

อัตราการรอดชีวิตในการรักษามะเร็งหลังโพรงจมูกในโรงพยาบาลศรีนครินทร์: ศึกษาย้อนหลัง 10 ปี

พรเทพ เกษมศิริ^{1,4*}, คัทลียา ทองรอง^{2,4}, กฤติกา สุวรรณรุ่งเรือง^{3,4}

¹ภาควิชาโสต ศอ นาสิกวิทยา, ²ภาควิชาวิสัญญีวิทยา, ³หน่วยมะเร็ง คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น 40002

⁴มหาวิทยาลัยขอนแก่น, กลุ่มวิจัยมะเร็งแบบองค์รวม

Long-term Survival Outcome of Treatment for Nasopharyngeal Carcinoma in Srinagarind Hospital, Thailand: 10-year Retrospective Analysis

Pornthep Kasemsiri^{1,4*}, Cattleya Thongrong^{2,4}, Krittika Suwanrungruang^{3,4}

Department of ¹Otorhinolaryngology, ²Anesthesiology, ³Cancer Unit, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

⁴Khon Kaen University, Comprehensive Cancer Research Group (KKU CCRG)

หลักการและวัตถุประสงค์: ถึงแม้ว่ามะเร็งหลังโพรงจมูกเป็นมะเร็งที่ตอบสนองดีต่อการฉายแสง แต่สำหรับประเทศไทย การรักษามะเร็งหลังโพรงจมูกก็ยังคงเป็นปัญหาอยู่ ดังนั้นวัตถุประสงค์ของการศึกษานี้ต้องการศึกษาระบาดวิทยาและอัตราการรอดชีวิตของมะเร็งหลังโพรงจมูก

วิธีการศึกษา: ศึกษาย้อนหลังจากข้อมูลผู้ป่วยของหน่วยมะเร็งโรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ตั้งแต่ 1 มกราคม 2546 ถึง 31 ธันวาคม 2555 โดยวิเคราะห์ข้อมูลพื้นฐานอาการทางคลินิกและอัตราการรอดชีวิต

ผลการศึกษา: ผู้ป่วย 1,193 ราย เพศชาย 849 ราย เพศหญิง 344 ราย อายุระหว่าง 6-88 ปี 2 ใน 3 ของผู้ป่วยอยู่ในระยะ 3 และ 4 (ร้อยละ 1.8 ของผู้ป่วยอยู่ในระยะ 1, ร้อยละ 5.8 ของผู้ป่วยอยู่ในระยะ 2, ร้อยละ 12.9 ของผู้ป่วยอยู่ในระยะ 3, ร้อยละ 54.0 ของผู้ป่วยอยู่ในระยะ 4, ร้อยละ 25.5 ของผู้ป่วยไม่ระบุระยะของโรคมะเร็ง) การรักษามีทั้งการฉายแสง (ร้อยละ 57.8) และเคมีบำบัด (ร้อยละ 23.6) การรักษามะเร็งหลังโพรงจมูกนั้น การฉายแสงหรือการให้เคมีบำบัดร่วมกับการฉายแสงถือว่าเป็นหลักในการรักษา ส่วนการผ่าตัดนั้นจะมีข้อบ่งชี้ในกรณีที่ฉายแสงไปแล้วยังมีมะเร็งหลงเหลืออยู่หรือมะเร็งที่ขึ้นใหม่ อัตราการรอดชีวิต 5 ปี ในภาพรวมพบร้อยละ 39

Background and Objectives: Nasopharyngeal carcinoma (NPC) is the commonest radiosensitive cancer; however, it is still a major health problem in Thailand. The aim of this study was to assessed the epidemiological characteristics and serried survival rate of NPC treatment.

Materials and methods: A retrospective study was conducted in Srinagarind hospital, Faculty of Medicine, Khon Kaen University by analyzing demographic, clinical, and survival data of nasopharyngeal carcinoma patients from registry database of cancer unit during January 1, 2003- December 31, 2012.

