Anaplastic thyroid carcinoma: updates on WHO classification, clinicopathological features and staging

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DOI: 10.14670/HH-18-277
Article type: REVIEW
Accepted: 2020-11-10
Epub ahead of print: 2020-11-10

This article has been peer reviewed and published immediately upon acceptance. Articles in “Histology and Histopathology” are listed in Pubmed. Pre-print author's version
Anaplastic thyroid carcinoma: updates on WHO classification, clinicopathological features and staging.

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Short title: Anaplastic carcinoma of thyroid
Abstract

Anaplastic thyroid carcinoma is an uncommon carcinoma representing 1 to 4% of all thyroid cancers. The carcinoma is most common in females of the eight decades. It is a locally advanced cancer with frequent infiltration of surrounding organs, blood vessels and skin of neck. Paraneoplastic manifestations could occur. Approximately half of the patients with anaplastic thyroid carcinoma had distant metastasis with lung and brain as the most frequent sites of metastasis. The median survival of patients with anaplastic thyroid carcinoma reported was from 1 to 6 months. The current terminology of the cancer in World Health Organization is “anaplastic thyroid carcinoma” rather than “undifferentiated thyroid carcinoma”. In the latest American Joint Committee on Cancer (AJCC) TNM staging system for anaplastic thyroid carcinoma, there are updates on T and N categories. To conclude, updated knowledge of clinicopathological features, classification, pathological staging will improve our understanding of the cancer and will help in the management of the patients with this aggressive cancer.

Keywords: anaplastic thyroid carcinoma; AJCC; WHO; staging
Introduction

Anaplastic (undifferentiated) thyroid carcinoma is defined as a highly aggressive thyroid malignancy formed of undifferentiated follicular thyroid cells (El-Nagger et al., 2017). Most patients with anaplastic thyroid carcinoma die within a year of diagnosis (Lo et al., 1999; Lam et al., 2000). Recently, the new 4th edition World Health Organization classification for thyroid tumours was issued. Besides the update knowledges of clinical and pathological features of anaplastic thyroid carcinoma, this version of WHO Classification incorporates the new information of the complex genomic profiles of anaplastic thyroid carcinoma which have potential for improvement patient management in the future (El-Nagger et al., 2017; Lam, 2017]. In addition, 8th edition of American Joint Committee on Cancer (AJCC) on pathological staging system was issued in the same year (Michael Tuttle et al., 2017). In this article, we review these data on classification and staging, updated the epidemiology, clinical and pathological features of anaplastic thyroid carcinoma which has impacts on the current management of patients with anaplastic thyroid carcinoma.
Epidemiology

Anaplastic (undifferentiated) thyroid carcinoma is an uncommon carcinoma representing 1 to 4% of all thyroid cancers (Gilliland et al., 1997; Hundahl et al., 1998; Lam et al., 2000; Neff et al., 2008; Pereira et al., 2020), but accounts for 14-39% of thyroid carcinoma deaths (Hundahl et al., 1998; Kitamura et al., 1999). In large studies, the carcinoma is most common in the eight decades (Lo et al., 1999; Lam et al., 2000; Kebebew et al., 2005; Hvilsom et al., 2018). Approximately 75% of patients with anaplastic thyroid carcinoma were older than 65 years (Lo et al., 1999). There were some young patients with anaplastic thyroid carcinoma, whose survival was reported to be better than that of elder patients (Kebebew et al., 2005; Yau et al., 2008; Sugitani et al., 2018).

The incidence of anaplastic thyroid carcinoma appears to decrease recently (Farahati et al., 2019; Pereira et al., 2020). This could be due to two main reasons. Firstly, detection of small thyroid tumours due to the widespread use of ultrasonography which lead to relative increase in more indolent thyroid malignancies such as papillary thyroid carcinoma and decrease in aggressive tumours such as anaplastic thyroid carcinoma. The other reason may be related to the improvement in WHO guidelines and actual pathological knowledge leading to more accurate diagnosis of other thyroid malignancies (such as poorly differentiated thyroid carcinoma, squamous cell carcinoma and lymphoma) instead of mislabelling them as anaplastic thyroid carcinoma.

