Survival Benefit of Intervention Treatment in Advanced Anaplastic Thyroid Cancer

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Abstract

Background

Management of anaplastic thyroid cancer (ATC) is a controversial issue; thus, proper treatment and prognostic factors should be investigated.

Objectives

To compare the survival outcomes of intervention and palliative treatment in ATC patients.

Methods

A hospital-based retrospective study was conducted in a single tertiary university hospital. The medical record charts were retrieved from November 20, 1987 to December 31, 2016. The final follow-up was ended by December 31, 2017. Patients' demographic data, laboratory data, clinical presentation, and results of treatment modalities were analyzed.

Results

One hundred twenty-one records were analyzed that one-year overall survival rate of 3.5% (median survival time of 77 days); however, there was insufficient data on 16 cases to classify staging and treatment modalities. Therefore 105 ATC patients (37 stage IVa, 39 stage IVb, 29 stage IVc) were included with one-year overall survival rate of 4.0% (median survival time of 82 days). Intervention treatment allowed longer median survival times ($p < 0.05$) and a better survival rate ($p < 0.05$). Among the intervention treatment group, post-operative chemoradiation yielded the longest median survival time (187 days) and the longest survival rate (20%) ($p < 0.05$). At all stages, intervention modality allowed better median survival time, especially in stage IVa ($p < 0.05$). Unfavorable prognostic factors were adjusted with multiple cox regression model that showed significant factors included age ≥ 65 years (HR of 2.57), palliative treatment (HR of 1.85), and leukocytosis ≥ 10,000/mm^3(HR of 2.76).

Conclusions

Intervention treatment provided a better survival outcome in all stages, especially in stage IVa with a significantly better median survival time. Among intervention treatments, postoperative chemoradiation offered the longest survival rate; thus, suggesting this should be considered in ATC patients who have resectable tumors and no poor prognostic factors such as older age and leukocytosis.

Background

Anaplastic thyroid cancer (ATC) is a rare disease. Although ATC only accounts for 1–2% of all thyroid malignancy, it is a rapid growth tumor with extremely aggressive behavior that provides more than 50% of all thyroid-related mortality[1–3]. Several studies report a median overall survival rate of less than 6 months and a 1-year survival rate of 20%[3–5]. Regarding the treatment of ATC, the combination of multimodality treatment (including surgery, systemic therapy, and radiotherapy) is required for improved survival rates. However, these interventional treatments do not achieve universally beneficial outcomes; conversely, adverse side effects from interventional treatments may worsen outcomes and affect poor survival rate. Therefore, interventional treatment should be reserved for the patients with good performance status who are able to tolerate treatment side effects. For patients with poor performance status, supportive or palliative treatment should be considered to improve quality of life and to avoid side effects of the interventional treatments. However, survival rate data in patients with palliative treatment is lacking, as is comparative data assessing palliative care outcomes against the benefits of interventional treatments. Therefore, this study was developed to compare survival outcomes from palliative vs intervention care and investigate unfavorite prognostic factors predictive of short survival outcomes.

Methods

A hospital-based retrospective study was conducted with anaplastic thyroid cancer patients seen in a single tertiary university hospital. Medical record charts from ATC patients were retrieved from November 20, 1987 to December 31, 2016. The ATC was diagnosed based on fine-needle aspiration cytology and/or histopathology from the biopsy or surgical specimen. Patients' demographic data, laboratory data, clinical presentation, and results of treatment modalities were assessed. For the staging of ATC, we used the standard TNM of 8th edition AJCC staging. Regarding our treatment modality, total thyroidectomy was performed in patients with tumor localized at thyroid gland whereas thyroidectomy with extensive resection of the surrounding tissue was preserved for patients who had resectable extra-thyroid invasion. Neck dissection at level II to VI was performed in patients with clinical or cytopathological lymph nodes while with patients with clinical negative cervical lymph nodes, neck dissection at level VI was performed. Other modalities of treatment, radiotherapy was classified according to total radiation dose. We allocated patients who received doses of more than 40 Gy to the intervention group, and those with less than 40 Gy to the palliative group. For chemotherapy modality, we classified chemotherapy plus other therapy modalities (surgery and/or radiotherapy) as an intervention group whereas single chemotherapy modality was defined as the palliative group. The palliative group was reserved for patients who had a tumor that was beyond surgery and poor health status and was not a candidate for definite radiotherapy. The follow-up time started from the date of the first treatment and ended by December 31, 2017.

