RESEARCH ARTICLE

# Incidence and Survival Rates among Pediatric Osteogenic Sarcoma Cases in Khon Kaen, Thailand, 1985-2010

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## Abstract

**Background: Osteosarcoma is the most common bone cancer in children, responsible for a high rate of amputation and death. This is the first long-term, population-based, epidemiologic and survival study in Thailand. Objective: To study the incidence and survival rates of pediatric osteosarcoma in Khon Kaen. Method: Childhood osteosarcoma cases (0-19 years) diagnosed between 1985-2010 were reviewed. The data were retrieved from the population-based data set of the Khon Kaen Cancer Registry and medical records from Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. All cases were censored until the end of April 2012. The age-standardized incidence rate (ASR) was calculated using the standard method. Survival experience was analyzed using the standard survival function (STATA 9.0) and presented with a Kaplan-Meier curve. Results: 58 cases were enrolled. The overall ASR was 14.1 per million. Males and females were equally affected. The peak incidence was for 15-19 year-olds in both sexes (ASR=10.4 per million in males and 8.5 in females). The 5-year overall survival rate was 27.6% (95% CI: 15.8-40.8%). The median survival time was 1.6 years (95% CI: 1.2-2.1). In a subgroup analysis, the patients who received only chemotherapy survived longer (5-year survival 45.7%, median survival time 4.1 years, p=0.12). Conclusion: The incidence rate for childhood osteosarcoma was slightly less than those reported for Western countries. The survival rate was also lower than reports from developed countries. Further evaluation of the treatment protocol and risk factor stratification is needed.**

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## Introduction

Osteosarcoma is the most common primary bone sarcoma. It remains a common cause of limb amputation among the young and it has a poor treatment outcome among affected patients. According to the Thai Pediatric Oncology Study Group, it comprises 2.4% of all childhood cancers with an incidence of 1.9 per million (Wiangnon et al., 2011). The world incidence for males was 4.2 per million and 3.4 for females (Mirabello et al., 2009). Individuals with localized disease have an average 5-year survival of about 80%, but those with metastasis have a much poorer outcome (Picci et al., 2010). The survival rate has improved overtime (Allison et al., 2012).

Khon Kaen is located in the northeastern region of Thailand. The Khon Kaen Cancer Registry (KKCR) was established in 1984. It provides the data of prolonged cancer registration. Despite its longstanding operation, no information on childhood osteosarcoma has been reported previous to the current review.

## Materials and Methods

Childhood osteosarcoma cases, between 0-19 years of age, diagnosed between January 1985 and December 2010 were reviewed. The data were retrieved from the population-based data set of KKCR. The medical records of Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, were reviewed for more detail.

The osteosarcoma cases were classified according to the International Classification of Disease for Oncology Version 3 (ICDO-3, code 9180-9200). To ensure that all of the population-based cases in Khon Kaen were covered, a case-matching search was done concomitantly with a data set from the Bangkok Cancer Registry from the National Cancer Institute and from the Udonthani Cancer Registry (a provincial cancer center north of Khon Kaen). Patient status was verified by searching the Thailand National Statistical Office website for the data from the Bureau of Registration Administration (BORA) using each patient's personal identification number. All cases were censored until the end of April 2012.

Incidence rates were estimated using the standard method according to the age-standardized population (vis-à-vis the world population) and presented as a rate per million (Parkin et al., 1998). The numbers of the Khon Kaen population were extrapolated from the Thailand National Census (Thailand National Statistical Office,

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2003). The survival experience was analyzed using the standard survival function in STATA 9.0 and presented on a Kaplan-Meier curve with the 'number at risk' at different points in time. The survival experiences for each treatment group were compared using the Log-rank and Wilcoxon test.

## Results

Over the 26 years included in the study, 58 cases of pediatric osteosarcoma were included (29 males; 29 females). The respective mean and median age at diagnosis was 14.6 (SD=3.7) and 15 years (range 4-19). The disease commonly affected teenagers and young adults; with 58.6% of sufferers being between 15-19 years of age. Eight cases were lost to follow up and 36 died. The most common primary site was at the long bone of the lower limb (82.8%). There were no primary tumors at the skull, facial bones or vertebrae. Fifty-five cases had been microscopically verified (94.8%). Due to the inherent limitations of population-based registration data, the majority of cases were not classified by staging (68.9%). Fifteen patients were not treated, 15 had undergone both amputation and chemotherapy, while 15 had amputation only and 13 chemotherapy only (Table 1).

