Platin-based chemotherapy does not improve survival in patients with non-metastatic resected typical carcinoid tumors

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Abstract. Chemotherapy is controversial in non-metastatic typical carcinoid (TC) tumors. Therefore, it was aimed to evaluate the impact of platin-based chemotherapy on the survival of patients with lung TC. The medical records of patients who underwent surgical resection for non-metastatic TC from 2002 to 2020 at our institution were retrospectively reviewed. Multivariate regression analysis was performed for chemotherapy and prognostic factors in disease-free survival (DFS) in 72 patients. The pathological stages of patients were as follows: 73.6% of the patients were in stage I, 15.3% in stage II and 11.1% in stage III. A total of 5 patients (6.9%) received platin-based chemotherapy and 6 patients (8.3%) had recurrences. The DFS rates at 12, 36 and 60 months were 98.5, 95.1 and 92.5%, respectively. Log-rank testing showed that patients who received chemotherapy and had stage III disease had shorter DFS (P=0.021 for chemotherapy and P<0.001 for stage). However, multivariate analysis revealed that the pathological stage was the only statistically significant factor affecting DFS (P=0.016). Platin-based chemotherapy did not improve DFS, and the eighth edition of TNM (tumor, nodes, metastases) staging did have prognostic value for patients with non-metastatic TC. Although resection has satisfying long-term outcomes, studies on new agents are needed to decrease the recurrence rate, particularly in patients with stage III disease.

Introduction

Lung carcinoid (LC) tumors are rare neuroendocrine neoplasms that represent less than 2% of all lung malignancies (1,2). However, the incidence of LC is increasing, likely related to improved imaging and other diagnostic techniques (2,3). The World Health Organization (WHO) classifies LC into typical (TC) and atypical (AC) carcinoids (4). TC accounts for more than 75% of LC, and presentation with *de novo* metastatic disease is rare-less than 10% (5-7). Surgery is the mainstay of treatment for patients with TC (8-10). Although non-metastatic TC has excellent postsurgical outcomes, with a five-year survival rate of over 90%, up to 10% of patients have recurrences (11). In numerous solid organ tumors, adjuvant treatment modalities are rational options for decreasing recurrence and prolonging survival. Adjuvant cytotoxic chemotherapy in patients with LC remains controversial due to the lack of prospective randomized controlled trials (RCT) studying the efficacy of cytotoxic chemotherapy in this setting (12-14).

Some scientific evidence on this issue has been provided by several retrospective studies (7,15-18); however, these studies included both AC and TC, which have different clinical courses (19). Studies investigating chemotherapy efficacy in patients with TC and excluding AC are limited (20). Therefore, it was aimed to determine the impact of platin-based chemotherapy on the survival of patients with TC. Potential prognostic factors, such as clinical characteristics, type of surgical procedure and pathological features of patients were also investigated.

Materials and methods

Study population. The electronic medical records of patients admitted to the Departments of Medical Oncology or Thoracic Surgery at Bursa Uludag University between January 2002 and December 2020 due to lung carcinoid tumors were retrospectively reviewed. A patient flow diagram is provided in Fig. 1. Patients with a history of other malignancies, patients with incomplete data and patients aged <18 were excluded. According to the criteria specified by the WHO 2015 classification of lung tumors (4), patients with non-metastatic TC were enrolled in the present study. Patients who received adjuvant cytotoxic chemotherapy other than platin-based regimens were also excluded. The present study was approved (approval no. 2021-5/19) by the Clinical Research Ethics Committee of Bursa Uludag University Faculty of Medicine (Bursa, Turkey).