Statistics were analyzed with STATA (v 10.0: Stata Corp., Texas, USA). Survival duration was analyzed using days from the date of diagnosis to the date of death. The Kaplan-Meier analysis was used to demonstrate the survival curve. Patients who were lost to follow-up or survived were considered as censors. The comparison of the survival curve between the intervention group and the palliative group was analyzed using a log-rank test in each staging. Furthermore, univariate analysis was used to

calculate the Cox proportional hazard regression for identifying significant prognostic factors. Thereafter the statistical significances of covariates on survival were adjusted with the multiple cox regression analysis to identify independent prognostic factors. $P < 0.05$ was considered statistically significant. The study was exempted by the local ethics research committee (HE611221).

Results

One hundred twenty-one patients with ATC (42 males and 79 females) were retrieved from the hospital database (Table 1). Almost half of the patients (40.5%) were in the 61 to 70 years age range. Most patients presented a tumor ≥ 5 cm (72.7%) and 11.6% extra-thyroid invasion of vital structures including the carotid sheath, subclavian artery, and intrathoracic structures. One-year overall survival rate of 3.5% (median survival time of 77 days (95%CI: 57–88)) with a median follow up time of 74 days (range 5 – 4,061 days) was observed in our 121 patients (Fig. 1A); however, 16 ATC patients had insufficient data to classify TNM staging and treatment modalities. The remaining 105 ATC patients were classified into staging IVa 37 patients, IVb 39 patients, and IVc 29 patients. The common pattern of regional cervical lymph node metastasis was unilateral single node (19.8%); whereas, the most common site of distant metastasis was the lung (22.6%). Regarding treatment modality, 49 ATC patients had received palliative treatment (35.2% supportive treatment and 11.4% palliative radiation) while 56 ATC patients received intervention treatment including surgery alone (27.6%), chemoradiation (8.5%), surgery combined radiation (12.4%), and surgery combined chemoradiation (4.7%). The overall survival rate was 4.0% in 1 year (median survival time of 82 days (95%CI: 63–96)) in the 105 patients (Fig. 1B). From comparison of intervention and palliative treatments, the overall median survival time of intervention treatment (110 days) was almost twice as long and significantly different statistically (log-rank test; $p < 0.05$; Fig. 2A) to the palliative treatment group (58 days). Among the intervention treatment group, surgery with post-operative chemoradiation, yielded the longest median survival time of 187 days and the longest survival rate of 20% (log-rank test; $p < 0.05$) (Fig. 2B). The median survival time of intervention and palliative treatment was also compared in each staging. In stage IVa, the intervention treatment group (118 days (95%CI: 54–160)) had significantly longer survival than palliative treatment (33 days (95%CI: 10–46)) ($p = 0.00$; Fig. 3A); whereas, the median survival time of the intervention treatment group was not significantly longer than palliative treatment group in staging IVb (intervention, 110 days (95%CI: 64–177) vs palliative, 63 days (95%CI: 49–133) ($p = 0.63$) Fig. 3B) and IVc (intervention, 96 days (95%CI: 10–168) vs palliative, 64 days (95%CI: 37–93) ($p = 0.06$) Fig. 3C). Regarding prognostic factors, univariate analysis found significantly poorer outcomes for the variables of age ≥ 65 years (hazard ratio (HR) of 1.6), palliative treatment (HR of 2.0), hypothyroid (HR of 4.5), and leukocytosis (HR of 2.1). Thereafter, these poor variable factors were adjusted with multivariate analysis that showed significant independent poor variable factors including age ≥ 65 years (HR of 2.6), palliative treatment (HR of 1.9), and leukocytosis (HR of 2.8).

Table 1
Demographic data

Characteristic	N (%)	95% CI
Gender		
Female	79 (65.3)	56.5–73.2
Male	42 (34.7)	26.8–43.6
Age (years)		
≤ 40	3 (2.5)	0.9-7.0
41–50	6 (4.9)	2.3–10.4
51–60	23 (19.0)	13.0-26.9
61–70	49 (40.5)	32.2–49.4
≥ 70	40 (33.1)	25.3–41.9
Underlying disease		
No/Unknown	88 (72.7)	64.2–79.9
Diabetes mellitus	19 (15.7)	10.3–23.2
Hypertension	17 (14.1)	8.9–21.4
Dyslipidemia	3 (2.5)	0.9-7.0
Other	15 (12.4)	7.7–19.5
Thyroid function test		
Hypothyroid	8 (6.6)	3.4–12.5
Euthyroid	17 (14.1)	8.9–21.4
Hyperthyroid	3 (2.5)	0.9-7.0
Unknown	93 (76.9)	68.6–83.5
WBC		
≥10,000	48 (39.7)	31.4–48.6
< 10,000	31 (25.6)	18.7–34.1
Unknown	42 (34.7)	26.8–43.6
Tumor size (cm)		
< 5	6 (4.9)	2.3–10.4
≥ 5	88 (72.7)	64.2–79.7

