นิพนธ์ต้นฉบับ . Original Article

ผลกระทบของการส่งต่อผู้ป่วยต่อการรอดชีพของผู้ป่วยมะเร็งศีรษะและคอที่รับการรักษา ที่โรงพยาบาลขอนแก่น ประเทศไทย

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Impact of Referring on Survival of Patients with Head and Neck Cancer Treated in Khon Kaen Hospital, Thailand

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บทคัดย่อ

หลักการและวัตถุประสงค์: จากข้อจำกัดด้านศักยภาพในการรักษามะเร็งศีรษะและคอทำให้ผู้ป่วยส่วนใหญ่ที่ได้รับการวินิจฉัยในโรงพยาบาลระดับปฐมภูมิจำเป็นต้องถูกส่งต่อไปรับการรักษาในโรงพยาบาลที่มีศักยภาพสูงกว่าซึ่งอาจทำให้ระยะเวลารอการรักษานานขึ้น ในการศึกษาครั้งนี้ มีวัตถุประสงค์เพื่อเปรียบเทียบการรอดชีพของผู้ป่วยมะเร็งศีรษะและคอที่มีภูมิลำเนาในจังหวัดขอนแก่นกับที่ส่งต่อมาจากโรงพยาบาลอื่น ที่ได้รับการรักษาในโรงพยาบาลขอนแก่น

วิธีการศึกษา: ข้อมูลผู้ป่วยมะเร็งศีรษะและคอที่รักษาในโรงพยาบาลขอนแก่นระหว่างปี พ.ศ. 2555 ถึง 2560 โดยเก็บข้อมูลจากทะเบียนมะเร็งและวิเคราะห์การรอดชีพของผู้ป่วยที่มีภูมิลำเนาในจังหวัดขอนแก่นกับผู้ป่วยที่ถูกส่งต่อจากโรงพยาบาลอื่น

ผลการศึกษา: จากการศึกษาข้อมูลผู้ป่วยมะเร็งศีรษะและคอทั้งหมด 927 ราย ในช่วงอายุระหว่าง 40-80 ปี ส่วนใหญ่เป็นเพศชาย (ร้อยละ 60) ตำแหน่งที่พบมากที่สุด คือ ช่องปาก (ร้อยละ 38.2) คอหอยส่วนจมูก (ร้อยละ 30.9) กล่องเสียง คอหอยส่วนกล่องเสียง (ร้อยละ 14.4) และคอหอยส่วนปาก (ร้อยละ 9.9) ตามลำดับ โดยพบว่า ผู้ป่วยจำนวนมากกว่าครึ่งมีภูมิลำเนาในจังหวัดขอนแก่น (ร้อยละ 57.9) สำหรับมะเร็งระยะเริ่มต้น พบว่า ระยะเวลาการรอดชีพของผู้มีภูมิลำเนาจังหวัดขอนแก่นนานกว่าผู้มีภูมิลำเนาจังหวัดอื่นอย่างมีนัยสำคัญ (7.21 และ 3.96 ปี) ส่วนระยะลุกลามพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญ

สรุป: ผู้ป่วยมะเร็งศีรษะและคอระยะเริ่มต้นที่ถูกส่งต่อจากโรงพยาบาลอื่นมีการรอดชีพแย่กว่าผู้ที่มีภูมิลำเนาจังหวัดขอนแก่น ดังนั้นควรส่งเสริมการพัฒนาความสามารถในการรักษาผู้ป่วยระยะเริ่มต้นในโรงพยาบาลระดับจังหวัด

คำสำคัญ: มะเร็งศีรษะและคอ, การรอดชีพ, การส่งต่อ, ประเทศไทย

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Abstract

Background and Objective: Because of the limited treatment facilities in the primary hospital, most head and neck cancer (HNC) patients had to be referred to higher centers lead to long waiting time. The aim of this study was to compare the survival of patients with HNC treated at Khon Kaen Hospital, between those who resided in Khon Kaen and those who were referred from outside.

Methods: A retrospective cohort study was conducted. The data of HNC patients treated at Khon Kaen Hospital between 2012 and 2017 were obtained from a hospital-based cancer registry. Survival analysis was performed to compare the patients residing in Khon Kaen province with those referred from outside.