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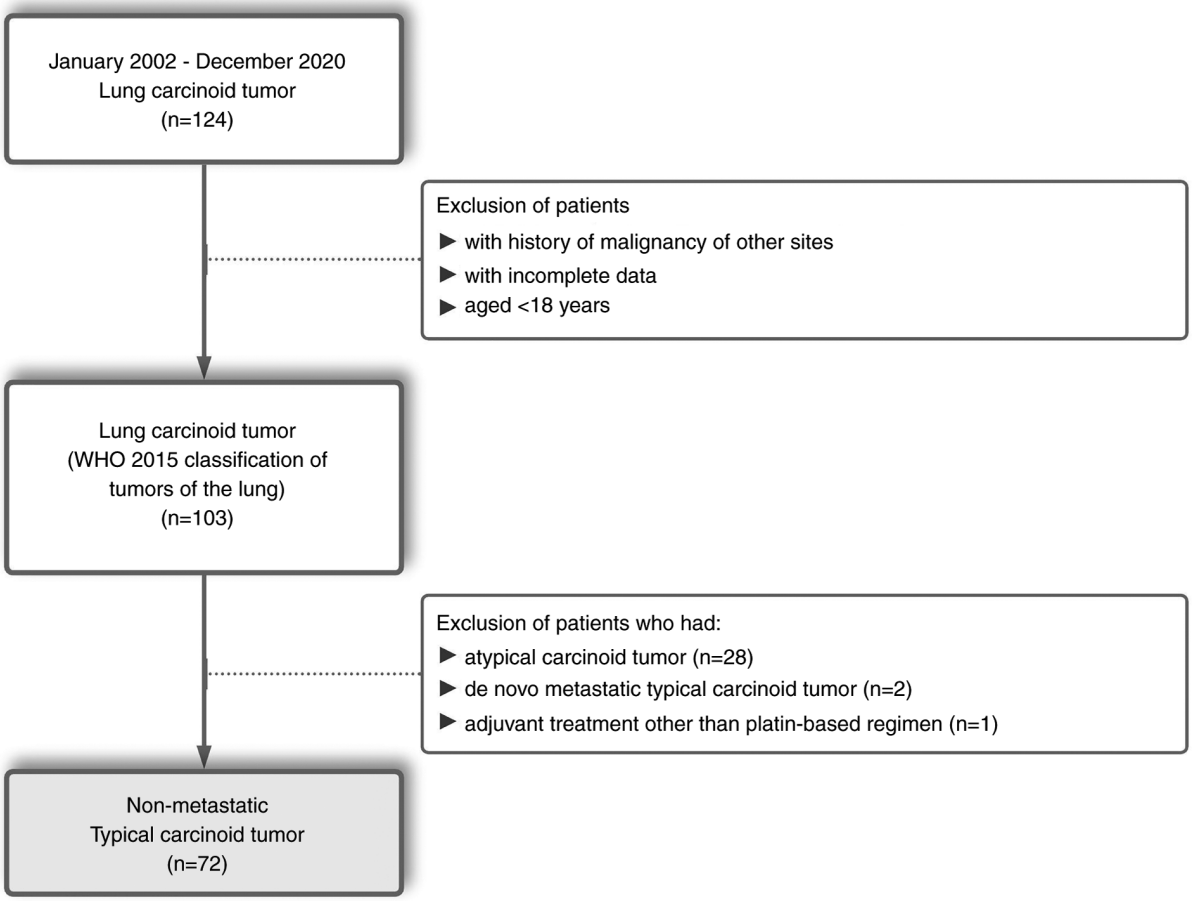

Figure 1. Flow diagram of patients.

Data collection. The following demographic and clinical features of the participants were extracted from their electronic records: age, sex, symptoms at presentation, imaging modality, tumor laterality, tumor localization, clinical stage, surgical procedure and (neo)adjuvant treatment. A preoperative evaluation was performed as previously described (21). Octreotide scintigraphy or Ga68-Dotatate positron emission tomography-computed tomography was performed in patients with a preoperative diagnosis of LC (when available). Cranial magnetic resonance imaging was performed only when clinically indicated. Mediastinal lymph node (MLN) dissection was performed on all patients who underwent lobectomy and segmentectomy. In patients who underwent wedge resection, MLN sampling was performed in the case of suspicious MLN on imaging. The staging was determined following the eighth edition of the TNM staging system (22). Our multidisciplinary thoracic oncology team evaluated the patients and histopathological features were obtained from the pathology reports of patients, including tumor size, lymphovascular invasion, Ki-67 percentage and surgical margins. Patients who received platin-based neoadjuvant or adjuvant chemotherapy were included in the study. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) (23).

Follow-up, patient outcomes and statistical analysis. After surgical resection, computed tomography (CT) was performed every three to six months for up to two years and then annually. Disease-free survival (DFS) was calculated based on the amount of time from surgery until disease recurrence, confirmed by histological examination or imaging modalities, or death for any reason, whichever occurred first. Overall survival (OS) was determined as the length of time from diagnosis until death from any cause. Statistical analyses were performed using SPSS version 22 software (IBM Corp.). Continuous and categorical variables were expressed as median (minimum-maximum) and frequency values. Kaplan-Meier analysis was employed for survival rates. Log-rank testing was used to compare groups of patients according to their disease stage and whether they received chemotherapy. The possible factors affecting DFS were examined using Cox regression analysis. A backward stepwise model was used with parameters with a P-value <0.25. $P<0.05$ was considered to indicate a statistically significant difference.