Characteristic	N (%)	95% CI
Unknown	27 (22.3)	15.8–30.5
Extra-thyroid invasion involved vital structures	14 (11.6)	7.0-18.5
Cervical lymph node metastasis		
No/Unknown	69 (57.0)	48.1–65.5
Unilateral single	24 (19.8)	13.7–27.8
Unilateral multiple	18 (14.9)	9.6–22.3
Bilateral	10 (8.3)	4.6–14.6
Distance metastasis		
No/Unknown	89 (71.8)	63.3–78.9
Lung	28 (22.6)	16.1–30.7
Bone	5 (4.0)	1.7–9.1
Liver	2 (1.6)	0.4–5.7
Staging		
IVa	37 (30.6)	23.1–39.3
IVb	39 (32.2)	24.6–40.9
IVc	29 (23.9)	17.2–32.3
Unknown	16 (13.2)	8.3–20.4
Treatment		
Supportive treatment	37 (30.6)	23.1–39.3
Palliative radiation	12 (9.9)	5.8–16.5
Surgery alone	29 (23.9)	17.2–32.3
Chemoradiation	9 (7.4)	3.9–13,5
Surgery combined radiation	13 (10.7)	6.4–17.5
Surgery combined chemoradiation	5 (4.1)	1.8–9.3
Unknown	16 (13.2)	8.2–20.4

Table 2
Unadjusted univariable Cox proportional hazard model of prognostic factor

Variable	Hazard ratio (95% CI)	P-value
Age		
< 65	Reference	0.022
≥ 65	1.6(1.1–2.0)	
Treatment		
Intervention	Reference	0.001
Palliative	2.0(1.3–3.0)	
Staging		
4a	Reference	
4b	0.95(0.7–1.7)	0.819
4c	1.35(0.92–2.27)	0.221
Thyroid function test		
Euthyroid	Reference	
Hypothyroid	4.50(1.19–13.57)	0.008
Hyperthyroid	3.75(0.93–15.07)	0.063
White blood cell		
<10000	Reference	
≥10000	2.05(1.25–3.35)	0.004
Underlying disease		
Absent	Reference	
Present	1.19(0.79–1.81)	0.403
Tumor size (cm)		
< 5	Reference	
≥ 5	2.32(0.84–6.38)	0.104
Extra-thyroid extension		
No	Reference	
Yes	1.12(0.75–1.69)	0.569

Variable	Hazard ratio (95% CI)	P-value
Cervical lymph node metastasis		
No	Reference	
Unilateral single	1.03(0.64–1.65)	0.914
Unilateral multiple	0.76(0.44–1.31)	0.328
Bilateral	1.41(0.71–2.77)	0.323
Distance metastasis		
No	Reference	
Present (Lung, Bone and Liver)	1.33	0.183

Table 3
Adjusted multivariable Cox proportional hazard models of prognostic factor

Variable	Adjust Hazard ratio (95% CI)	P value
Age		
< 65	Reference	
≥ 65	2.6(1.5–4.4)	0.001
Treatment		
Intervention	Reference	
Palliation	1.9(1.1–3.1)	0.016
White blood cell		
< 10000	Reference	
≥ 10000	2.8(1.6–4.9)	< 0.001

Discussion

Our results showed the majority of ATC were older than 60 years (73.6%) with a male to female ratio of 1:1.9, very similar to previous findings [6–9]. However, most of our ATC patients (72.7%) presented with tumors ≥ 5 cm in diameters slightly larger than in previous studies (53.0–68.9%)[6,10]. According to TNM staging, our patients were approximately equally distributed across each staging (35.2% IVa, 37.1% IVb, and 27.6% IVc). In the case of stage IVb and IVc cases with extra-thyroid invasion, thyroid gland surrounding tissue was frequently involved making complete removal difficult in patients with extensive involvement of vital structures. We found that 11.6% of our patients presented with tumors involving vital structures. Distant metastasis was also a poor survival outcome prognostic factor found in 22.6% in our