Results: A total of 927 cases were retrieved, with age between 40 and 80 years, 60% were male. Cancer of oral cavity was the most common site (38.2%), followed by nasopharynx (30.9%), larynx and hypopharynx combined (14.4%) and oropharynx (9.9%). More than half of the patients resided in Khon Kaen province (57.9%). For early-stage cancer, median survival time was significantly better in the residence group than in the referring group (7.21 and 3.96 years, respectively). Likewise, in the advanced stage, median survival time and observed survivals were not significantly different.

Conclusions: Referring of early-stage HNC cases results in a poorer survival for patients compared with those treated within the area of their residences. Therefore, the ability to treat at least an early-stage HNC should be improved in provincial hospital.

Keywords: Head and Neck Cancer, survival, referral, Thailand

Introduction

Head and neck cancer (HNC) is the seventh most common cancer worldwide, with 890,000 new cases and 450,000 deaths in 2018[1].The incidence of HNC is particularly high in South and Southeast Asia[2]. In Thailand, it is one of the five leading cancers, with oral cancer being the most common[3]. The primary modalities for the treatment of HNC consist of surgery and radiotherapy, with systemic therapy gradually gaining importance. Depending on stage and type of cancer, and the patient's conditions, the goals of treatment are to eradicate the disease, preserve organ function and improve quality of life[4–6] .

Since the treatment of HNC is mainly based on surgery and radiotherapy, no significant improvement in survival of HNC has ever been observed. Improvement in survival of the patients with HNC would be likely if they had access to the health care system and could be treated at earlier stage. It is unfortunate that an improvement in survival was not demonstrate for oral cancer after universal coverage was introduced in Thailand[7]. In Thailand, almost all patients with HNC were treated in tertiary or super-tertiary hospitals, with a small number of specialists in this field. Therefore, most patients were referred instead of being treated in local hospitals. It is likely that patients' survival is affected by delayed treatment due to referring time, especially for early-stage cancer where surgery is a primary modality and potentially be treated at the primary hospital. However, the assumption has never been proven. Therefore, the aim of this study was to evaluate the overall survival of patients with HNC treated at Khon Kaen hospital who were residents of Khon Kaen compared to those who were referred from other provinces.

Materials and Methods

This study used a retrospective cohort design, with the data from the hospital-based cancer registry of Khon Kaen hospital, a tertiary center for the treatment of cancer in Khon Kaen province, Thailand. All patients with HNC treated at Khon Kaen hospital during 2012-2017 were included. Cases with histological type of lymphoma were excluded from the cohort. The variables used in the analysis were demographic data including data of birth, age, sex, residence; and clinical data including cancer sites, histopathology, stages, date of diagnosis, date of treatment, and modality of primary treatment. All data were verified by cross checking with other sources, i.e., the hospital cancer registry of Srinagarind hospital, the super-tertiary center for cancer treatment in the same province and the database of the HNC clinic of the Khon Kaen hospital.

The main outcome is death. The last vital status of patients was obtained by linkage with the database of the Bureau of Policy and Strategy, Ministry of Public Health, and the last date of follow up was 31 December 2020.

This study has been considered by the committee of Ethics in Human Research, Khon Kaen University no HE64068

Statistical analysis

Patient demographics and disease characteristics were presented as frequencies and percentages in categorical form. For patient characteristics, a comparison was made between the resident and referring groups on the basis of their residences, using Chi-square test. Survival analysis was performed selectively for all cases with histological confirmation of squamous cell carcinoma. The start date was defined by the date of clinical diagnosis. The end of follow-up was on 31 December 2020. The last date of follow up was the date of death, the censored date, or the end of follow-up, which ever occurred first. The Kaplan-Meier method was used to estimate overall survival, and the Log-rank test was used to compare HNC survival between resident and referring groups. The p-value < 0.05 was considered statistically significant. Median survival time was also reported with 95% confidence intervals. All statistical analyses were performed using STATA version 10.1.

