

Clinical Outcomes of Cervical Node Metastasis from an Unknown Primary in Songklanagarind Hospital

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Objective: To study the clinical outcomes of cervical lymph node metastases from an unknown primary site.

Material and Method: A retrospective review of 139 patients diagnosed with cervical neck node metastases from an unknown primary site in Songklanagarind Hospital between 2000 and 2010 was included. The data of patient and tumor characteristics, diagnostic procedures, and treatment outcomes were recorded. The disease-free and overall survival rates were calculated.

Results: Age ranged from 33 to 95 years with male predominance in 121 patients (87%). The majority of histological finding was squamous cell carcinoma and poorly differentiated grading was predominant. The 3- and 5-year disease-free/overall survival rates were 55.5/33.9% and 48.6/27.8%, respectively. The survival rate was lower significantly in level IV, N3 stage, extracapsular spread, and distant metastasis. The surgery followed by radiation seemed to improve the overall survival of 32.6% at five years. By the average follow-up time of 29.8 months, the emerging primary tumor was found in 12 patients (8.6%).

Conclusion: The important prognostic factors are nodal status, metastasis, and extracapsular extension. Panendoscopy is recommended for routine diagnostic work-up, as well as the treatment with surgery followed by radiation is useful for improving the survival outcome.

Keywords: Clinical outcome, Cervical node metastasis, Unknown primary, Occult primary tumor

J Med Assoc Thai 2012; 95 (9): 1200-4

Full text. e-Journal: <http://jmat.mat.or.th>

Cancer of Unknown Primary (CUP) is defined as the histological diagnosis of metastasis with unspecified primary site. It is the seventh most common form of cancers worldwide, and ranks the fourth cause of death from cancers. The CUP accounts for a 3 to 5% of all malignancies^(1,2) and a 5 to 10% of head and neck cancers⁽³⁾. Mostly, patients are the elderly. As well, CUP occurs equally in both men and women. Moreover, the risk factors are still unknown and there are no effectively screening tools. The majority of the histopathological results of CUP are adenocarcinoma (up to 50%) or undifferentiated carcinoma. Less commonly, squamous cell carcinoma, neuroendocrine tumor, lymphoma, or melanoma can also present^(1,2,4).

Cervical lymph node metastasis from an unknown primary constitutes about 10% of all

patients with carcinoma of unknown primary site⁽⁵⁾. The histological result of cervical CUP frequently shows a squamous cell carcinoma (65 to 76%)⁽⁶⁾. Approximately, 10 to 40% of cervical CUP with a full diagnostic workup establishes a clear pathological diagnosis^(3,6,7). Occult primary tumor can predict by the localization of cervical lymph nodes. Metastases in the upper and middle neck (levels I-II-III-V) are generally attributed to head and neck regions (especially from tonsils, tongue base, nasopharynx, or hypopharynx). However, the lower neck (level IV), and supraclavicular involvement are often associated with primary origin outside head and neck regions.

There are several guidelines on the diagnostic management of cervical CUP but they remain debatable. In general, the routine diagnosis workup includes a thorough physical examination, panendoscopy with randomized biopsies, imaging with computerized tomography (CT) or Magnetic Resonance Image. Additionally ipsilateral tonsillectomy, the primary tonsil cancer is found approximately 20 to 40%^(8,9). Some authors suggest bilateral tonsillectomy with 10% of occult contralateral tonsil lesions⁽³⁾. In addition,

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positron emission tomography (PET) or PET/CT seems to be an attractive option for primary tumor detection. With the sensitivity of 62% and specificity of 82%, allows detection of primary tumors in 25% of patients^(5,10). The choices of treatment vary from surgery alone, surgery with additional radiation, primary radiation, and chemoradiation. The standard treatment remains controversial and is different among physicians.

The aim of the present study was to analyze the clinical outcomes of cervical CUP patients treated in last 10-year period.

Material and Method

A retrospective study was conducted. The medical records were included of 139 patients diagnosed with cervical CUP and underwent diagnostic work-up procedures at the Department of Otolaryngology, Songklanagarind Hospital from 2000 to 2010. The incomplete data were excluded from the present study. The present study was approved by the medical ethic committee of the hospital.

The following data were recorded for every patient including age, gender, smoking and drinking history, histological finding and grading, clinical examination, results of diagnostic work-up and treatment, pathological reports, tumor recurrence, emerging primary tumor, last follow-up status and the date of death. The authors defined disease-free survival as the time from the first day of treatment to tumor recurrence, and overall survival as the time from treatment to death of disease.

