RESEARCH COMMUNICATION

# Metastatic Adenocarcinoma to the Cervical Lymph Node: A Significant Proportion of Cholangiocarcinoma in Thai Patients

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## Abstract

**Objective: To determine distribution of the primary site of metastatic adenocarcinoma to the cervical lymph node in Thai population with histological correlation. Materials and Methods: 72 Thai patients with metastatic adenocarcinoma to the cervical lymph node were retrospectively analyzed. Results: Thyroid gland (papillary carcinoma) was the commonest source of tumor (41%), followed by lung (25%), bile duct (17%) and breast (7%). Metastatic cholangiocarcinoma typically produced distinct glandular pattern, and frequently involved the right supraclavicular lymph node. Brush border of the gland-forming tumor cells was a consistent finding in metastatic cholangiocarcinoma, with 100% sensitivity and 97% specificity. Conclusions: Cholangiocarcinoma represents a significant portion of primary tumor in Thai patients with cervical nodal metastasis. This figure may hold true for countries where bile duct malignancy is endemic, and may be of clinical usefulness in identification of primary cancer.**

**Key Words:** Cervical metastasis - adenocarcinoma - primary tumor - cholangiocarcinoma

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## Introduction

Lymph node metastasis is one of the major adverse prognostic factors in all malignant tumors (Giancarlo et al., 1998). The presence or absence of metastatic disease influences not only the treatment plan, but also the outcome of cancer patients (Mamelle et al., 1994; Stevens et al., 1985). Cervical lymph nodes receive lymph drainage from several regions, including the head, neck, thorax, and abdomen. Therefore, lymph nodes in this area can be considered as either regional nodes for some malignancies or as a distant metastatic site for others (Medini et al., 1998; Jereczek-Fossa et al., 2004; Calabrese et al., 2005;). Squamous carcinoma is the most frequent subtype of cervical nodal metastasis, accounting for more than three fourth of the cases, followed by adenocarcinoma, undifferentiated carcinoma and melanoma (Jesse et al., 1973; Templer et al., 1981; Mamelle et al., 1994; Giancarlo et al., 1998; Koivunen et al., 2002;). For metastatic squamous carcinoma, it is well-documented that the head and neck organs are the major source of tumor, followed by the lung (Jesse et al., 1973; Templer et al., 1981; Koivunen et al., 2002; Calabrese et al., 2005). On the other hand, the origin of metastatic adenocarcinoma to the neck node is more complex, and has only rarely been studied (Lee et al., 1991). In addition to the head and neck regions, adenocarcinomas from other sites such as breast, lung, gastrointestinal tract, prostate and gynecologic organs could metastasize via the lymphatic networks to the neck lymph nodes (Lee et al., 1991; Templer et al., 1981; Imamura and Suzuki, 2004; ).

The primary objective of our study was to ascertain the incidence of primary source of metastatic adenocarcinoma to the neck nodes in Thai population, whether it differs from elsewhere, and to assess certain microscopic features that may be useful for prediction of the primary site.

## Materials and Methods

Seventy-two cases of metastatic adenocarcinoma to the lymph nodes of the neck region, with histologically- and/or radiologically-proven primary site, were retrieved from the Pathology File at the King Chulalongkorn Memorial Hospital between the years 2001 to 2004. Clinical data was obtained from the pathology request forms and medical charts. Locations of involved lymph nodes were specified, with respect to the sternocleidomastoid muscle and the internal jugular vein. The greatest diameter of lymph node was recorded, and the largest one measured when multiple. Hematoxylin and eosin-stained sections were reviewed without knowledge of the origin of malignancy.