Results

Between 2012 and 2017, a total of 927 HNC cases were treated at Khon Kaen hospital. The majority of patients were male and aged between 40 and 80 years. Cancer of the oral cavity was the most common site (38.2%), followed by nasopharynx (30.9%), larynx and hypopharynx combined (14.4%). Squamous cell carcinoma was the most common histopathology type (83.3%), and more than 70% of patients were at an advanced stage. More than half of the patients with HNC were in the resident group (57.9%). In the referring group, most cases (20.4%) were from Mahasarakam province, which is the closest to Khon Kaen (Table 1).

Patients' characteristics were comparable between the resident and referring groups, with a slightly higher proportion of males in the resident group (Table 2).

The longest median survival time was found for cancer of the major salivary glands (3.6 years), followed by nasopharynx (2.3 years). The shortest median survival time was found in cancer of the oropharynx (0.99 years), followed by the larynx and hypopharynx combined (1.21 years) (Table 3, Figure 1).

For early-stage cancer, the median survival time of patients in the resident group was significantly better than that of the referring group (7.21 and 3.96 years, respectively). Similarly, the 5-year survival rate in the resident group was 64.9% (95% CI 54,45 – 73.53) which better than the referring group, 40.13% (95% CI: 27.17 - 52.74, p = 0.01 (Table 4, Fig 2A). In the advanced stage, median survival time and observed survival rate were not significantly different (p = 0.07) (Table 4, Fig 2B).

Table 1 Characteristics of the HNC patients treated at Khon Kaen hospital

Characteristics	Number (n=927) N (%)
Gender	
Male	555 (59.87)
Female	372 (40.13)
Age (years)	
< 20	6 (0.65)
20 - 40	67 (7.23)
40 - 60	399 (43.04)
60 - 80	364 (39.27)
> 80	91 (9.82)
Residence	
Khon Kaen	537 (57.93)
Outside Khon Kaen	390 (42.07)
Mahasarakam	189 (20.39)
Roi-Ed	12 (1.29)
Kalasin	88 (9.49)
Chaiyapoom	54 (5.83)
Others	47 (5.07)
Primary site	
Oral cavity	355 (38.3)
NPC	286 (30.85)
Oropharynx	91 (9.82)
Larynx/Hypopharynx	135 (14.56)
Nose & PNS	23 (2.48)
Major salivary gland	37 (3.99)
Staging	
I	78 (8.41)
II	113 (12.19)
III	157 (16.94)
IV	380 (40.99)
Unknown	199 (21.47)
Pathology	
SCCA (all SCCA)	770 (83.06)
Other non-SCCA	157 (16.94)

Table 2 Characteristics of the HNC patients comparing between cases resided

Characteristics	Local n (%)	Referral n (%)	Overall n (%)	p-value
Gender				
Male	343 (63.87)	212 (54.36)	555 (59.87)	0.004
Female	194 (36.13)	178 (45.64)	372 (40.13)	
Age (years)				
< 20	2 (0.37)	4 (1.03)	6 (0.65)	0.496
20 - 40	39 (7.26)	28 (7.18)	67 (7.23)	
40 - 60	241 (44.88)	158 (40.51)	399 (43.04)	
60 - 80	202 (37.62)	162 (41.54)	364 (39.27)	
> 80	53 (9.87)	38 (9.74)	91 (9.82)	
Primary site				
Oral cavity	204 (37.99)	151 (38.72)	355 (38.3)	0.239
NPC	159 (29.61)	127 (32.56)	286 (30.85)	
Oropharynx	51 (9.5)	40 (10.26)	91 (9.82)	
Larynx/Hypopharynx	91 (16.95)	44 (11.28)	135 (14.56)	
Nose & PNS	11 (2.05)	12 (3.08)	23 (2.48)	
Major salivary gland	21 (3.91)	16 (4.1)	37 (3.99)	
Staging				
Early	107 (19.93)	84 (21.54)	191 (20.6)	0.777
Advanced	316 (58.85)	221 (56.67)	537 (57.93)	
Unknown	114 (21.23)	85 (21.79)	199 (21.47)	
Pathology				
SCCA	445 (82.87)	325 (83.33)	770 (83.06)	0.852
Other non-SCCA	92 (17.13)	65 (16.67)	157 (16.94)	

Khon Kaen province and those referred from the outside.