The statistical analysis was performed using the Epidata software (version 3.1) and R software (version 2.13.0). The Chi-square test or Fishers' exact test was used for comparisons of categorical data. The disease-free and overall survival analysis was analyzed with Kaplan-Meier methods. A p-value of less than 0.05 was statistically significant.

Results

There were 121 males (87.0%) among 139 patients, with the average age of 63.6 years old (range of 33 to 95 years). Metastatic cervical lymph nodes were frequently localized on level II (n = 92), followed by level III (n = 56), IV (n = 40), V (n = 33), I (n = 19) and VI (n = 1). The node sizes were classified as N2 (n = 61), N3 (n = 48) and N1 (n = 24), as shown in Table 1. Only 10 patients (7.2%) had distant metastasis. In 139 patients, squamous cell carcinoma was the most frequent histological finding of 104 (74.8%), followed by undifferentiated

carcinoma in 22 (15.8%), adenocarcinoma in six (4.3%), small cell carcinoma in two (1.4%), metastatic carcinoma in two (1.4%), neuroendocrine tumor in one (0.7%), non-small cell carcinoma in one (0.7%), and the remains had no microscopic result. The histological grading were not recognized in all of the case. The documented report of poorly differentiated was predominant in 26 (18.7%), whereas the lower proportions were moderately differentiated in seven (5.0%), and well differentiated in six (4.3%).

The variety of investigations was conducted. The panendoscopy under general anesthesia was performed in 89 of 139. In those 89 patients, either panendoscopy or guided biopsy was performed in suspected patients in 17. Only 13 underwent panendoscopy, guided biopsy, and CT. Eight had additional ipsilateral or bilateral tonsillectomy. The primary tumor was not found after these diagnostic procedures.

Ninety-six patients underwent treatments including surgery in 17 (12.2%), radiation in 10 (7.1%), surgery and postoperative radiation in 40 (28.7%), surgery and postoperative chemoradiation in 9 (6.4%),

Table 1. Patient characteristics

Characteristics (n = 139)	No. (%)
Male	121 (87.0)
Mean age [range]	63.6 [33 to 95]
Node localization	
Level I	19 (3.7)
Level II	92 (66.2)
Level III	56 (40.3)
Level IV	40 (28.8)
Level V	33 (23.7)
Level VI	1 (0.7)
N stage	
N1	24 (17.3)
N2	61 (43.9)
N3	48 (34.5)
Unknown	6 (4.3)
Histopathology	
Squamous cell Ca	104 (74.8)
Undifferentiated Ca	22 (15.8)
Adenocarcinoma	6 (4.3)
Small cell Ca	2 (1.4)
Other	5 (3.6)

concurrent chemoradiation in five (3.5%), and palliative radiation in 15 (10.7%). The remaining 43 patients (30.9%) had no treatment.

On 66 patients, an ipsilateral neck dissection was mostly performed on 65. The radical neck dissection technique was done on 46, followed by modified neck dissection of 19, and selective neck dissection of one. The positive dissected nodes ranged from 0 to 48 nodes (mean 4.9 nodes). Only 23 cases had the extracapsular spread.

Of the 96 treated patients, 30 (21.6%) developed recurrent disease in the follow-up time. There was local recurrent (n = 16), regional recurrent (n = 3) and distant metastasis (n = 11). The first recurrence time was 12.8 months (0.5 to 52.3). This occurred in 19 patients (63.3%) within the first year after diagnosis. Seven (23.3%), two (6.6%), and one patients (3.3%) developed recurrence after two, three and four years, respectively. Only one case (3.3%) developed after five years. Among these patients, four cases developed the second recurrent disease within an average time of 25.5 months.

The emerging primary tumor was found during the follow-up period in 12 of 139 patients (8.6%) at an average time of 29.79 months (3.88 to 130.43 months) after diagnosis. The primary tumor sites were found in oropharynx (n = 3), nasopharynx

(n = 2), oral cavity (n = 2), esophagus (n = 2), larynx (n = 1), ethmoid sinus (n = 1) and nasal cavity (n = 1). There was no second primary tumor diagnosed.

In general, the 3- and 5-year disease-free/overall survival rates were 55.5/33.9% and 48.6/27.8%, respectively. There were significantly worsen survival outcomes according to level IV node, N3 stage, distant metastasis and extracapsular spread, as shown in Table 2.

