77	18	61.1 ± 11.0	0.427	55.6 ± 11.2	0.238
NPC1-like ⁶	17	94.1 ± 8.1		94.1 ± 8.1	
NPTP-CRT-PF	6	83.3 ± 15.2 ⁵		83.3 ± 15.2 ⁵	
NPTP-YBP	5	60.0 ± 19.0		60.0 ± 19.0	
No Protocol	6	50.0 ± 20.4		50.0 ± 20.4	
RT to Primary Tumor					
RT to primary <50 Gy	16	50.0 ± 11.8	0.044	43.8 ± 11.6	0.048
RT to primary ≥50 Gy	43	73.8 ± 8.9		71.4 ± 9.3	
RT to Nodes					
RT to nodes <50 Gy	21	47.6 ± 11.5	0.018	38.1 ± 11.3	0.054
RT to nodes ≥50 Gy	38	78.2 ± 8.6		78.2 ± 8.6	
Cisplatin & Primary RT Dose					
Cisplatin & primary RT ≥50 Gy	28	81.0 ± 10.7	0.088	81.0 ± 10.7	0.042
No cisplatin & primary RT ≥50 Gy ⁷	15	60.0 ± 13.4		53.3 ± 13.8	
No cisplatin & primary RT <50 Gy	16	50.0 ± 11.8		43.8 ± 11.6	

¹ P-values were obtained using exact log rank tests.

² Comparison of AJCC stages III vs. IV.

³ Includes the following protocols/treatments: 85N2, NPC1 (excluding the 1 patient who received RT only without chemotherapy on NPC1), NPTP-CRT-PF, NPTP-BPM and NPTP-VBP.

⁴ Includes the following protocols/treatments: NPC-77, NPTP-CM, NPTP-CMF, NPTP-VC, NPTP-VCM and NPTP-VDC

⁵ 5-year estimate; data not mature to 15 years.

⁶ Includes NPC1 and 85N2 protocols.

⁷ Includes 7 patients who had no chemotherapy (but received >50 Gy RT to primary)

Table 4

Estimates of the 15-Year cumulative incidence (CI) of various morbidities

	No. of patients with morbidity	CI at 15-years \pm 1 Standard Error (%)
Any morbidity	49	83.7 \pm 5.4
Sensorineural hearing Loss	32	52.9 \pm 6.7
Primary hypothyroidism	27	42.7 \pm 6.6
Trismus	20	32.3 \pm 6.2
Chronic/recurrent sinusitis	12	18.9 \pm 5.2
Chronic/recurrent otitis media	10	17.6 \pm 5.2
Growth hormone deficiency	10	14.1 \pm 4.7
LH/FSH deficiency	10	14.4 \pm 4.8
Visual impairment	7	10.9 \pm 4.3
Osteopenia	7	10.5 \pm 4.1
TSH deficiency	6	8.5 \pm 3.7
Cranial nerve palsy	5	8.5 \pm 3.7
Renal dysfunction	5	8.5 \pm 3.7
Pulmonary fibrosis	5	6.8 \pm 3.3
ACTH deficiency	5	8.6 \pm 3.7
Hyperprolactinemia	4	6.8 \pm 3.3
Esophageal stricture	2	3.4 \pm 2.4
Osteonecrosis	1	1.7 \pm 1.7

Table 5

Proportions of patients with sensorineural hearing loss (SNHL) at different radiotherapy dose to primary tumor

RT dose (Gy)	N	SNHL (grade 1/2/3)	Severe SNHL (\geq grade 3)
>65	20	14 (70.0%)	5 (25.0%)
50–65	23	15 (65.2%)	1 (4.3%)
<50	16	3 (18.8%)	0 (0.0%)