In a large series of 188 patients with anaplastic thyroid carcinoma from Slovenia, the female to male ratio is 2.2 to 1 (Besic et al., 2005). Overall, the female to male ratio is multiple series were found to be 1.3 to 3.7 to 1. (Lo et al., 1999; Besic et al., 2005; Kebebew et al., 2005; Deeken-Draisey et al., 2018; Hvilsom et al., 2018; Corrigan et al., 2019). There is no ethnics difference in prevalence of the cancer (Gilliland et al., 1997).

A long history of goitre was reported in >30% of patients with anaplastic thyroid carcinoma (Zivaljevic et al., 2014; Paunovic et al., 2015; Steggink et al., 2015). Well-differentiated thyroid carcinomas (papillary thyroid carcinoma, follicular thyroid carcinoma and Hurthle cell carcinoma) are precursors in the development of anaplastic thyroid carcinoma (Aldinger et al., 1978; Smallridge et al., 2012; Pozdeyev et al., 2018;
Yoo et al., 2019). McIver and co-workers showed 23% of patients with anaplastic thyroid carcinoma had a history of well-differentiated thyroid carcinoma (McIver et al., 2001). Poorly differentiated (insular) thyroid carcinoma is also known to be associated with anaplastic thyroid carcinoma (Lam, 2017). Studies showed that 23 to 55% of anaplastic thyroid carcinoma had co-existing differentiated thyroid carcinoma and poorly differentiated (insular) thyroid carcinoma (Lo et al., 1999; Lam et al., 2000; Mohebati et al., 2014).

**Clinical presentation**

Anaplastic thyroid carcinoma is a locally advanced cancer with infiltration of surrounding organs and blood vessels (Neff et al., 2008). Owing to the extremely rapid and aggressive progression of anaplastic thyroid carcinoma, most patients with anaplastic thyroid carcinoma present with rapidly enlarging tumour in the neck. It may also directly infiltrate the skin of the neck. Some patients with anaplastic thyroid carcinoma present with symptoms associated with compression of local structures, which include oesophagus, trachea, and neck vessels, such as dysphagia, dyspnoea, shortness of breath, and hoarseness of voice (Lo et al., 1999; Pierie et al., 2002; Kebebew et al., 2005; Sun et al., 2013; Haddad et al., 2015; El-Nagger et al., 2017). Cervical lymph node and recurrent laryngeal nerve involvement are often detected in patients with anaplastic thyroid carcinoma (Nel et al., 1985; Hadar et al., 1993). It was reported that 29 to 64 % of patients with anaplastic thyroid carcinoma had cervical lymphadenopathy (Lo et al., 1999; Yau et al., 2008; Deeken-Draisey et al., 2018; Hvilsom et al., 2018).