For the treatment modalities, neck dissection and postoperative radiation seemed to improve the disease-free/overall survival of with 47.3/47.7% and 42.0/32.6% at three and five years. The variety of therapies and its disease-free/overall survival are demonstrated in Table 3, without statistical significances.

Discussion

The 3- and 5-year disease-free survival rates of cervical CUP were 55.5% and 48.6% respectively, while 3- and 5-year overall survival rates were 33.9% and 27.8% respectively. The 5-year overall survival rate in the present study slightly lower than the range of 5-year overall survival rates varies from 36 to 42.7%^(6,7,11).

One-fourth of the patients in the present study were treated by surgery followed by radiotherapy

Table 2. Tumor characteristics and outcome data

Tumor characteristics	3-year DFS (%)	5-year DFS (%)	3-year OS (%)	5-year OS (%)
Level IV node	49.9	49.9	26.8*	10.0*
N1	75.3	66.9	79.3*	65.8*
N2	54.4	48.4	33.5	26.8
N3	69.0*	60.5*	10.9*	5.4*
Extracapsular spread	29.2*	#	1.7*	#
Distant metastasis	50.0	#	21.1*	#

* p < 0.05, # too small number for analysis
DFS = disease free survival; OS = overall survival

Table 3. Treatment modality and outcome data (n = 139)

Treatment modality	No. (%)	3-year DFS (%)	5-year DFS (%)	3-year OS (%)	5-year OS (%)
Surgery alone	17 (12.2)	54.5	43.6	43.9	36.6
Surgery plus postoperative radiation	40 (28.7)	47.3	42.0	47.7	32.6
Surgery plus postoperative chemoradiation	9 (6.4)	66.7	#	59.3	#
Primary radiation	10 (7.1)	50.0	50.0	22.5	22.5

too small number for analysis
DFS = disease free survival; OS = overall survival

to add the positive therapeutic effect. However, the 5-year disease-free survival and overall survival rates were 42.0 and 32.6%, respectively. The 5-year overall survival rate of combined surgery and radiation is relatively low, in contrast with the range of 37 to 63% in western countries^(12,13).

The level IV node metastasis had significantly worst 5-year overall survival rate than other level, as well as the N3 stage had lowest 5-year overall survival rate, comparable with the present study of Issing et al, and Grau et al^(6,11).

In conclusion, the important prognostic factors are nodal status, metastasis, and extracapsular extension. Panendoscopy is recommended for routine diagnostic work-up, as well as the treatment with surgery followed by radiation is useful for improving the survival outcome.

Potential conflicts of interest

None.

References

1. ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of cancers of unknown primary site (CUP). *Ann Oncol* 2001; 12: 1057-8.
2. Pavlidis N, Fizazi K. Carcinoma of unknown primary (CUP). *Crit Rev Oncol Hematol* 2009; 69: 271-8.
3. Kothari P, Randhawa PS, Farrell R. Role of tonsillectomy in the search for a squamous cell carcinoma from an unknown primary in the head and neck. *Br J Oral Maxillofac Surg* 2008; 46: 283-7.
4. Jereczek-Fossa BA, Jassem J, Orecchia R. Cervical lymph node metastases of squamous cell carcinoma from an unknown primary. *Cancer Treat Rev* 2004; 30: 153-64.
5. Calabrese L, Jereczek-Fossa BA, Jassem J, Rocca A, Bruschini R, Orecchia R, et al. Diagnosis and management of neck metastases from an unknown primary. *Acta Otorhinolaryngol Ital* 2005; 25: 2-12.
6. Issing WJ, Taleban B, Tauber S. Diagnosis and management of carcinoma of unknown primary in the head and neck. *Eur Arch Otorhinolaryngol* 2003; 260: 436-43.
7. Christiansen H, Hermann RM, Martin A, Nitsche M, Schmidberger H, Pradier O. Neck lymph node metastases from an unknown primary tumor retrospective study and review of literature. *Strahlenther Onkol* 2005; 181: 355-62.
8. Mendenhall WM, Mancuso AA, Amdur RJ, Stringer SP, Villaret DB, Cassisi NJ. Squamous cell carcinoma metastatic to the neck from an unknown head and neck primary site. *Am J Otolaryngol* 2001; 22: 261-7.
9. Greven KM, Keyes JW Jr, Williams DW III, McGuirt WF, Joyce WT III. Occult primary tumors of the head and neck: lack of benefit from positron emission tomography imaging with 2-[F-18] fluoro-2-deoxy-D-glucose. *Cancer* 1999; 86: 114-8.
10. Nieder C, Gregoire V, Ang KK. Cervical lymph node metastases from occult squamous cell carcinoma: cut down a tree to get an apple? *Int J Radiat Oncol Biol Phys* 2001; 50: 727-33.
11. Grau C, Johansen LV, Jakobsen J, Geertsen P, Andersen E, Jensen BB. Cervical lymph node metastases from unknown primary tumours. Results from a national survey by the Danish Society for Head and Neck Oncology. *Radiother Oncol* 2000; 55: 121-9.
12. Strojjan P, Anicin A. Combined surgery and postoperative radiotherapy for cervical lymph node metastases from an unknown primary tumour. *Radiother Oncol* 1998; 49: 33-40.
13. Wang RC, Goepfert H, Barber AE, Wolf P. Unknown primary squamous cell carcinoma metastatic to the neck. *Arch Otolaryngol Head Neck Surg* 1990; 116: 1388-93.