Results

A total of 72 patients were included in the present study. The demographic and clinical characteristics of the patients are provided in Table I. The median age was 50.2 (18.1-81.1) years. Nearly two-thirds of the patients were female. Cough was the most common symptom, and one-third of all patients were asymptomatic at presentation. All patients were evaluated using CT scans during staging. A total of 48 patients (66%)

Table I. Demographic and clinical characteristics of the patients.

Characteristic	Total (n=72)	Percentage (%)
Age, years [Median, (range)]	50.2	(18.1-81.1)
Sex		
Male	44	(61.1)
Female	28	(38.9)
Presentation at diagnosis		
Cough	34	(47.2)
Dyspnea	10	(13.9)
Hemoptysis	5	(6.9)
Pneumonia	3	(4.2)
Carcinoid Syndrome	3	(4.2)
Asymptomatic	24	(33.3)
Imaging		
Computed tomography	72	(100.0)
Octreotide scintigraphy	20	(27.8)
Ga68-Dotatate PET CT	18	(25.0)
Tumor laterality		
Right	53	(73.6)
Left	19	(26.4)
Localization		
Central	48	(66.7)
Peripheral	24	(33.3)
Clinical Stage		
I	45	(62.5)
II	15	(20.8)
III	12	(16.7)

PET-CT, positron emission tomography-computed tomography.

Table II. Pathological features and adjuvant treatment of the patients with non-metastatic disease.

Characteristic	Total (n=72)	Percentage (%)
Surgery		
Lobectomy	49	(68.1)
Wedge	18	(25.0)
Bronchoplasty	3	(4.2)
Segmentectomy	2	(2.7)
Tumor size, mm [Median, (range)]		18 (5-70)
Ki-67 index, % [Median, (range)]		2 (0-10)
Lymphovascular invasion		
Present	8	(11.1)
Absent	64	(88.9)
Pathological T stage		
T1	50	(69.4)
T2	12	(16.7)
T3	4	(5.6)
T4	6	(8.3)
Pathological N stage		
N0	48	(66.7)
N1	7	(9.7)
N2	2	(2.8)
Nx	15	(20.8)
Pathological stage		
I	53	(73.6)
II	11	(15.3)
III	8	(11.1)
(Neo)Adjuvant treatment		
Chemotherapy	5	(6.9)
Median (range), cycles		6 (4-6)
Cisplatin plus etoposide	3	(4.2)
Carboplatin plus etoposide	2	(2.7)
Radiotherapy	2	(2,7)
Observation	67	(93.1)

Nx, mediastinal lymph node staging was not performed.

had centrally located tumors. The biopsies of three patients were reported as non-small-cell lung cancer. Of the patients, 68% underwent a lobectomy (Table II). The medians of the tumor size and the Ki-67 index were 18 mm (5-70) and 2% (0-10), respectively. The pathological stages of patients were as follows: 73.6% were in stage I, 15.3% were in stage II and 11.1% were in stage III. All patients underwent surgery with a negative surgical margin. A total of 5 patients received platin-based chemotherapy, 2 in the neoadjuvant setting and 3 in the adjuvant setting. A total of 3 patients were treated with cisplatin (75 mg/m^2 intravenous on day 1) and etoposide (100 mg/m^2 intravenous on days 1-3) and 2 patients received carboplatin (area under the curve of five intravenous on day 1) and etoposide. The regimens were administered every 21 days. The median number of chemotherapy cycles was 6 (range: 4-6). Of the patients, 93.1% received no adjuvant treatment. Nausea and hematological toxicity were observed in patients receiving chemotherapy; the only grade 3 and higher adverse event was grade 3 neutropenia observed in 2 patients.

The median amount of time from diagnosis to the final visit was 68.5 (0.7-210.9) months. A total of 6 patients (8.3%) had recurrences. Half of these patients presented with distant metastasis. The 12-, 36- and 60-month DFS rates were 98.5, 95.1 and 92.5%, respectively. The 12-, 36- and 60-month OS rates were 100, 98.5 and 96.0%, respectively.