Despite being often having local invasive diseases, distant metastases are also detected in patients with anaplastic thyroid carcinoma. Recent studies showed more patients had distant metastases than those of past studies likely as a result of application of more sophisticated radiological investigations. Approximately half (38 to 55%) of patients with anaplastic thyroid carcinoma had distant metastasis (Lo et al., 1999; Kebebew et al., 2005; Chen et al., 2008; Glaser et al., 2016; Deeken-Draisey et al., 2018; Hvilsom et al., 2018). Lung and brain are the most frequent sites of metastasis (Tan et al., 1995; Besic et al., 2001).
Anaplastic thyroid carcinoma is a non-functioning (hormone secreting) cancer in most instances. A couple of patients with anaplastic thyroid carcinoma presents with thyrotoxicosis (Philip et al., 2007; Daroszewski et al., 2018) which may be related to the rapid destruction of the thyroid by the carcinoma with release of thyroxine. Paraneoplastic manifestations may also present. Becker and co-workers showed 5 of 30 patients with anaplastic thyroid carcinoma presented with ectopic human chorionic gonadotropin (hCG) secretion and their tumours were positive for beta-hCG on immunostaining (Becker et al., 2014). Gu and co-workers showed 3 of 11 anaplastic thyroid carcinomas were positive for beta-hCG and the positive immunoreaction was associated poor prognosis of patients (Gu et al., 2018). Hypercalcemia caused by producing parathyroid hormone-related peptide (PTHrP) were also reported (Yazawa et al., 1995; Iwai et al., 2004). Nakashima and co-workers showed all tumours of 4 patients with anaplastic thyroid carcinoma were positive for PTHrP immunostaining (Nakashima et al., 1995). Patients with anaplastic thyroid carcinoma were reported to present leucocytosis caused by producing granulocyte colony-stimulating hormone, macrophage colony-stimulating factor, or IL-6 (Yazawa et al., 1995; Sato et al., 2000; Kang et al., 2013). Recently, disseminated maculopapular eruption and neutrophilia caused by producing granulocyte macrophage colony-stimulating factor and improved after lenvatinib administration have also been reported (Kasuya et al., 2019). In addition, osteomalasia due to secretion of ectopic fibroblastic growth factor 23 was noted in patient with anaplastic thyroid carcinoma (Abate et al., 2016). Furthermore, hypertrophic osteoarthropathy likely by the effect of secretion of platelet derived growth factor or vascular endothelial growth factor was also reported as paraneoplastic manifestation of anaplastic thyroid carcinoma (Vico et al., 1992).

Neck ultrasound examination usually shows a hypoechoic irregular tumour with or without local invasion and lymph node metastasis. To evaluate the progress of tumour invasion and lymph node metastasis precisely, contrast-enhanced neck computed tomography (CT) is recommended. For evaluation of distant metastases, fluorodeoxyglucose (FDG)- positron emission tomography (PET) and brain magnetic resonance imaging (MRI) are also recommended (Smallridge et al., 2012). Endoscopic examination of the upper aerodigestive tract should be used to assess the extent of the
involvements of adjacent organs or exclude any primary lesions in the upper aerodigestive tract.

Fine needle aspiration biopsy of tumour and/or enlarged lymph node under the guidance of ultrasound should be undertaken for confirmation of diagnosis of anaplastic thyroid carcinoma before planning treatment. Anaplastic thyroid carcinoma should be suspected if there are cells with highly malignant cellular features and overt nuclear pleomorphism (Figure 1). There could be background tumour diathesis, inflammation and marked necrosis. The cellular elements could comprise of epithelioid tumour cells and spindle tumour cells with osteoclast-like tumour giant cells (El-Nagger et al., 2017). It is important to consider the diagnosis of anaplastic thyroid carcinoma in correct clinical settings. Cell block obtained from cytology samples is important as immunohistochemical studies on the cell block is useful to differentiate the tumour from metastatic malignancies (Lam, 2020) (Figure 2).

Because of the extreme aggressiveness of anaplastic thyroid carcinoma, 85% of non-referred patients died within one month and median survival could be as low as days (Chintakuntlawar et al., 2019). In general, the median survival of patients with anaplastic thyroid carcinoma reported was from 1 to 6 months (Lo et al., 1999; Chintakuntlawar et al., 2019). Most patients with anaplastic thyroid carcinoma die within a year of diagnosis (Lo et al., 1999; Lam et al., 2000). In a large series of patients with anaplastic thyroid carcinoma, the 2-year survival rate was 4% (Lo et al., 1999).

Additional Prognostic factors

Apart from TNM staging, there are other clinical and pathological parameters having prognostic impacts in patients with anaplastic thyroid carcinoma. Elderly patients with anaplastic thyroid carcinoma (patients aged ≥60/≥ 65/≥ 70 years) had poorer prognosis than younger patients (Kebebew et al., 2005; Yau et al., 2008; Sugitani et al., 2018). Some studies showed male patients with anaplastic thyroid carcinoma had poorer prognosis than female patients (Kebebew et al., 2005; Sugitani et al., 2018). History of radiation exposure was also a poor prognostic factor (Kebebew et al., 2005; Yau et al., 2008; Sugitani et al., 2018; Huang et al., 2019). In addition, Yau and co-workers indicated history of surgical resection was the poor prognostic factor (Yau et
al., 2008). Sugitani and co-workers showed presence of hypercalcemia or leucocytosis are poor prognostic factors (Sugitani et al., 2018).