*p-value form chi-square test

Table 3 Survivals of the HNC patients by sites

Primary sites	Median survival time (year) (95% CI)	Observed survival rate (95% CI)		
		1-year	3-year	5-year
Oral cavity	1.37 (1.14 - 1.81)	59.13 (53.72 - 64.12)	37.08 (31.85 - 42.31)	28.94 (23.86 - 34.2)
NPC	2.26 (1.94 - 2.95)	74.43 (69.03 - 79.04)	42.98 (37.17 - 48.64)	31.73 (26.18 - 37.4)
Oropharynx	0.99 (0.74 - 1.42)	48.17 (37.66 - 57.91)	30.61 (21.33 - 40.36)	24.45 (15.7 - 34.24)
Larynx/Hypopharynx	1.21 (0.92 - 1.71)	56.26 (47.61 - 64.02)	23.13 (16.37 - 30.59)	15.58 (9.9 - 22.42)
Nose & PNS	1.48 (0.44 - 5.65)	68.18 (44.62 - 83.38)	44.32 (23.16 - 63.58)	35.45 (14.42 - 57.4)
Major salivary glands	3.56 (1.94 - NA) *	71.67 (53.63 - 83.69)	53.59 (35.67 - 68.56)	43.28 (24.36 - 60.86)

* Number of deaths in major salivary glands was insufficient to calculate the upper limit of 95% CI

Table 4 Survivals of the HNC patients comparing between cases resided in Khon Kaen province, and those referred from outside.

Stage	Median survival time (year) (95% CI)	Observed survival rate (95% CI)		
		1-year	3-year	5-year
Early stage				
Local	7.21 (5.56 - NA)	85.05 (76.42 - 90.71)	66.1 (55.73 - 74.59)	64.9 (54.45 - 73.53)
Referring	3.96 (1.97 - 5.75)	78.57 (66.91 - 86.52)	52.69 (39.45 - 64.31)	40.13 (27.17 - 52.74)
Advanced stage				
Local	1.54 (1.15 - 1.77)	60.87 (55.19 - 66.06)	29.9 (24.82 - 35.12)	21.88 (17.18 - 26.95)
Referring	1.33 (1.12 - 1.68)	59.26 (52.27 - 65.58)	30.03 (23.81 - 36.47)	21.03 (15.43 - 27.23)

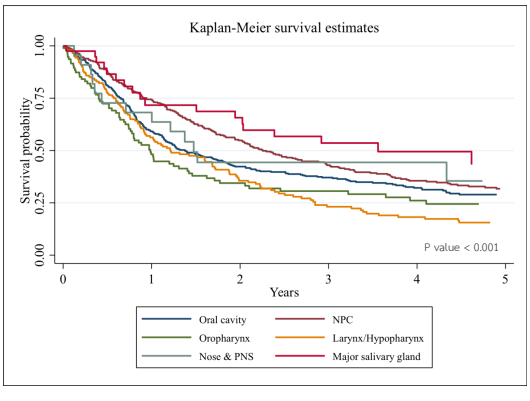
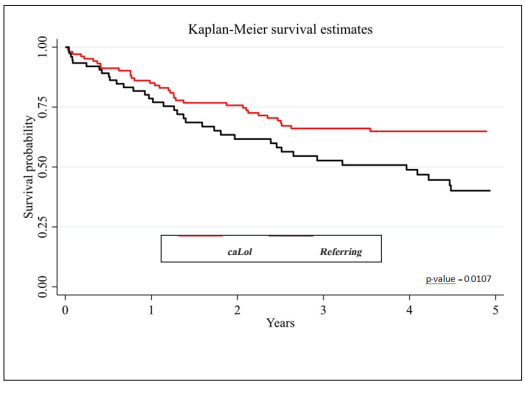


Figure 1 Kaplan-Meier survivals of the HNC by sites

2A



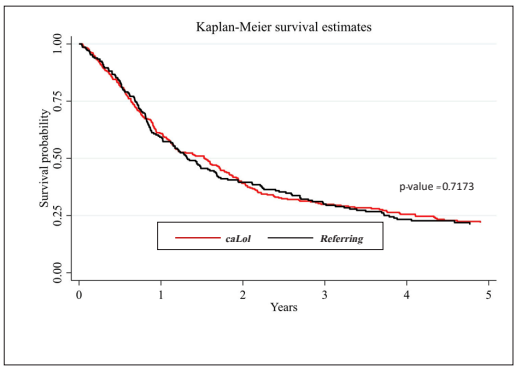


Figure 2 Kaplan-Meier survivals of the HNC 2A for early stage and 2B for advanced stage, comparing between cases resided in Khon Kaen (local), and those referred from outside (referring), with log rank test.