series. Previous research reported ATC survival outcomes ranging from 2–10 months and > 2-year survival rate of 0–10%[11,] that similar to our findings of median survival time and 1-year survival rate of 77–82 days and 3.5-4.0%, respectively. Survival outcomes in prior retrospective studies vary depending on sample size, baseline demographic data, and selection bias. Our survival outcomes were likely worse than previous studies due to numerous cases with a huge tumor, involving vital structures, and distant metastasis. Treatment modality has important effects on survival outcomes. Some studies advocate multimodality treatment has benefits[12–14]; however, few studies report significant survival benefit from multimodality treatment[15,16]. Our study found that intervention treatments provided better survival outcomes than palliative treatment ($p < 0.05$) in overall staging. However, among the intervention treatment groups, the surgery and postoperative chemoradiation combination provided the best 1-year survival rate of 20.0%. These findings compare well with a previous study[14] that showed complete ATC resection combined with postoperative adjuvant chemotherapy and irradiation resulted in longer-term survival, even with persistent minimal disease. Although intervention treatment overall seemed to provide superior survival outcome benefit, we were also investigated possible differential effects across different staging levels. We found intervention provided significantly better outcomes over palliative care in stage IVa ($p < 0.05$). Intervention treatment was also better than palliative care in stage IVb and IVc ($p > 0.05$) but not at a statistically significant level possibly due to more aggressive tumors in these advanced stages.

Age, gender, tumor size, the extent of disease at presentation, acute symptoms, distant metastasis, leukocytosis, and multimodality therapy) are previously reported prognostic variables for survival outcome [13,14,17–21]. In our study, the ATC patients' prognosis mainly depended on age, leukocytosis, and treatment. Glaser et al[22] reported that age ≥ 65 years was an unfavorable prognostic factor. This finding was similar to our study that showed older age as the significant higher mortality factor (HR of 1.55). Other authors had also reported that older age was a poor prognosis factor but old age was variously defined. Old age range was reported as ≥ 60–75 years in the previous studies[20,23,24]. Furthermore, leukocytosis was observed that also predicted poor survival outcomes. Jiang et al[6] and Sugitani et al[25] found the HR of 1.12 and 1.48, respectively. In our series, a white blood cell count ≥ 10,000/ml^3 was analyzed with Cox regression that revealed a hazard ratio of 2.76 ($p < 0.001$). This finding was comparable with previous reports investigating effects of leukemoid paraneoplastic reaction by ATC tumor secreted cytokines including granulocyte-colony stimulating factor, granulocyte macrophage-CSF, and interleukin-6[26,27]. The last significant prognostic factor in our study, treatment modality, revealed that palliative treatment predicted the poorest overall survival outcome with a HR of 1.85 ($p < 0.05$). However, selection bias makes this finding unsurprising given that palliative care patients usually had advanced disease with high mortality.

Sugitani et al[25] classified the modality benefits in each ATC staging and found post-operative chemoradiation was a significantly favorable prognostic factor in stage IVb (HR of 0.45; $p = 0.083$) whereas at stage IVa its benefits did not reach a statistically significant level (HR of 0.21; $p = 0.19$). Although there is still controversy about proper ATC treatment protocol, several previous studies suggest

multimodal treatment allows a longer ATC survival rate. Kobayashi et al[19] suggested active multimodality for the early stage. The multimodality protocol of surgery and chemoradiation has been advocated as offering the longest survival rate[28–30]. In the present study, the combined modality of postoperative chemoradiation and radiotherapy offered a longer median survival time of 187 days and 177 days, respectively, over surgery alone, which provided a survival rate of 64 days, again supporting a multi-modality advantage in the survival outcomes. A negative prognostic effect has been reported for hypothyroidism. Our study found hypothyroidism was a negative predictor with using univariate analysis but the multivariate regression model analysis showed that this difference was not statistically significant. Jiang et al[6] found similar findings where serum T4 level was not found statistically significant in Cox regression analysis. However, they observed that patients with low T4 level had significantly lower survival rates than those with normal T4 levels. Several authors proposed that hypothyroidism may be occurring via tumor destruction of the normal thyroid tissue[31,32] and inhibition of changing of T4 to T4 binding globulin by unsaturated fatty acid from hypoxic or injured tissue in severe illness patients[33]. Therefore, low T4 levels may represent a late stage of ATC with severe disease that indicates poor survival outcomes.

ATC is an extremely aggressive rapidly progressing tumor that makes it difficult to use a randomized prospective protocol for evaluation of treatment and survival outcomes; therefore, a retrospective chart review was selected on feasibility basis for this study. Although our study includes the limitations of retrospective studies, it did show multi-modality treatment was superior to palliative modality, especially the combination of surgery and chemoradiation. Furthermore, we found that not only palliative treatment but also age and leukocytosis were unfavorable prognostic factors for predicting mortality outcomes. In future, more laboratory information and detailed clinical data would allow for better investigation of prognostic factors.