The results of the univariate and multivariate Cox regression analyses of DFS are presented in Table III. Kaplan-Meier curves of DFS according to pathological stage and adjuvant chemotherapy (Fig. 2A and B). Log-rank testing showed that patients with stage III disease and patients who received chemotherapy had significantly worse survival rates (P<0.001 and P=0.021, respectively). Although univariate analyses displayed that patients who did not receive chemotherapy had improved DFS than those who received it, the multivariate Cox regression analysis revealed that the pathological stage was the only statistically significant factor affecting DFS (P=0.016).

Table III. Univariate and multivariate cox regression analysis of the predictors for recurrence.

	Univariate analysis			Multivariate analysis		
Factor	HR	95% CI	P-value	HR	95% CI	P-value
Age, years	1.042	0.982-1.107	0.176			
Sex [male (R) vs. female]	2.666	0.310-22.945	0.372			
Tumor laterality [right (R) vs. left]	0.602	0.066-4.832	0.5564			
Localization [central (R) vs. peripheral]	3.167	0.369-27.201	0.293			
Surgery [lobectomy (R) vs. sublobar resection]	1.221	0.223-6.694	0.818			
Tumor size, mm	1.010	0.963-1.058	0.690			
Ki-67 index, %	1.318	0.895-1.941	0.162			
Lymphovascular invasion [absent (R) vs. present]	2.271	0.264-19.497	0.455			
Pathological stage						
I(R)	1		0.015	1		0.016
II	4.567	0.286-73.037	0.283	4.367	0.273-68.839	0.297
III	22.188	2.472-199.188	0.006	21.216	2.363-190.462	0.006
Chemotherapy [no (R) vs. yes]	5.824	1.063-31.918	0.042			

HR, hazard ratio; CI, confidence interval; R, reference variable.

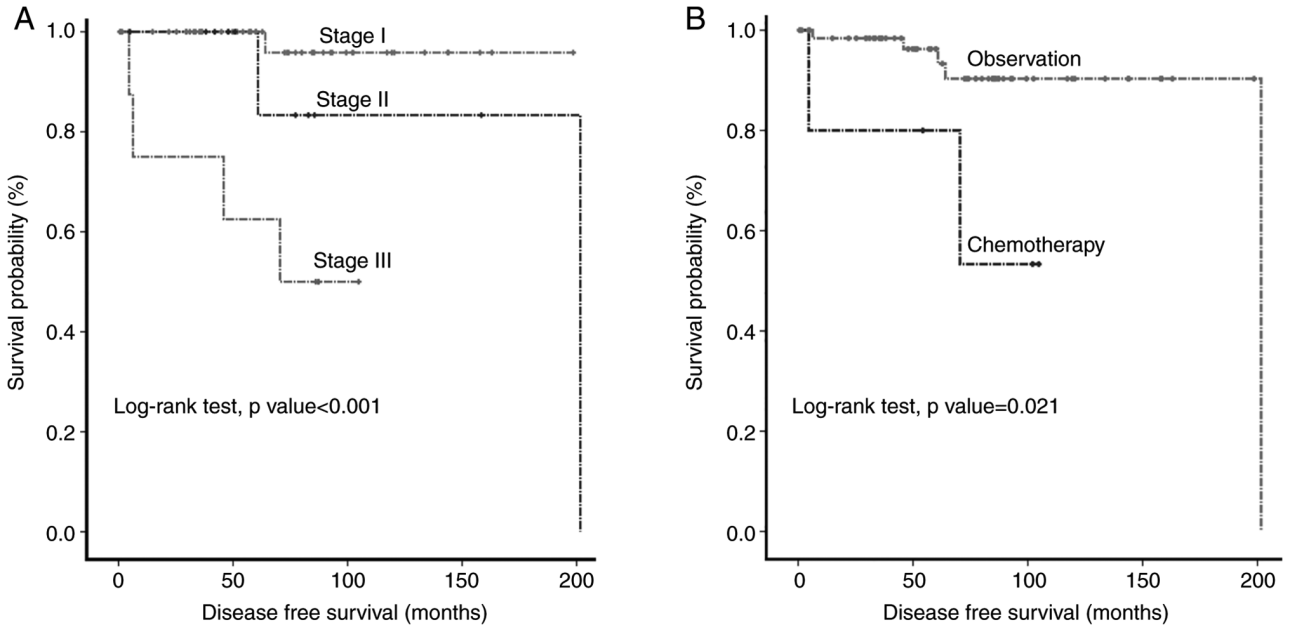

Figure 2. Kaplan-Meier curves of disease-free survival according to (A) the pathological stage and (B) adjuvant chemotherapy.