การศึกษาผลการรักษาทางคลินิกของมะเร็งต่อมน้ำเหลืองที่คอ ชนิดที่ไม่ทราบตำแหน่งปฐมภูมิ ในโรงพยาบาลสงขลานครินทร์

กรองทอง วงศ์ศรีตรัง, สุเมธ เฟื่องกาลุน

วัตถุประสงค์: ศึกษาถึงผลที่ได้รับทางคลินิกของผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองที่คอชนิดที่ไม่ทราบตำแหน่งปฐมภูมิ

วัสดุและวิธีการ: ทบทวนข้อมูลย้อนหลังของผู้ป่วย 139 คน ที่ได้รับการวินิจฉัยมะเร็งต่อมน้ำเหลืองที่คอ ชนิดที่ไม่ทราบตำแหน่งปฐมภูมิ ในโรงพยาบาลสงขลานครินทร์ ตั้งแต่ปี พ.ศ. 2543 ถึง พ.ศ. 2553 โดยเก็บรวบรวมข้อมูลพื้นฐานผู้ป่วย ข้อมูลเกี่ยวกับมะเร็ง ขั้นตอนการตรวจวินิจฉัย วิธีการรักษา และผลที่ได้รับจากการรักษา รวมถึงวิเคราะห์อัตราการปลอดโรค และอัตราการรอดชีวิตของผู้ป่วย

ผลการศึกษา: อายุเฉลี่ยของผู้ป่วย 33 ถึง 95 ปี ส่วนใหญ่เป็นผู้ชายจำนวน 121 ราย (ร้อยละ 87) ส่วนใหญ่ผลการตรวจทางพยาธิวิทยาส่วนใหญ่เป็นมะเร็งชนิด squamous cell และเป็น poorly differentiated อัตราการรอดชีวิตปราศจากโรคที่ 3 และ 5 ปี เท่ากับร้อยละ 55.5 และ 48.6 ตามลำดับ อัตราการรอดชีวิตโดยรวมที่ 3 และ 5 ปี เท่ากับร้อยละ 33.9 และ 27.8 ตามลำดับ อัตราการรอดชีวิตลดลงอย่างมีนัยสำคัญในกลุ่มต่อมน้ำเหลืองตำแหน่งระดับ 4 กลุ่มต่อมน้ำเหลืองระยะ N3 การลุกลามออกนอกแคปซูล และการลุกลามที่ไกล ส่วนการผ่าตัดตามหลังการฉายแสงดูเหมือนทำให้ผลที่ได้รับอัตราการรอดชีวิตที่ 5 ปี เท่ากับร้อยละ 32.6 สำหรับระยะการติดตามเฉลี่ย 29.8 เดือน การปรากฏเนื้องอกปฐมภูมิพบในผู้ป่วย 12 ราย (ร้อยละ 8.6)

สรุป: สถานะต่อมน้ำเหลือง การลุกลามที่ไกล และการลุกลามออกนอกแคปซูล เป็นปัจจัยทำนายสำคัญ การส่องกล้องตรวจควรกระทำเป็นแบบแผนประจำ เช่นเดียวกับการผ่าตัดตามหลังการฉายแสงเป็นประโยชน์ต่อผลที่ได้รับการรอดชีวิต