The following morphologic features were recorded: glandular formation, papillary pattern, tumor necrosis,

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**Table 1. Anatomical distribution of cervical lymph node metastasis**

| Location | Left (primary site) | Right (primary site) | Total (%) |
|---|---|---|---|
| Postauricular | | 1 (thyroid) | 2 (3%) |
| | | 1 (lung) | |
| Upper jugular | | 2 (thyroid) | 2 (3%) |
| Middle jugular | 3 (thyroid) | 1 (thyroid) | 5 (7%) |
| | 1 (bile duct) | | |
| Lower jugular | 1 (bile duct) | 1 (thyroid) | 2 (3%) |
| Supraclavicular | 3 (thyroid) | 6 (thyroid) | 45 (62%) |
| | 3 (breast) | 10 (bile duct) | |
| | 8 (lung ) | 2 (breast) | |
| | 7 (others*) | 6 (lung) | |
| Multiple** | 13 (thyroid) | | 16 (22%) |
| | 3 (lung) | | |

* Consisting of 4 cases of stomach, and one each of colon, pancreas and prostate.**Metastasis identified in more than one lymph node (either ipsilateral or contralateral)

colloid material, nuclear groove, and intranuclear pseudoinclusion. The first three microscopic parameters were scored as ≤50% or >50%. The remaining features were scored as < 10%, 10-25%, >25-50%, >50-75%, and > 75%. Brush border, resembling that observed in the epithelial cell of small intestine, was recorded as presence or absence.

Data was analyzed by statistical program SPSS for Windows (version 11.5). Comparison of the locations and histologic characters, including nodal size, was assessed by chi-square, Fisher's exact and Mann–Whitney U tests when applicable. Confidence intervals were 95%. P value of less than 0.05 was considered to be statistical significance.

## Results

Cases included 33 male (46%) and 39 female (54%) patients, with a mean age of 54 years (range from 23-89 years). Thyroid gland was responsible for the majority of primary site of tumor (30 cases, 41.6 %), followed by lung (18 cases, 25%), bile duct (12 cases, 17%), breast (5 cases, 7%), stomach (4 cases, 5.5%), and one of each (1.5%) of colon, pancreas, and prostate. An average size of the metastatic node from thyroid (1.4 cm) was greater than that of the non-thyroid sources (1 cm) (P < 0.001). Fifty-six cases had single nodal lesion (Table 1), 30 (42%) and 26 cases (36%) of which were on the right and left side of neck respectively. Multiple nodal involvements were found in the remaining (16 cases, 22%).

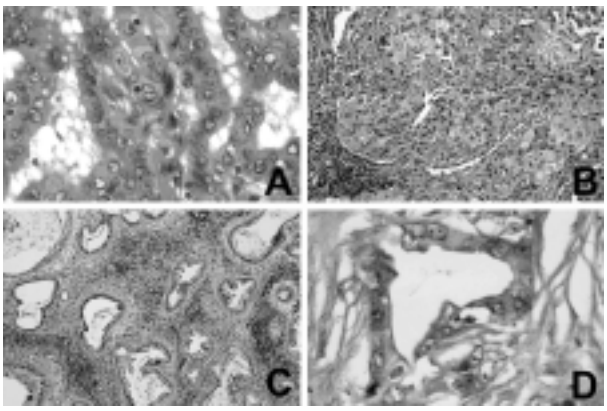


**Figure 1. Metastatic adenocarcinoma to cervical lymph node. Papillary thyroid carcinoma (A) with characteristic nuclear features is shown. Metastastic pulmonary adenocarcinoma (B) is depicted. Note sheeting pattern with minimal gland formation. Metastatic cholangiocarcinoma typically shows well-formed glands (C) with brush border (D). (A-D, hematoxylin and eosin stain)**

In metastatic thyroid subgroup (30 cases), all were of the papillary carcinoma subtype (Figure 1 A). Among these patients, the vast majority (87%) displayed papillary structures in at least 25% of the total tumor volume. Colloid material, nuclear groove and intranuclear pseudoinclusion were present to variable extent, but at least 2 of these 3 microscopic features were identified in all metastatic papillary thyroid carcinomas. Together with the papillary formation, all of these morphological features enabled a firm diagnosis of thyroid origin in all cases (100% sensitivity and specificity).