Discussion

In the present retrospective study, the effect of platin-based chemotherapy and other clinicopathologic parameters on DFS in patients with non-metastatic resected TC were investigated. It was observed that chemotherapy did not improve DFS and that pathological stage was the only independent risk factor for DFS.

The guidelines provided by the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) suggested considering adjuvant platin-based chemotherapy in LC patients with aggressive clinicopathological features such as AC, N2 disease and a high proliferative index in multidisciplinary councils (8,9). In contrast to ESMO and NCCN, the North American Neuroendocrine Tumor Society does not recommend any adjuvant treatment modality (24). These recommendations are based on retrospective studies, as no previous randomized clinical trials have been conducted to study adjuvant therapy modalities in LC. Table IV shows previous studies in the international literature that have investigated the impact of chemotherapy on survival in non-metastatic disease.

In 2013, Filosso *et al* (15) reported that 7.4% of 81 patients with non-metastatic TC received adjuvant treatment, including

Table IV. Studies investigating the efficacy of chemotherapy in non-metastatic typical carcinoid.

Authors	Year	Patients	Chemotherapy	Analysis	Results
Our study	2021	TC Single-center study, 2002-2020 72 non-metastatic TC	6.9% received platin plus etoposide	Multivariate	Although patients receiving CT had worse DFS in univariate analyses, multivariate analysis revealed that CT was not associated with inferior DFS
He *et al* (18)	2021	TC + AC The SEER database, 1975-2016, 1702 all staged TC	5.8% of all patients received CT, but regimens were not reported	Multivariate	CT was associated with inferior CSS in all TC patients
Girelli *et al* (25)	2020	TC + AC + LCNEC Single-center study, 1998-2016, 21 non-metastatic N+ TC	14.2% of all patients received CT, but regimens were not reported	Univariate	(Neo)Adjuvant CT was associated with inferior OS
Gosain *et al* (16)	2019	TC + AC The NCDB, 2004-2014, 5727 non-metastatic TC	2.9% of all patients received CT, but regimens were not reported	Univariate, Multivariate	CT was associated with inferior OS in the subgroup analysis of TC
Westin *et al* (17)	2017	TC + AC, The NCDB, 2004-2012, 651 non-metastatic N + TC	6% of TC patients received CT, but regimens were not reported	Multivariate	CT was associated with inferior OS
Nussbaum *et al* (20)	2015	TC, The NCDB, 1998-2006, 4612 non-metastatic TC	5.9% of TC patients received CT, but regimens were not reported	Univariate, PSMA	CT was associated with inferior OS in univariate analysis. After PSMA, CT was associated with a trend toward inferior OS, which was not statistically significant
Filosso *et al* (15)	2013	TC + AC, Single-center study, 1995-2010, 81 non-metastatic TC	Adjuvant treatment, including platin-based CT, RT, and SSA, was administered to 7.4% of TC patients	Multivariate	Adjuvant treatment was not an independent factor for survival

TC, typical carcinoid; AC, atypical carcinoid; LCNEC, large cell neuroendocrine carcinoma; CT, chemotherapy; DFS, disease-free survival; SEER, Surveillance, Epidemiology, and End Results; CSS, cancer-specific survival; N+, node-positive disease; NCDB, National Cancer Database; PSMA, Propensity score match analysis; RT, radiotherapy; SSA, somatostatin analogs.

platin-based chemotherapy, radiotherapy and somatostatin analogs. Multivariate analysis revealed that adjuvant therapy did not affect survival. Nussbaum *et al* (20) conducted one of the most prominent studies investigating adjuvant chemotherapy, evaluating 4,612 non-metastatic TC patients from the National Cancer Database (NCDB). It was found that chemotherapy was associated with a trend toward inferior OS, which was not statistically significant in the propensity score match analysis. Two other large-scale studies in the NCDB identified that patients receiving chemotherapy had worse survival rates than those who did not receive it (16,17). In a single-center study evaluating patients with node-positive TC, univariate analysis revealed that (neo)adjuvant chemotherapy was associated with inferior OS (25). Recently, He *et al* (18) published a study that included 1,702 TC patients from the Surveillance, Epidemiology, and End Results database. It was identified that patients who received chemotherapy had shorter cancer-specific survival than those who did not receive it (18). These studies support the present findings that chemotherapy does not improve survival, even though it may be harmful in non-metastatic disease. Although the aforementioned studies provided the scientific evidence that underlies the recommendations contained in international treatment guidelines, a significant limitation to these studies is that they do not report the regimens used or the duration of the chemotherapy administration. In this context, to the best of our knowledge, this is the first study demonstrating the results of administering a platin-based chemotherapy regimen to patients.