The pathological staging factors- T and M are shown to independently affect the prognosis. Tumour extension (> 50mm and extra-thyroidal invasion) and presence of distant metastasis were also predictive factors for poor prognosis (Kebebew et al., 2005; Yau et al., 2008; Sugitani et al., 2018; Huang et al., 2019). In addition, p53 expression in the tumour was reported to shorten duration of survival of patients with anaplastic thyroid carcinoma (Lam et al., 2000).

Pathology

In the 2nd and 3rd edition of World Health Organization (WHO) classification of tumours of endocrine tumour, the term used for this tumour is “undifferentiated (anaplastic) carcinoma” (Hedinger et al., 1993; Ordonez et al., 2004). As anaplastic thyroid carcinoma is the more well-known terminology, the tumour is re-labelled as “anaplastic thyroid carcinoma” in the 4th edition of WHO classification of endocrine tumours.

On macroscopic examination, the tumour is often large with involvement of both lobes and extend outside the thyroid (Figure 3). The mean diameter of anaplastic thyroid is 80 mm (Lam et al., 2000). Histologically, the carcinoma shows highly malignant morphology with prominent nuclear pleomorphism, frequent mitotic figures, with marked necrosis and inflammation in the stroma. Heterologous differentiation (bone and cartilage) and multinucleated osteoclast-like giant cells could be present (Gaffey et al., 1991; Caillou et al., 2011; Gopal et al., 2011; El-Nagger et al., 2017). The carcinoma has infiltrative border and with vascular invasion are often noted. It is categorized into 3 main types; sarcomatoid type, giant cell type, and epithelial type, and which occur singly or some combinations (El-Nagger et al., 2017; Lam, 2017).

The sarcomatoid form is composed of malignant spindle cells with features like high grade pleomorphic sarcoma. The giant cell type is comprised of highly pleomorphic malignant cells, and a part of them contain multiple nuclei as the dominant component. The epithelial form showing epithelioid morphology (Figure 4) and could compose of squamoid or squamous cohesive tumour nests with abundant eosinophilic
cytoplasm, and some of them contain occasional keratinization. This pattern needs to
differentiate from primary squamous cell carcinoma of thyroid in which the carcinoma
comprises entirely of carcinoma with squamous differentiation (Lam, 2020). Although
there is controversy whether that squamous cell carcinoma and anaplastic thyroid
carcinoma with squamous differentiation are the same tumour, clinical and pathological
evidences in the literature show that there are differences between them to justify them
as distinct entities (Lam, 2020). We need to wait for genomic studies to see whether
anaplastic thyroid carcinoma and squamous cell carcinoma show identical or distinctive
molecular changes.

Other rare variants have been described in anaplastic thyroid carcinoma. These include
angiomatic (Mills et al., 1994), lymphoepithelioma-like (Dominguez-Malagon et al., 2001), osteoclastic (with non-neoplastic giant cells) (Shelly et al., 2019), rhabdoid (one to multiple eccentric, large, rounded nuclei with a prominent
nucleolus, moderate to abundant, globoid cytoplasm which oftentimes harbor a pale
para-nuclear inclusion) (Feng et al., 2015; Lai et al., 2005). Paucicellular variant is
important as it mimics Riedel’s thyroiditis which is characterised by acellular fibrous or
infarcted tissue with central dystrophic calcification, as well as hypocellular foci
comprising mildly atypical spindle cells intermingled with collagen
and small lymphocytes (Wan et al., 1996; Canos et al., 2001).