Conclusion

Although there is no standardized successful ATC treatment protocol, we showed that intervention treatment had better survival outcomes in all stages of ATC, especially in stage IVa. Among intervention treatment, postoperative chemoradiation offered the longest survival rate and should be considered for ATC patients who had a resectable tumor and no poor prognostic factors. Unfavorable predictive prognosis factors included older age ≥ 65 years, leukocytosis ≥ 10,000/ml^3, and palliative treatment.

Abbreviations

ATC Anaplastic thyroid cancer

AJCC American Joint Committee on Cancer

HR Hazard ratio

Declarations

Ethic approval and consent to participate

This study was approved by Khon Kaen University Ethic Committee for Human Research (HE611221). Regarding the consent form, it was not applicable due to retrieving retrospective data from the medical chart.

Consent for publication

Not applicable

Availability of data and material

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

Competing interests

Not applicable

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Authors' contributions

PK, PS, PV participated in the concept preparation. PK and PS participated in data collection and/or processing. PK and PS participated in drafting the article. PK, PC, PV, CT, SL, WT, TR, and SS participated in critically revising the article.

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Figures

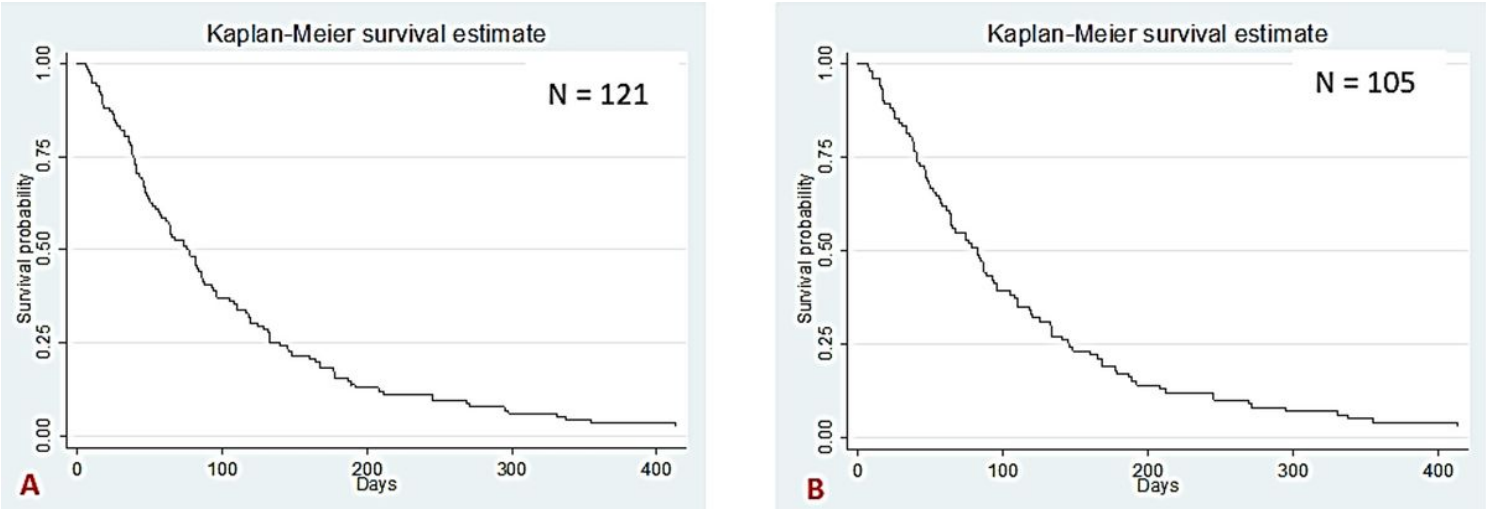
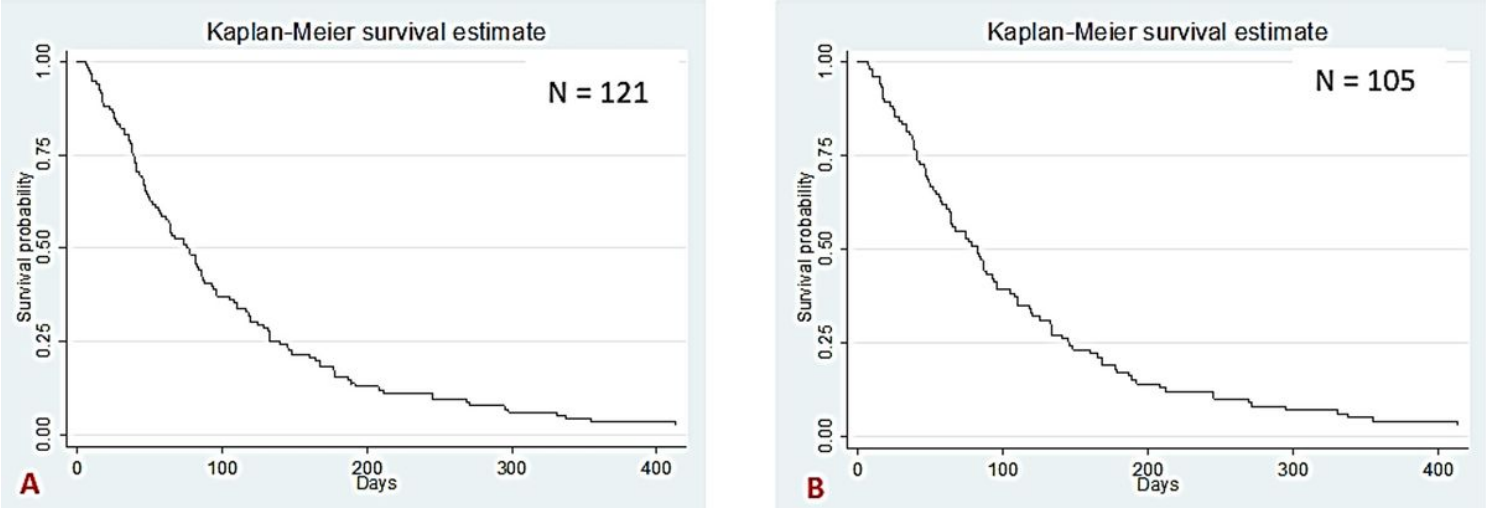