After entering the cell, platinum compounds interact with the purine bases of DNA, resulting in interstrand cross-links (26). Adjuvant platin-based chemotherapy combinations are standard therapies in numerous aggressive, rapidly proliferative solid organ tumors, such as lung cancer. However, TC is a well-differentiated, low-grade tumor, which can explain the low efficacy of platin agents in this setting. In addition, genomic alterations in DNA repair pathways, such as BRCA 1/2, which cause cancer to be more sensitive to platin agents, were not observed in neuroendocrine tumors (27,28). Considering these data and the adverse effects of platinum-based combination regimens, clinicians should offer adjuvant platin-based chemotherapy only to selected patients, such as patients with recurrent or N3 disease.

Recent studies have reported that older age, left side and high ki-67 index were poor prognostic factors (29-31). In addition, female patients are expected to have improved outcomes due to the protective effect of progesterone and estrogen via regulating immune cell response and suppressing tumor growth in mainly low-grade neuroendocrine neoplasms (32,33). The low recurrence risk in our study group, possibly due to a lower median age than is found in the literature, more right-side tumors, and female predominance, may be the reasons that no benefits of adjuvant chemotherapy were found.

Although chemotherapy is not suggested for patients with resected non-metastatic TC according to the current guidelines, a clinician survey conducted by Mansoor *et al* (34) indicated that 11% of respondents considered offering adjuvant treatment after surgical resection in patients with node-positive non-metastatic TC. Therefore, RCTs should be conducted to investigate the efficacy of new agents, including immunotherapy and targeted therapy, by detecting the genomic alterations that underlie the disease.

LC is the only neuroendocrine neoplasm that does not have a specific staging system (9). Nevertheless, the number of publications asserting the limitations of TNM staging in LC has been increasing (12,35-37). Combining TNM staging and histopathological features, such as grade, tumor size and Ki-67 index, was reported to improve the prediction of cancer-specific survival (37-40). In addition, nomograms and prognostic scores have been developed to predict survival more accurately (5,18,41). However, updated international guidelines recommend using the eighth TNM staging system (8,9,24) since it is the most important prognostic parameter after histological grade (12). Several recent studies support the present findings, indicating the prognostic value of TNM staging (42,43).

Surgery is the primary treatment modality for TC (8,9,24). The surgical approach aims to achieve complete resection of the tumor with parenchymal-preserving anatomic lung resection and lymph node dissection (44). Surgeons may select different surgical procedures according to the type, stage and localization of the tumor and performance status of the patient. The treatment guidelines for non-small-cell lung cancer resection should be followed if a diagnosis of TC cannot be made preoperatively or intraoperatively (44). Negative surgical margins should be examined during surgery. The present findings support the idea that patients who undergo optimal resection that achieves negative surgical margins have excellent clinical outcomes.

There are several limitations to the present study, including its retrospective design and the fact that it was conducted in a single center. In addition, the number of patients receiving chemotherapy was low due to the recommendations of international treatment guidelines. Moreover, the effect of chemotherapy on OS could not be analyzed due to the limited number of patients who succumbed.

In conclusion, the administration of platin-based chemotherapy may not provide a survival benefit to patients with non-metastatic TC. Therefore, clinicians should offer chemotherapy only to carefully selected patients with a high recurrence risk. In addition, the eighth edition of the TNM staging has prognostic value in this population. Although optimal surgery has satisfying long-term outcomes, RCTs studying new agents are needed in the adjuvant setting to decrease the recurrence rate, particularly in stage III disease.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ABS and HM designed the study. ABS, BO, SOO, AD, BC and BE collected the data. ABS performed the analysis. TE, ASB, EC, HM, BO and EUA made contributions to the interpretation of data. ABS wrote the manuscript, while HM was a major contributor in writing the manuscript. TE, ASB, EC, EUA, AD, SOO and BC edited the manuscript. ABS, HM, BO, SOO and BE confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. 2021-5/19) by the Clinical Research Ethics Committee of Bursa Uludag University Faculty of Medicine (Bursa, Turkey) and was conducted in accordance with the 1964 Declaration of Helsinki. Informed consent was not necessary due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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