*Incidence*

The majority of patients were older than 10 years of age: the most commonly affected age were persons between 15-19 years (58.6%). There was only one case under 5 years of age. The overall ASR was 3.1 per million. The respective ASRs of patients between 0-4, 5-9, 10-14 and 15-19 years of age were 0.3, 1.2, 4.1 and 8 per million (Table 2).

*Survival*

With respect to the total group of patients (58 cases), there were 2,641.7 months of time at risk, with an incidence density of 1.4 per 100 person-months. The respective mean and median follow-up time of the patients in this study was 45.5 months (SD=75.3) and 15.9 months (0.03-296.1 months). The median survival time was 19.1 months (95% CI: 14.1-25.6). The respective overall survival at 1, 3, 5 years of age was 67.7%, 32.5% and 27.6%. After 5 years, the survival rate remained stable (Figure 1A). Females had a slightly better 5-year survival than males (33.3% vs. 21.7%, p=0.76). Survival of patients with a primary site at the upper limb was similar to those with a primary at a lower part of the body. The respective median survival time was 1.5 and 1.7 years (p=0.59).

According to treatment modality, 15 cases (25.9%) underwent only an amputation, while 13 (22.4%) received only chemotherapy and 15 received both modalities. Notably, 15 cases had no curative treatment.

Considering survival in terms of surgery, the median survival of patients who underwent vs. who did not undergo amputation was 1.7 and 1.4 years, respectively (p=0.96), while the respective 5-year survival was 24.1% and 33.5%.

With respect to chemotherapy, the respective median survival time and 5-year survival was 1.9 years and 33.8%, while for those in the non-chemotherapy group it was 1.2 years (p=0.05) and 20.2%.

In the subgroup analyses, patients were categorized

**Table 1. Characteristics of Osteosarcoma Patients**

| | Number of cases | | |
|---|---|---|---|
| Demographics | Males | Females | Total |
| Sex | 29 (50%) | 29 (50%) | 58 (100%) |
| Age (years) | | | |
| 0-4 | 0 | 1 | 1 (1.7%) |
| 5-9 | 2 | 3 | 5 (8.6%) |
| 10-14 | 7 | 11 | 18 (31.1%) |
| 15-19 | 20 | 14 | 34 (58.6%) |
| Primary site | | | |
| Long bone of upper limb | 1 | 2 | 3 (5.2%) |
| Long bone of lower limb | 25 | 23 | 48 (82.8%) |
| Short bone of upper limb | 0 | 1 | 1 (1.7%) |
| Short bone of lower limb | 1 | 1 | 2 (3.5%) |
| Pelvic bone and sacrum | 1 | 0 | 1 (1.7%) |
| Unknown | 1 | 2 | 3 (5.2%) |
| Staging (Enneking system) | | | |
| I | 0 | 0 | 0 |
| II | 2 | 0 | 2 (3.5%) |
| III | 10 | 6 | 16 (27.6%) |
| Unknown | 17 | 23 | 40 (68.9%) |
| Treatment modality | | | |
| Amputation only | 9 | 6 | 15 (25.9%) |
| Chemotherapy only | 8 | 5 | 13 (22.3%) |
| Chemotherapy and amputation | 8 | 7 | 15 (25.9%) |
| None | 4 | 11 | 15 (25.9%) |

**Table 2. Age Standardized Incidence Rate (ASR per million persons per year)**

| | Males (n) | ASR | Females (n) | ASR | Both sexes (n) | ASR |
|---|---|---|---|---|---|---|
| Age group (years) | | | | | | |
| 0-4 | 0 | 0 | 1 | 0.6 | 1 | 0.3 |
| 5-9 | 2 | 1 | 3 | 1.4 | 5 | 1.2 |
| 10-14 | 7 | 3.3 | 11 | 5 | 18 | 4.1 |
| 15-19 | 20 | 9.4 | 14 | 6.6 | 34 | 8 |
| Total | 29 | 3.1 | 29 | 3.1 | 58 | 3.1 |