Anaplastic thyroid carcinoma is positive for cytokeratin, but often negative
for TTF-1 (Lam et al., 2001; Lam, 2017; Lam, 2020). Paired-box gene 8 (Pax-8) is
positive in approximately 50% of anaplastic thyroid carcinomas and useful for diagnosis
of anaplastic thyroid carcinoma as it is usually negative for TTF-1 (Nonaka et al., 2008;
Bishop et al., 2011; El-Nagger et al., 2017; Lam, 2017; Deeken-Draisey et al., 2018).
Nevertheless, it is worth noting that Pax-8 could be present in carcinomas like renal cell
carcinoma, ovarian carcinoma and pancreatic neuroendocrine tumour (Xiang and Kong,
2013). In addition, different from well differentiated thyroid carcinoma, high Ki-67
proliferative rate and p53 expression are often present in anaplastic thyroid carcinoma
(Lam et al., 2000; Deeken-Draisey et al., 2018).

Anaplastic thyroid carcinoma should be differentiated from lymphoma. In fact,
in the past, some lymphomas have been misdiagnosed as anaplastic thyroid carcinoma.
(Lam et al., 1999). The differential diagnosis could be done with the help of cytokeratin and lymphoid markers. In some instance, giant cell lung carcinoma needs to be differentiated from anaplastic thyroid carcinoma. Use of PAX-8 or thyroglobulin may help to differentiate anaplastic thyroid carcinoma from giant cell carcinoma as the latter is negative for these markers.

Some anaplastic thyroid carcinomas have differentiated component with different molecular features from the anaplastic component. Lam and co-workers showed p53 expression was positive only in anaplastic component but not in the differentiated component such as papillary thyroid carcinoma (Lam et al., 2000). Ragazzi and co-workers also showed not only p53 expression but also smooth muscle actin, p63, and p16 were more positive in anaplastic component than differentiated component, while TTF-1, pankeratin, and Pax-8 were more positive in differentiated component than anaplastic component (Ragazzi et al., 2020).

Pathological Staging

Pathological staging is important to predict the prognosis and formulating the treatment protocols for the patients with anaplastic thyroid carcinoma. In the latest American Joint Committee on Cancer (AJCC) TNM staging system (8th edition) for anaplastic thyroid carcinoma, the descriptions of the T and N categories were different from the 7th edition of AJCC (Table 1) (Edge et al., 2010; Michael Tuttle et al., 2017). The T category of anaplastic thyroid carcinoma in the 8th edition of AJCC is of the same definition as differentiated thyroid carcinoma (divided into T1 to T4) whereas the T category of anaplastic thyroid carcinoma is always T4 in the 7th edition of AJCC.

Stages T1-T3a are defined as intrathyroidal anaplastic thyroid carcinoma and T3b-T4b are defined as anaplastic thyroid carcinoma with gross extrathyroidal extension (comparable to T4a and T4b described in the 7th edition). It is worth noting that T3 in the new staging system is subdivided into T3a and T3b. T3a is any tumour more than 4 cm. T3b is gross extrathyroidal extension invading of tumour of any size to strap muscles. Previous studies revealed extrathyroidal extension could associate with poor survival of patients with differentiated thyroid carcinoma and medullary thyroid carcinoma (Radowsky et al., 2017; Youngwirth et al., 2017), while there were no studies
about anaplastic thyroid carcinoma. Different from the 7th edition of AJCC, involvement
of perithyroidal soft tissue or microscopic involvement of muscles do not classify a
thyroid tumour as T3. Moreover, the 8th edition of AJCC mentioned the distinction of
T3b disease apart from T4a and T4b disease considering the degree and areas of
invasion (Perrier et al., 2018). The N category of the anaplastic thyroid carcinoma in
the 8th edition of AJCC was grouped in more detail when compared to that in the 7th
edition. N0a is defined as no lymph node metastasis pathologically and N0b is defined
as no lymph nodes metastases clinically or radiologically. This is based on the studies
on differentiated thyroid carcinoma that clinical N0 (N0b) with small volume
pathological N1 induces little prognostic impact with equal survival outcome compared
to pathological N0 (N0a) (Zaydfudim et al., 2008; Beal et al., 2010). It is worth noting
that there is no similar study on anaplastic thyroid carcinoma.