Results: One thousand and one hundred ninety three patients, 849 males and 344 females, aged between 6-88 years were recruited. Two-third patients presented at an advanced stage (1.8% stage I, 5.8% stage II, 12.9% stage III, 54.0% stage IV, 25.5% unknown stage). The therapies applies include 57.8% radiotherapy, and 23.6% chemotherapy. Radiotherapy or concurrent chemoradiotherapy is still the mainstay of treatment NPC; whereas, surgery is reserved for persistent or recurrent tumor. Overall 5-year survival rate was 39% (95% CI:

*Corresponding author:

Pornthep Kasemsiri, Department of Otorhinolaryngology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. E-mail: pkasemsiri99@gmail.com

(95% CI: 35% - 44%) หากแบ่งตามระยะของมะเร็ง พบว่า อัตราการรอดชีวิตที่ 5 ปี ในระยะที่ 1 ร้อยละ 63.8 (95% CI: 42.5% - 95.7%) ระยะที่ 2 ร้อยละ 55.4 (95% CI: 39.3% - 78.1%) ระยะที่ 3 ร้อยละ 48.6 (95% CI: 34.8% - 67.9%) ระยะที่ 4 ร้อยละ 32.7 (95% CI: 27.5% - 38.8%) จากการศึกษายังพบอีกว่าอัตราการรอดชีวิต 5 ปี ในเพศหญิงดีกว่าเพศชาย ($p = 0.011$) และในผู้ป่วยอายุน้อยกว่า 40 ปี ดีกว่าผู้ป่วยสูงอายุ ($p = 0.010$) อย่างมีนัยสำคัญทางสถิติ

สรุป: มะเร็งหลังโพรงจมูกเป็นหนึ่งในมะเร็งศีรษะและคอที่อยู่ในบริเวณที่ตรวจพบได้ยาก ไม่ค่อยแสดงอาการทำให้ผู้ป่วยมักมาพบแพทย์ด้วยระยะท้ายของโรคมะเร็ง ซึ่งระยะของมะเร็งนั้นเป็นปัจจัยสำคัญในการพยากรณ์โรค ดังนั้น การให้ความสำคัญกับการตรวจมะเร็งมีความจำเป็นอย่างยิ่งต่อผลการรักษาที่ดี

คำสำคัญ: มะเร็งหลังโพรงจมูก, อัตราการรอดชีวิต, การฉายแสง, การฉายแสงร่วมกับการให้เคมีบำบัด

35% - 44%). According to stages, the 5-year survival rate were 63.8% (95% CI: 42.5% - 95.7%) for stage I, 55.4% (95% CI: 39.3% - 78.1%) for stage II, 48.6% (95% CI: 34.8% - 67.9%) for stage III, and 32.7% (95% CI: 27.5% - 38.8%) for stage IV. Regarding gender and age group, the 5-year survival rate was better in female group ($p = 0.011$) and patients who was younger than 40 years old ($p = 0.010$).

Conclusion: Nasopharynx is a one of the silent areas of head and neck cancer; therefore, most of patients resented with advanced stages. The clinical staging seems to be the most important prognostic factor of NPC; hence, the early concern and detection are necessary to achieve an excellent treatment outcome.

Key words: nasopharyngeal carcinoma, survival rate, radiotherapy, concurrent chemoradiation

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Introduction

Nasopharyngeal carcinomas (NPC) are endemic in Southern China and Southeast Asia, with an incidence of 10-50 per 100,000 populations per year¹. In endemic regions, the incidence gradually increases with age, peaking around 50-59 years, and declines thereafter; conversely, in low risk populations, it increases with increasing age. Furthermore, many studies purpose that peak of incidence was observed among adolescent and young adults in Southeast Asia, Africa, and the United States²⁻⁹. The exposure to carcinogenic agents early in life was purposed to explain the causation; however, there is lack of data.

Regarding types of NPC, the keratinizing type (WHO type I) mainly occurs in Western countries; whereas, Asians predominantly present with non-keratinizing and undifferentiated type (WHO type II, III)¹⁰ (REF). These histopathological types affect to the treatment outcomes. The study reported the correlation between histopathology and survival rate of NPC that 5-year survival was 65% for the non-keratinizing and undifferentiated carcinomas of the nasopharynx and 37% for the keratinizing variety¹⁰. These outcomes showed that

non-keratinizing and undifferentiated NPC have better survival rate than keratinizing NPC due to more radio-responsiveness. The mainstay of treatment for NPC is radiotherapy based; however, chemotherapy plays role as combined therapy in current treatment. Two meta-analyses demonstrated that allow achieving survival benefit of 4-6% at 5 years^{11,12}.

Furthermore, advanced radiotherapy techniques (i.e. Intensity-Modulated Radiotherapy (IMRT), three-dimensional conformal radiotherapy (3DCRT)) have been developed to improve outcomes. Overall survival rate of patient who underwent IMRT was reported of 83.1% -90%¹³⁻¹⁵. 3DCRT also reported that improved survival rate (81.8% for stage I, 77.9% for stage II, 47.4% for stage III, and 25.9% for stage IV)¹⁶. Concurrent chemoradiotherapy and advanced radiotherapy techniques seem to allow benefit outcomes; however, there is still a paucity of treatment outcomes in Thailand. The aim of this study was to investigate the outcomes of the patients who were treated in our institution.