Figure 1

One-year overall survival rate and the median survival time of all ATC patients were 3.5% (95%CI: 1.7-8.0) and 77 days (95%CI: 57-88), respectively (A); however, 16 ATC patients had insufficient data to classify the staging and the modality of treatment. Thus, 105 ATC patients showed 1-year overall survival rate of 4% (95%CI: 1.3-9.2) and the median survival time of 82 days (95%CI: 63-96) (B).



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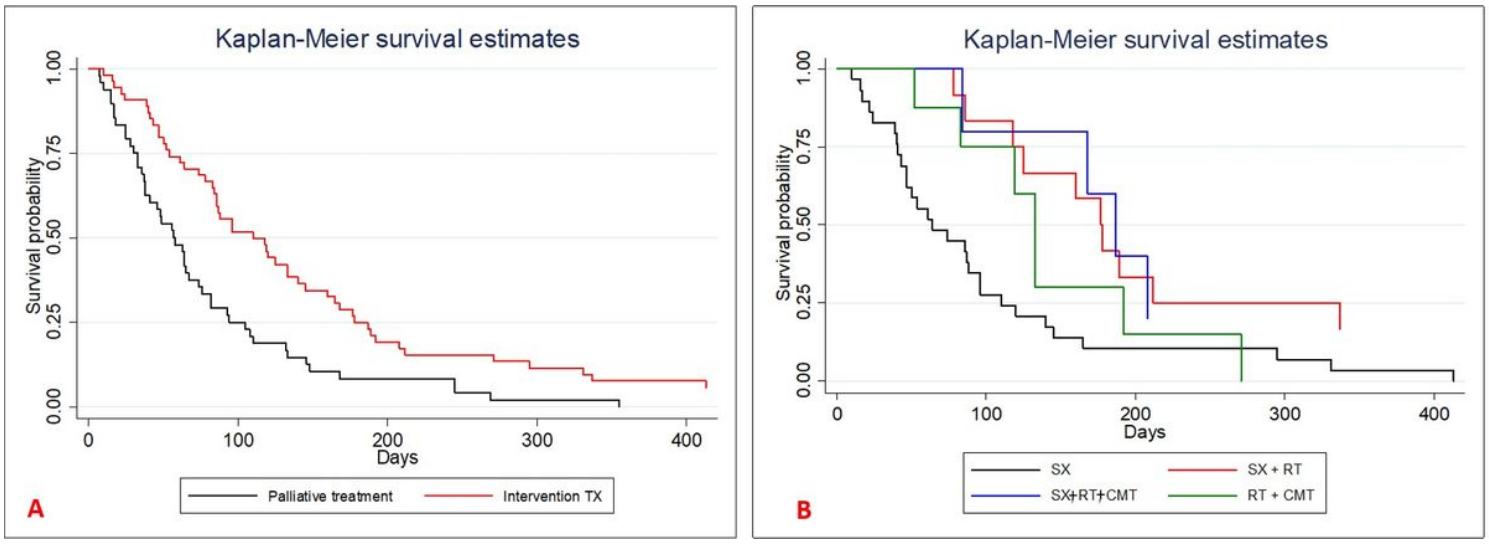
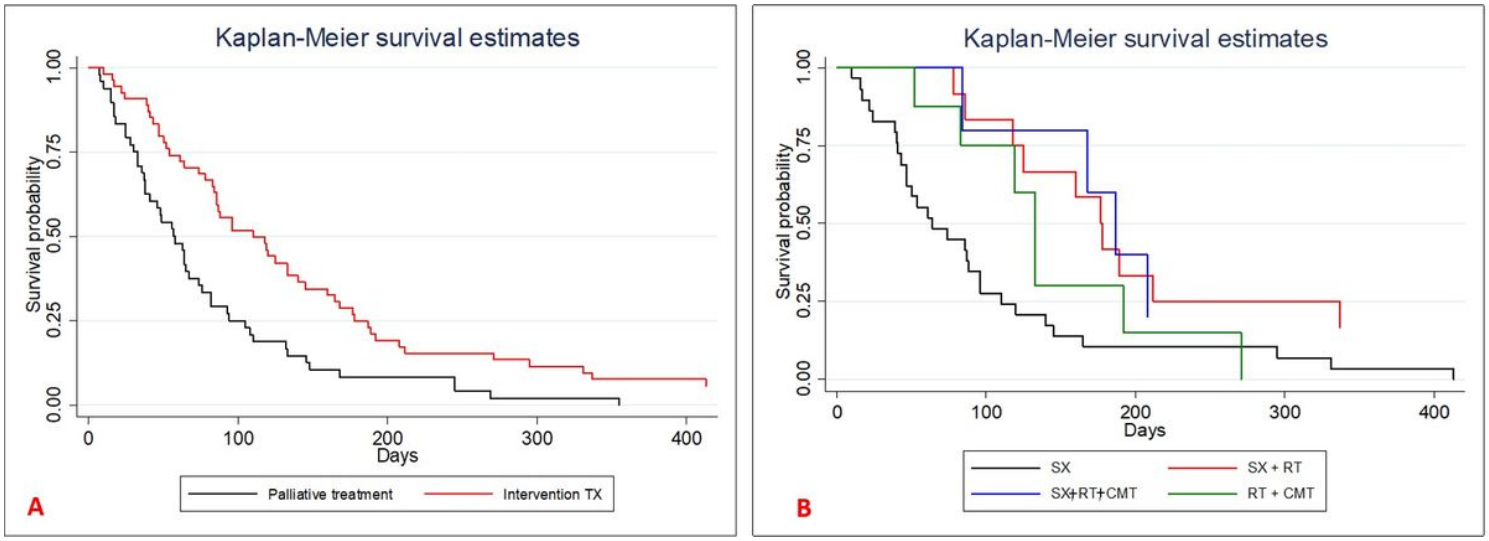


Figure 2

One hundred and five ATC patients had classified that received palliative modality of 49 patients whereas 56 patients received intervention treatment. Intervention treatment allowed the median survival time of 110 days (95%CI: 84-140) that were better than the palliative treatment. The palliative treatment allowed the median survival time of 58 days (95%CI: 38-74). Furthermore, the Kaplan-Meier survival curve was analyzed with a log-rank test that the intervention treatment was significantly better than the palliative treatment (p = 0.0006) (A). In the intervention treatment, the combination of surgery with postoperative chemoradiation showed the best survival rate (log-rank test; p = 0.01). The median survival time of intervention modalities was subgroup analyzed that 187 days (95%CI: 84-208) in the surgery combined postoperative chemoradiation treatment, 177 days (95%CI: 86-337) in the surgery combined radiation, 133 days (95% CI: 52-192) in the chemoradiation, and 64 days (95%CI: 43-96) in the surgery alone (B).



