Investigation of the Validity of UICC Stage Grouping of Anaplastic Carcinoma of the Thyroid

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OBJECTIVE: Anaplastic thyroid carcinoma arises from differentiated carcinoma and has a very aggressive character. In this study, we investigated the prognosis of patients with anaplastic carcinoma based on UICC stage.

PATIENTS AND METHODS: We investigated the prognosis of 75 patients who were diagnosed as having anaplastic carcinoma at Kuma Hospital between 1983 and 2006. Of these patients, 14, 49 and 12 were classified into Stages IVA, IVB, and IVC respectively.

RESULTS: Stage IVA patients showed a significantly better prognosis than Stage IVB or IVC patients ($p=0.0017$). All patients with Stage IVC died of carcinoma within 1 year regardless of whether locally complete resection was performed. Prognosis of Stage IVB patients who underwent curative surgery did not differ from that of Stage IVA patients, but the prognosis of those who did not undergo surgery or only received palliative surgery was as poor as that of Stage IVC patients.

CONCLUSIONS: Extensive surgical treatment is recommended for Stage IVA patients and palliative care is appropriate for Stage IVC patients. For Stage IVB patients, surgical treatment as a primary therapy is appropriate only when curative resection of the tumour is expected. [Asian J Surg 2009;32(1):47–50]

Key Words: anaplastic carcinoma, prognosis, thyroid

Introduction

Thyroid carcinoma is a representative malignancy originating from the endocrine organs. The two kinds of carcinoma arising from thyroid follicular cells are papillary and follicular carcinomas, which are also called differentiated carcinoma and generally have a mild biological characteristic. However, when these lesions dedifferentiate and become anaplastic (undifferentiated), patients show a far more adverse prognosis than those with differentiated carcinoma. Although this event is uncommon, and previous studies have shown some prognostic factors of anaplastic carcinoma,1–6 long-term survival could not be expected for most patients with undifferentiated carcinoma even if they underwent multimodal therapy, combining surgery, chemotherapy and radiotherapy.7,8 Furthermore, a previous study demonstrated that curative resection is the strongest prognostic factor for this carcinoma.9

To evaluate the biological characteristics of thyroid carcinoma, several staging systems have been published and the UICC stage grouping is the most widely accepted. This system was revised in 2002 (6th edition),10 and we previously demonstrated that T4 and N1b, which are components of Stage IV for patients aged 45 years or older, independently affected both disease-free survival (DFS)
and cause-specific survival (CSS) of patients with papillary carcinoma.\textsuperscript{11} Stage grouping for anaplastic carcinoma was also revised at the same time. All anaplastic carcinomas were classified into Stage IV, which is further divided into three subcategories; Stage IVA, tumour limited to the thyroid; Stage IVB, tumour beyond the thyroid capsule; and Stage IVC, presence of distant metastasis. In this study, we investigated the prognosis of patients with anaplastic carcinoma treated at our institute and evaluated appropriate therapeutic strategies for patients at each stage.

**Patients and methods**

Seventy-five patients, who were diagnosed as having anaplastic carcinoma by cytological and/or pathological examinations in Kuma Hospital and treated in Kuma Hospital or associated hospitals between 1983 and 2006, were enrolled in this study. Specimens from all of these cases were re-examined by a coauthor (M.H.) and confirmed as anaplastic carcinoma. These patients consisted of 65 females and 10 males and the average patient age was 66.9 years. Patients with anaplastic transformation of recurrent tumours following surgery for differentiated carcinoma and those with anaplastic carcinoma detectable only in the lymph node but not in the primary tumour were excluded from this series. Follow-up periods after diagnosis ranged from 1 to 212 months and averaged 13.5 months. Surgical treatment was performed for 57 patients. Twenty-nine of these patients underwent curative surgery and the remaining 28 underwent palliative surgery only. The ranges of thyroidectomy for 29 patients who underwent curative surgery were total thyroidectomy in 18 patients, subtotal thyroidectomy in six patients, and lobectomy in five patients. Lymph node dissection was performed for 27 of these patients. Twenty-nine of these patients underwent curative surgery and the remaining 28 underwent palliative surgery only. The ranges of thyroidectomy for 29 patients who underwent curative surgery were total thyroidectomy in 18 patients, subtotal thyroidectomy in six patients, and lobectomy in five patients. Lymph node dissection was performed for 27 of these patients. Six patients underwent bilateral modified radical neck dissection (MND), 20 underwent unilateral MND. The range of dissection is unknown for the remaining one patient who underwent surgery at another hospital. Three patients also underwent dissection of the mediastinal lymph nodes. Forty patients (53.3%) underwent radiotherapy and 36 patients (48.0%) underwent chemotherapy. Twenty-four of these patients underwent both therapies. Three patients underwent radiotherapy as a primary therapy and two of these patients did not undergo surgical treatment. Twelve patients underwent chemotherapy as a primary therapy and four of these patients underwent surgical treatment thereafter.