2B

Discussion

This study demonstrates the results of treatment of HNC in a super-tertiary center in northeast Thailand, the largest region where one-third of the Thai population lives. The distribution of cancer sites consistent with the incidence at the population level[7]with oral cancer being the most common. Although, universal health insurance has been introduced in Thailand where medical costs for all Thai citizens are covered by the government, majority of cases were still diagnosed at an advanced stage. This explains why the survivals observed in this study is lower than in developed countries[8] .

For almost all cancers, treatment at an early stage is certain to result in a better outcome than at an advanced stage[9]. This study showed that patients with early-stage HNC who resided in the area to be treated at the center have a survival advantage compared to the referred patients. These survival disparities were not found for advanced stage. In addition, the distribution of cancer primary sites between local and referring cohorts were comparable. In fact, the patients referred from other hospitals required additional process for investigation and patients' preparation for treatment.

The Thai health care system forces patients to follow the referring pathway to be accepted into the health care system. By shortcutting the referring route and going directly to the super-tertiary center, the government coverage was discarded, and the patients had to pay their own medical cost. As a result, patients living in areas with inadequate cancer facilities are at risk of a worse prognosis for their diseases, especially in early stage of cancer. This finding is an evidence supporting the current trend of cancer care toward decentralization in a situation with limited resources[10,11]. However, a standard for quality care services should be maintained to ensure that the management is adequately carried out at least in an oncological aspect.

It is unfortunate that there is no effective screening program for HNC. Therefore, cancer control for HNC depends solely on early diagnosis and effective treatment. The main treatment method for HNC is surgery followed by radiation. The ecological study showed that an increase in the number of surgical workforces correlated with a decrease in the mortality-incidence ratio of the HNC[12]. In Thailand, HNC are mainly treated surgically by otolaryngologists, although plastic and reconstructive surgeons and oral and maxillofacial surgeons also contribute to the treatment of oral cancer in some hospitals. However, almost all surgeons involved in head and neck oncology are found only in university hospitals and a few super-tertiary hospitals with irregular distribution. The national database showed that more than 60% of head and neck surgical procedures were performed in the central region, which is at odds with the distribution of the population[13]. The shortage of manpower for head and neck surgery leads to overwhelming cases being referred in many centers, which affects survival, especially for early-stage cancer. This leads not only to poor cancer outcome but also to higher healthcare costs when the disease turns advanced[14]. Therefore, there is an urgent need to promote the head and neck surgery training program and provide positions for those areas with sparse head and neck surgeons. Another option is to encourage otolaryngologists to adequately treat early-stage cancer or non-complicated cancer case in their areas, to improve head and neck cancer control outcomes at the population level.

This study showed the situation of cancer treatment in Khon Kaen hospital in a setting with universal coverage scheme where referring pathways in the health care system are clear. However, some limitations remain. First, the number of cases was not sufficient to show the impact on each cancer site. Therefore, we instead presented all cancer sites combined. However, the effect of variance could be minimal because the distribution of cancer sites and stage was comparable between the two comparison

groups. Second, waiting time was not included in the analysis. Therefore, we could not draw a firm conclusion on the effect of referring on waiting time. However, in a similar health care system in the United Kingdom, the two-week waiting time model did not show survival benefits[15]. Third, overall survival is a main outcome for this study due to limited information of the mortality data, however the comparison was made within the study cohorts. Thus, the finding from this study can suggest direction of the difference.

In conclusion, referring of early-stage HNC cases results in a poorer survival for patients compared with those treated in their place of residence. Therefore, the referring system needs to be improved for shortening unnecessary process before treatment. Moreover, the capacity to treat early stage HNC should be improved to reduce unnecessary referring. In addition, training for head and neck surgical oncology is urgently needed to ensure adequate distribution of the head and neck surgeons. Further studies are needed to explore potential causes of this disparity and model for improving healthcare system for cancer.

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