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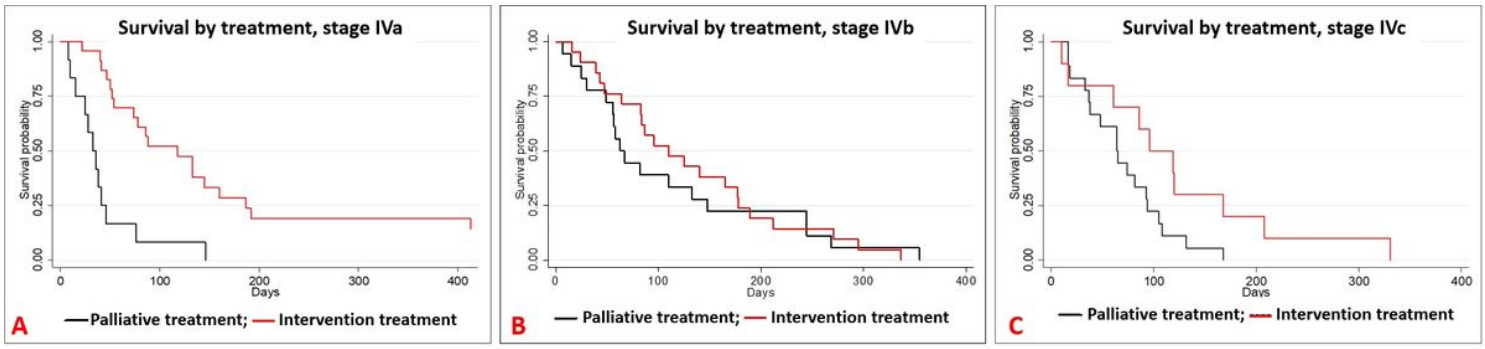
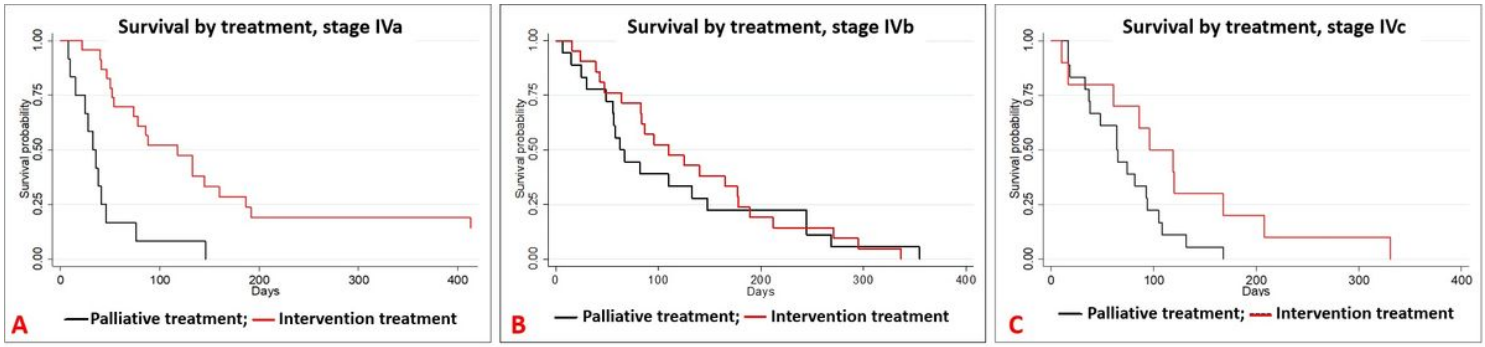


Figure 3

Thirty-seven ATC patients in stage IVa had the median survival time of 118 days (95%CI: 54-160) in the intervention treatment group whereas the palliative treatment group had 33 days (95%CI: 10-46). This difference was a statistical significance (p=0.00). The Kaplan-Meier curve showed the benefit survival rate in the intervention group (log-rank test; p = 0.00) (A). In 39 patients who suffered from ATC stage IVb, the intervention treatment allowed the median survival time of 110 days (95%CI: 64-177) that were better than the palliative treatment (median survival time of 63 days (95%CI: 49-133); however, the median time survival difference was not statistically significant (p=0.63). The Kaplan-Meier curve showed that the intervention group seemed superior to palliative treatment but not reached a statistical significance (log-rank test; p=0.67) (B). Regarding 29 patients with ATC stage IVc, their median survival time was observed that the intervention group (96 days (95%CI: 10-168)) was not significantly better than the palliative group (64 days (95%CI: 37-93)) (p = 0.06). However, the Kaplan-Meier survival curve of the intervention group was not significantly better than the palliative group (log-rank test; p=0.055) (C).



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