Material and methodology

A retrospective study was conducted in Srinagarind hospital, Faculty of Medicine, Khon Kaen University by retrieving data from patients treated during January 1, 2003- December 31, 2012. Patients' demography, NPC stage, and survival data were retrieved from registry database of cancer unit. Demographic data were analyzed by age and gender. Age data were divided into two groups including younger than 40 years of age and older than or equal to 40 years of age. NPC staging was clarified by American Joint Committee of Cancer (AJCC) TNM staging system. All patients had received either radiotherapy based alone or combined with chemotherapy. Patients were examined prior treatment and during the follow up period, which defined as the period from the date of diagnosis until death or until the last follow up time. The survival rate was defined as the time of diagnosis to the time of loss follow up or death from any causes. The last date of follow up of this cohort was December 31, 2013. RStudio version 0.98.953[®] 2009-2013 was used for analyzing data. The survival curves were analyzed with Kaplan-Meier method. For comparing survival curves of NPC patients between age < 40 years and age ≥ 40 years, a log-rank test was used to investigate this outcome with unadjusted variable. The study was approved by the Khon Kaen University Ethics Committee for Human Research (HE571238).

Results

One thousand and one hundred ninety three patients with diagnosed NPC were treated in Srinagarind hospital during January 1, 2003 - December 31, 2012. The demographic characteristics are summarized in Table 1. Most patients were in the 41-60 years age group (57.4%) with a mean age of 52 (SD 13.6) years for male and 51(SD 14.2) years for female. Male was the predominant patient presenting with NPC (71.2%). Advanced staging was commonly observed of 54.2% patients with AJCC stage IV. Radiotherapy based was given to NPC patients of 57.8% and chemotherapy was applied add on treatment of 23.6%. The 5 year overall

survival rate for the 1,193 patients was 39% (95% CI: 35% - 44%) (Figure 1). The survival data, including alive at start of interval and changed status during interval, was demonstrated in Table 2. For comparing survival rate of each stage, 5-year survival rate was observed that 63.8% (95% CI: 42.5% - 95.7%) for stage I, 55.4% (95% CI: 39.3% - 78.1%) for stage II, 48.6% (95% CI: 34.8% - 67.9%) for stage III, and 32.7% (95% CI: 27.5% - 38.8%) for stage IV (Figure 2). The 5 -year survival rate of male was worse than female ($p = 0.011$) (Figure 3). According to age group, the 5 -year survival rate of younger patients was better than elderly patients ($p = 0.008$) (Figure 4). However, 25.4% of all patients were not clarified their staging due to missing data. The 5-year survival rate was 49.2% (95% CI: 40.5% - 59.7%) in this group. Furthermore, 5-year survival rate of each stage were demonstrated by year in table 2.

Discussion

In the epidemiology of NPC, there were three major etiological factors including genetic susceptibility, early age exposure to chemical carcinogens, and latent EBV infection; therefore, incidence of NPC varies depend on the region. Previous data demonstrated the incidence relate to gender and age. Male to female was reported

Table 1 Demographic data

Item	Number	%
Gender		
Male	849	71.2
Female	344	28.8
Age (Years)		
6-30	123	10.3
31-40	182	15.3
41-50	348	29.2
51-60	337	28.2
61-70	160	13.4
>70	43	3.6
AJCC Staging		
I	21	1.8
II	69	5.8
III	154	12.9
IV	646	54.0
Unknown	306	25.5

Table 2 Analysis of Nasopharyngeal Carcinoma Survival

Stage	Start of interval (Year)	Alive at start of interval	Changed status during interval	
			Dead	Censored
I	1	21	2	5
	2	14	1	2
	3	11	2	0
	4	9	0	0
	5	9	0	0
II	1	69	5	40
	2	24	5	0
	3	19	1	2
	4	16	2	0
	5	14	0	0
III	1	154	5	99
	2	50	8	2
	3	40	5	5
	4	30	4	11
	5	15	1	1
IV	1	646	107	269
	2	270	77	14
	3	179	34	23
	4	122	15	25
	5	82	5	46
Unknown	1	306	39	184
	2	83	13	9
	3	61	9	9
	4	43	1	2
	5	40	0	0