Regarding stage grouping, all anaplastic thyroid carcinomas are classified as
stage IV in both 8th edition and 7th edition of AJCC. On the other hand, the stage
subgrouping (IVA and IVB) are different in two editions. In the 8th edition, stage IVA
cancers are defined as cancers with the primary lesion restricted to the thyroid gland
(T1-T3a), without regional lymph nodes metastasis (N0) or with unevaluable regional
lymph nodes metastasis (Nx), and without distant metastases (M0). Stage IVB cancers
are defined as cancers within the primary lesion restricted to the thyroid gland (T1-T3a),
with regional lymph nodes metastases (N1), and without distant metastases (M0) or
with gross extrathyroidal extension involving major structures (T3b, T4a, T4b), with or
without lymph nodes metastases (any N), and without distant metastases (M0). Stage
IVC cancers are defined as cancers with distant metastasis (any T, any N, and M1)
(Edge et al., 2010; Michael Tuttle et al., 2017).

Changes of definition of T category between 8th edition and 7th edition do not
affect stage grouping of anaplastic thyroid carcinoma. Meanwhile, changes of N
category affect stage grouping. N0 (or Nx) is required to define stage IVA, while
identifying N category did not affect staging in 7th edition. The 8th edition indicates the
importance of assessment of lymph nodes metastases in addition to the gross
extrathyroidal extension of anaplastic thyroid carcinoma.
Conclusions

Anaplastic thyroid carcinoma is uncommon but is one of the most aggressive and lethal tumours in human. The updated knowledge of clinicopathological features, current WHO classification, and AJCC Cancer Staging Manual shed lights on the understanding of the nature of the cancer, which could lead to the development of the approach.

Figure Legends

Figure 1. Cytological features of anaplastic thyroid carcinoma showing tumour cells with large and irregular nuclei with tumour diathesis

Figure 2. A Section from the cell block obtained from the smear of Figure 1 showing tumour cells with prominent nuclear pleomorphism and necrosis. 2B. The tumour cells are positive for cytokeratin.

Figure 3. Surgical specimen of anaplastic thyroid carcinoma shows nearly the whole thyroid gland is replaced by whitish necrotic tumour

Figure 4. Microscopic appearance of anaplastic thyroid carcinoma with epithelioid morphology. Some tumour cells show prominent nuclear pleomorphism and prominent nucleoli. Some entrapped thyroid follicles are noted.

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### Table 1. Comparison TNM and Stage Grouping between AJCC 7th edition and AJCC 8th edition for anaplastic thyroid carcinoma

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<th>AJCC 7th edition</th>
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<tr>
<td><strong>TNM classification</strong></td>
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<tr>
<td>T4a: Intrathyroidal anaplastic carcinoma</td>
<td>T4a: Tumour extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve</td>
</tr>
<tr>
<td>T4b: Anaplastic carcinoma with gross extrathyroid extension</td>
<td>T4b: Tumour invades prevertebral fascia, mediastinal vessels, or encases carotid artery</td>
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<tr>
<td>T4b: Anaplastic carcinoma with gross extrathyroidal extension invading strap muscles (sternothyroid, sternohyoid, or omohyoid muscles)</td>
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<td><strong>N</strong></td>
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<tr>
<td>N0: No regional lymph node metastasis</td>
<td>N0: No regional lymph node metastasis (one or more cytologically or histologically confirmed benign lymph nodes)</td>
</tr>
<tr>
<td>N1a: Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)</td>
<td>N1a: Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinum</td>
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<tr>
<td>N1b: Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)</td>
<td>N1b: Metastasis in other unilateral, bilateral or contralateral cervical (levels I, II, III, IV or V) or retropharyngeal</td>
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<td><strong>M</strong></td>
<td></td>
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<tr>
<td>M0: No distant metastasis</td>
<td>M0: No distant metastasis</td>
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<tr>
<td>M1: Distant metastasis</td>
<td>M1: Distant metastasis</td>
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**Staging grouping**

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<th>AJCC 8th edition</th>
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<td>IVA</td>
<td>T4a, Any N, M0</td>
<td>T1-T3b, N0/Nx, M0</td>
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<tr>
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<td>T1-T3a, N1, M0 or T3b-T4, Any N, M0</td>
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