**Grading of UICC stage grouping**

All patients were graded based on the UICC stage at the time of diagnosis.\textsuperscript{3} Extracapsular extension was diagnosed by palpation and various imaging studies such as ultrasonography and computed tomography (CT) scan. Distant metastasis was also diagnosed by imaging studies.

**Statistical analyses**

Fisher’s exact test was used for the analysis of variables. The Kaplan-Meier method and log rank test were adopted to analyse time-dependent variables. These analyses were performed using StatView-J 5.0. A $p$ value less than 0.05 was regarded as significant.

**Results**

We classified 75 patients with anaplastic carcinoma based on UICC stage. Of these patients, 14, 49, and 12 were classified into Stages IVA, IVB, and IVC, respectively. All Stage IVA patients underwent curative resection of the tumour. Adjuvant therapy was performed for 11 patients. Eleven patients underwent chemotherapy and eight underwent radiotherapy. Eight of these patients underwent both therapies. Stage IVA patients showed a significantly better CSS than those in Stage IVB or IVC ($p = 0.0017$) as shown in Figure 1. Six patients with Stage IVA were alive 1 year later, and four were alive longer than 5 years after diagnosis. One patient was confirmed alive more than 17 years (212 months) after diagnosis. All patients with Stage IVC died of carcinoma within 1 year regardless of whether locally complete resection was performed.

Of patients with Stage IVB, curative resection was achieved based on intra-operative findings in 15 patients. Thirteen of these patients underwent adjuvant therapy; 11 of these thirteen underwent radiotherapy and ten of the thirteen underwent chemotherapy. Eight patients underwent both therapies. One patient underwent paclitaxel administration as a primary therapy\textsuperscript{12} and underwent curative resection after tumour shrinkage. As shown in Figure 2, prognosis of these patients did not differ from that of those with Stage IVA. Of the remaining 34 patients who did not undergo surgery or underwent only palliative surgery. Of these 34, 19 underwent chemotherapy and/or radiotherapy. Amongst these 19, chemotherapy and radiotherapy were performed for 11 patients and 14 patients, respectively, and six underwent both of them. However all patients died of carcinoma within 18 months after...
diagnosis. Their prognoses were as poor as that of those with Stage IVC (Figure 3).

Figure 4 summarises the CSS of patients belonging to the four categories; Stage IVA, Stage IVB with curative surgery, Stage IVB with no or only palliative surgery, and Stage IVC. In total, five patients (four with Stage IVA and one with Stage IVB with curative surgery) survived longer than 5 years. There were no special pathological findings in these patients. All patients except for one with Stage IVA underwent radiotherapy and chemotherapy.

Discussion

In this study, we focused on the prognosis of anaplastic carcinoma patients at each UICC stage. Since tumours of Stage IVA patients do not extend to adjacent organs or show distant metastasis, it is reasonable to expect long-term survival after curative resection. Therefore, extensive surgical treatment can be the first line of therapy. Recently, radiotherapy and chemotherapy have been adopted as effective adjuvant therapies for anaplastic carcinoma.13–16 Also in our series, four of the five patients who survived more than 5 years underwent radiotherapy and chemotherapy, indicating the possibility that these therapies after curative surgery can further prolong patient survival. However, none of the patients having distant metastasis survived for more than 1 year, even if locally curative surgery was performed, indicating that surgical treatment has no survival benefit for Stage IVC patients. Therefore, palliative care should be considered the most appropriate for these patients.

In contrast to the prognosis of patients with Stages IVA and IVC, that of those with Stage IVB was polarised. Patients whose tumours were curatively resected based on intra-operative findings have a chance for long-term survival and their prognoses did not differ from those of patients in Stage IVA. However, patients who did not undergo surgery or underwent only palliative surgery could
not survive longer than 18 months and their prognosis was as poor as that of those with stage IVC. In our series, debulking surgery did not contribute to prolonged survival for these patients, which is discrepant with the findings reported by Sugino et al. However, that study excluded patients who developed novel distant metastasis during treatment and did not consider whether the primary tumours showed extrathyroid extension. Differences in patient background between their series and ours may be one reason for discrepancies among these data. The only advantage of debulking surgery may be to facilitate tracheostomy in order to prevent airway obstruction. Since stage grouping is based on pre-operative evaluation, further segmentation of Stage IVB should be difficult.

Intra-operative findings are the most important to predict the prognosis of patients classified as Stage IVB preoperatively. The therapeutic strategies of Stage IVB patients in whom curative surgery is expected can be the same as those of Stage IVA patients, that is, extensive surgical treatment followed by radiotherapy and chemotherapy. For Stage IVB patients in whom curative surgery cannot be expected, primary chemotherapy and radiotherapy for tumour shrinkage may be more appropriate as demonstrated by Besic et al. If tumour shrinkage allows the possibility of curative surgery, surgical treatment can be performed as a second line. Otherwise, long-term survival cannot be expected for these patients.

In this study, we recommended appropriate strategies for anaplastic carcinoma patients based on UICC staging system. Curative surgery and palliative care are recommended for patients with Stages IVA and IVC, respectively. However, therapeutic strategies for Stage IVB patients are polarised depending on whether curative surgery can be expected.

References