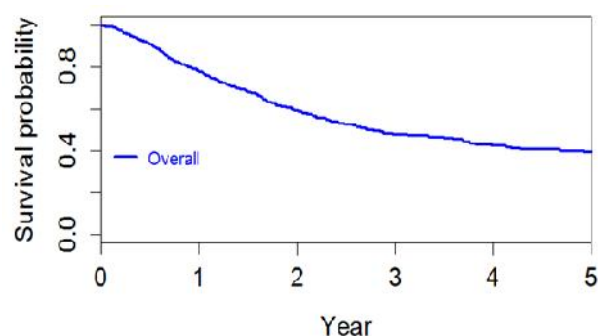


Figure 1 Demonstration of 5- years over all survival outcome of all NPC patients in Srinagarind hospital during January 1, 2003- December 31, 2012
NPC: Nasopharyngeal carcinoma

of 2-3 time^{17,18} and overall of the incidence rate peaked at age 50-59 years. These results seem like our series that are common in male whereas our peaked at 41-60 years. However, a bimodal age distribution has been mention that 20% of NPC patients being below 30 years in northern Africa. Addition Southeast Asia, and the United States, there are minor peaked incidence among adolescent and young adults, also²⁻⁹. These related the exposure to a common agent in early life¹⁹. In this series, we observed a number of juvenile NPC patients (age under 30 years) just only 10.48%; thus, a bimodal age distribution is unclear in our situation.

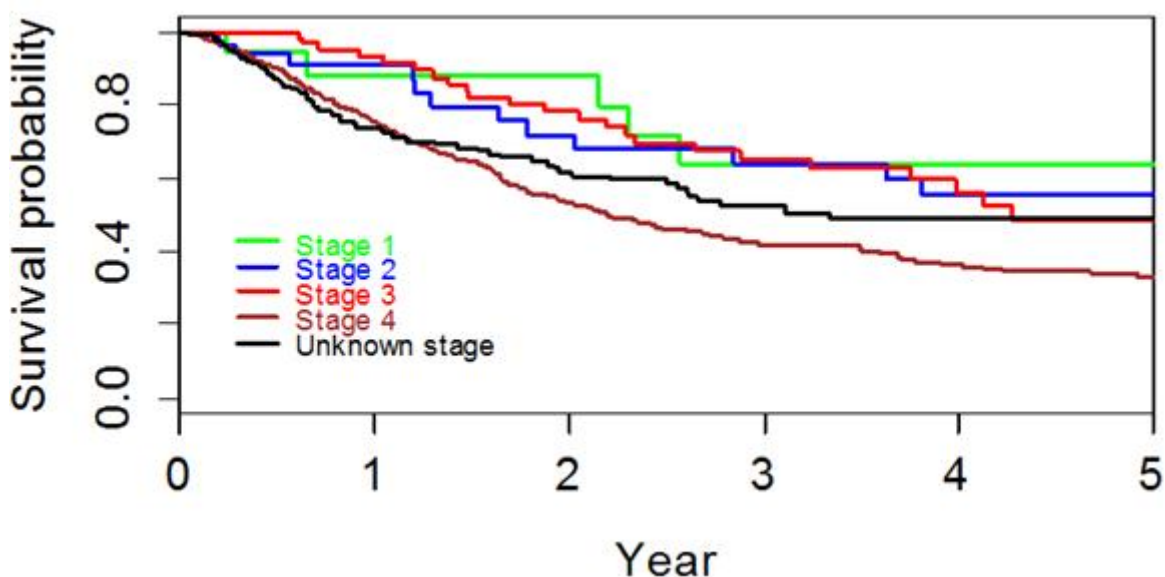


Figure 2 Comparison of overall survival outcome among the AJCC staging
AJCC: American Joint Committee on Cancer

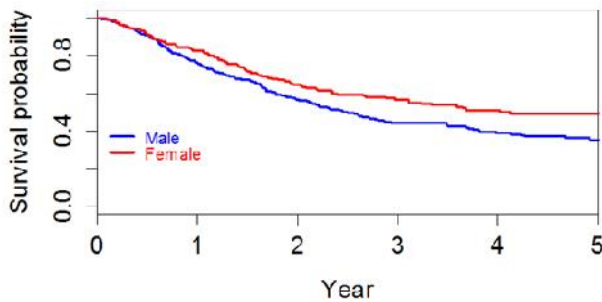


Figure 3 Comparison of overall survival outcome between male and female ($p = 0.011$)