In metastatic non-thyroid subgroup (42 cases), pulmonary adenocarcinoma represented the most common primary tumors (43%), followed by cholangiocarcinoma (29%), and mammary ductal carcinoma (12%). Primary tumors of the remaining consisted of 4 gastric cancers, and one of each of the colonic carcinoma, pancreatic ductal carcinoma and prostatic adenocarcinoma. Metastatic cholangiocarcinomas tended to involve the right supraclavicular lymph node (10/12 cases, P = 0.0001). Considering histomorphology, metastatic lung cancer (Figure 1. B) displayed smaller amount of both the glandular formation (P = 0.039) and necrosis (P = 0.028), compared to other non-thyroid tumors. The sensitivity and specificity of inconspicuous glandular pattern (less than 50% of the lesion) and uncommon necrosis (less than 50% of the lesion) in detection of metastatic pulmonary carcinoma were 83% and 89%, respectively. In metastatic cholangiocarcinoma, conspicuous glandular arrangement (Figure 1. C) was a significant finding (P < 0.001), with the sensitivity of 83% when present in more than half of the lesion. Brush border (Figure 1. D) was identified in all metastatic lesions from the gastrointestinal tract, but none in the other non-thyroid metastases (100% sensitivity and specificity). This finding was observed in all metastatic cholangiocarcinomas and in 1/4 of metastatic gastric cancer. The sensitivity and specificity for the presence of brush border for detection of bile duct tumors in metastatic non-thyroid cancer were 100% and 97%, respectively.

## Discussion

Neck node metastasis is one of the common manifestations of cancer patients. Since the cervical lymph nodes receive lymph drainage from several parts of the body, most cancers can metastasize to them, and despite extensive investigations with current diagnostic procedures, the primary site of tumor remains unknown in about 5-10% of cases (Jesse et al., 1973; Oen et al., 1995; Hammar, 1998; Medini et al., 1998; Imamura and

Suzuki, 2004; Jereczek-Fossa et al., 2004; Calabrese et al., 2005). In the present study, we focused on metastatic adenocarcinoma to the cervical lymph node. Though, similar to previous studies, thyroid and lung cancers represent the vast majority of primary site (66%), we found that adenocarcinoma of the biliary tract is accounted for a significant proportion in Thai patients (17% of all cases and 29% of non-thyroid metastases) (Oen et al., 1995; Hammar, 1998; Koivunen et al., 2002; Imamura and Suzuki, 2004). Interestingly, cervical lymph node metastasis from cholangiocarcinoma has only rarely been mentioned in the literature, with the first case recently reported in 2002 (Hardeman et al., 2002). The high incidence of cholangiocarcinoma in our patients with cervical metastatic adenocarcinoma is due mostly to the fact that Thailand is one of the endemic areas for the biliary tract malignancy (Nakanuma et al., 2000). The frequency of primary site of metastatic cancer parallels the cancer incidence, and this figure has recently been documented also in the study of metastatic ovarian cancer in Thailand in which a substantial portion of tumor was from the biliary tract tumor (Khunamornpong et al., 2006). This finding may also be true for other regions of the World where bile duct cancer is prevalent (Nakanuma et al., 2000), and may be of clinical usefulness for detection of primary site of cancer. It is also of note that the right supraclavicular lymph node is the most frequent site of metastatic cholangiocarcinoma to the neck.

Although metastatic adenocarcinoma is easily diagnosed by routine pathological examination, it is usually difficult to pinpoint the primary site of cancer, particularly in cases that lack past medical history (Imamura and Suzuki, 2004; Varadhachary et al., 2004; Dennis et al., 2005). This is particular true for non-thyroid tumors, which has no distinctive histologic features. Based on our morphological approach using conventional stain, we found that primary adenocarcinoma of the lung should be suspected when well-formed glands and necrosis are not prominent. Of interest, we demonstrated that all metastatic gastrointestinal tumors have well-developed glands with brush border, and 92% of these lesions were from the biliary tract. Continued study with additional cases and assessment with other techniques, particularly immunohistochemistry, deserve future investigations in our population.

In summary, cholangiocarcinoma is one of the common sources of cervical nodal metastasis in Thai patients. The presence of well-formed glands with brush border is an important histologic clue to suggest gastrointestinal origin of metastatic tumors. The relatively high incidence of biliary tract cancer in this metastatic study may hold true also for other regions of the World where the malignancy is endemic, and may be of clinical value in identification of the primary site of cancer.

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