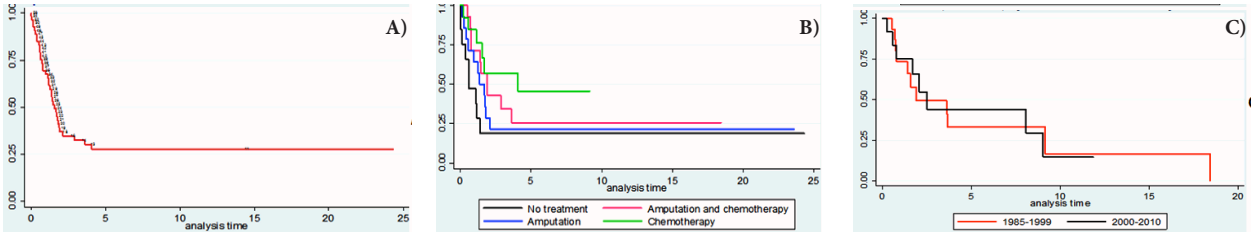


**Figure 1. Kaplan-Meier Survival Curves for Children with Osteosarcoma in Khon Kaen.** A) Overall Survival of Children with Osteosarcoma, B) Survival Curve of Each Treatment Group and C) Survival by Treatment Regimen Before and After 2000.

according to treatment modality. The respective median survival time was 0.6, 1.4, 4.1 and 1.9 years (p=0.12) for patients not receiving treatment, amputation only, chemotherapy only and both, while the respective 5-year survival was 18.9%, 21.4%, 45.7 and 25.7% (Figure 1B). Survival was also studied vis-à-vis patients limited to Srinagarind Hospital. Before 2000, the chemotherapy regimen for osteosarcoma comprised cisplatin, etoposide, ifosphamide and doxorubicin. After 2000, it was changed to a high-dose, methotrexate-based combination. Interestingly, survival was initially better in the latter (median survival time was 1.9 vs. 2.5 years (p=0.94), while 5-year overall survival was 33% vs. 43.8%); however, respective survival was similar in the long term (10 years) (Figure 1C).

## Discussion

AOsteosarcoma is a rare cancer among children and yet it is the most common primary bone cancer resulting in limb amputation and high mortality. It is the 8th most common childhood cancer in Thailand according to the aged-standardized rate (ASR) of 1.9 per million (Wiangnon et al., 2011).

The authors used the population-based registration data from the Khon Kaen Cancer Registry (KKCR), established in 1984, to study the incidence and long-term outcomes. The overall ASR was slightly lower than those reported for Western (ASR 3.9-5) and Asian countries (ASR 3.2-6.7) (Ries et al., 1999; Mirabello et al., 2009). Nevertheless, the age distribution was comparable to other studies.

In the current study, the peak incidence was in the adolescent age group (ASR 8) which accords with other reports from around the world (ASR 8-12) (Ries et al., 1999; Mirebello et al., 2009). It is rare in the younger age group <5 years; in whom the ASR has a similar incidence as the US population (ASR 0.3) (Ries et al., 1999; Mirebello et al., 2009).

In general, osteosarcoma is found predominantly in males and yet unlike other studies, we found males and females were equally affected.

According to the inherent limitations of population-based data, we could not specify the affected bone. Relatedly, the data on correct staging as per imaging of the chest by computer topography was limited because of a lack of equipment in the early years. Nevertheless, microscopic verification was within acceptable limits (94.8%).

The overall 5-year survival rate in our population was relatively poor compared to the rates reported in the USA (27.6 VS 50-63%) (Mirabello et al., 2009). In our practice (at a tertiary care centre), patients often present with an advanced stage and many patients refuse surgery. Treatment with any modality has a better outcome than no treatment. In addition, in early years patients with a low socioeconomic status might not fully access treatment at an early stage of disease. Since 2001, the Thai government has implemented a universal health security service. Thus, all patients can now receive early treatment; notwithstanding, latter period survival has not significantly improved.

After high-dose methrotrexate was introduced as the standard regimen in 2000, the 5-year survival rate improved from 33% to 43.3% initially but this result was not statistically significant in the long-term follow-up. The initial survival seems better than for those of the previous outcome, but the survival returned to the same lower rate because of recurrence of metastatic disease in the lung. Thus, the efficacy of high-dose methrotrexate must be reconsidered. A recent study shows that a cisplatin-based regimen was a good alternative to a high-dose methotrexate-based regimen with less toxicity and no need for pharmacokinetic monitoring (Daw et al., 2011).

Other factors that affected the prognosis included: site of metastasis, histopathologic type, percentage of tumor necrosis after chemotherapy, margin of resected tumor, and surgical technique (Davis et al., 1994). In the current study, we did not evaluate these factors. To improve the treatment outcome, risk stratification must be taken into account. Initial imaging of the chest to specify staging is also needed. Some of our patients could not be evaluated because of incomplete data. Further study is needed to thoroughy evaluate all factors.

To enhance treatment outcomes, not only needs the improvement of treatment modalities, but supportive care must be improved to ensure that the complications and side-effects of aggressive therapies are mitigated.

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