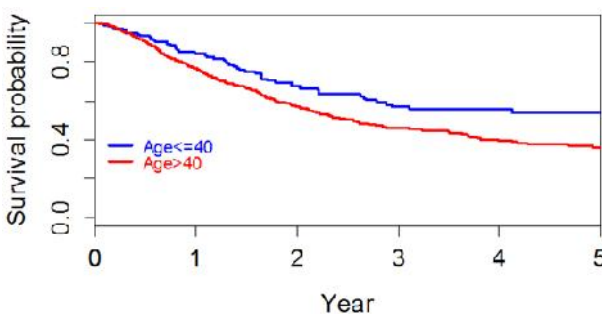


Figure 4 Comparison of overall survival outcome between age younger than 40 years and older than 40 years ($p = 0.010$)

The clinical staging is an important prognosis factor of NPC. Most of NPC patients presented with stage III or IV. In our series, advanced stage also is a major group (54.2%) due to nasopharynx is a deep-seated position in the central part of cranial base; therefore, patients often presented with other symptoms including cervical lymphadenopathy, aural fullness, headache, strabismus, and bone pain. These symptoms indicate involvement nearby normal structures or metastasis. Furthermore nasopharynx is a silent area; the delayed diagnosis may be occurred from the lack of patients' knowledge about early signs and symptoms of NPC, the unspecific symptoms mimicking upper respiratory tract infection during early stages, and economical restriction.

Regarding treatment, radiotherapy or concurrent chemoradiotherapy is the mainstay of treatment in primary nasopharyngeal carcinomas; whereas, surgery is reserved for persistent or recurrent loco-regional

tumor⁴. In our institute, patients with early stage are usually treated with radiotherapy alone but some patients with early stage, including healthy for chemotherapy and huge primary tumor (T), are considered for concurrent chemoradiotherapy. Furthermore, patients with advanced stage could be treated with concurrent chemoradiotherapy; however, the treatment outcomes for advanced NPC remain unsatisfactory. The 5 years OS were 45.8-80% and 28-61% in NPC stages III and IV, respectively²⁰⁻²⁴. Similarly, our study showed 5 years OS that 48.6% in stage III, and 32.7% in stage IV. The current understanding of molecular target in cancer has been purposed; therefore, the target NPC therapies have enabled to develop for improvement of treatment outcomes.

In present, concurrent chemoradiotherapy could be considered for NPC stage II. Cheng, et al²⁵ compared the efficacy between radiation alone and combined with chemotherapy in early stage NPC. The result was demonstrated that excellent prognosis of stage II NPC treated with concurrent chemoradiotherapy and an equal disease-free survival as stage I NPC treated with radiotherapy alone. In our series, the 2 years survival of stage II NPC was worse than stage III; therefore, concurrent chemoradiotherapy is alternative option to improve outcomes stage II. In additional, staging is the most important for choosing treatment strategy; thus, could be pay attention and careful. The missing staging will affect to poor treatment outcomes.

According gender, previous studies reported slightly better long term survival rates of NPC in female than male. Kawashima, et al¹⁷ reported a significantly higher 5-year OS for female patients compared to male patients ($p = 0.032$). Dou, et al²⁵ also reported a significantly better 5-year OS in female (85.73%) than male (62.85%) ($p = 0.004$). These results were similarly observed in our study that 5-year OS in female was better than male ($p=0.011$); therefore, suggesting that gender was an independent prognostic factor affecting OS²⁶.

Furthermore, age was also observed to be independent prognostic factor affecting the long term survival of NPC patients. The younger patients seem to

achieve the better results. Many literatures reviewed the 5 years OS in young patients that were satisfied results of 52-77%²⁷. Phua, et al²⁸ showed the risk of death within five years for NPC patients older than 70 years of age was 3.18 times that of patients younger than 50 years of age. Dou, et al²⁶ reported that the 5 years OS in patients older than 50 years of age was significantly lower than in patients younger than 50 years of age ($p=0.019$). In our study, the 5 years OS was demonstrated that elderly patients than 40 years of age were significantly lower than younger than 40 years of age ($p = 0.010$). However, Adham, et al²⁷ reported the poor treatment outcomes and 5 years OS in young NPC patients of 16-38% for patients without distant metastasis. This result might be caused by the late stage of initial presentation, insufficient treatment compliance, and poor follow up.

The main limitation of our study was its retrospective nature. There were 25.4% of all patients who were unable identified staging due to missing data; however, our results were closure to the other international literatures.

Conclusion

Age, gender, and clinical staging may be independent prognostic factors affecting OS of NPC patients, especially clinical staging. Awareness of physicians, patients and public health are the key point to allow the earlier diagnosis and treatment that achieve the excellent outcomes.

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