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ANAPLASTIC THYROID CANCER TREATED AT THE ENDOCRINE SURGERY UNIT OF SAN MARTINO HOSPITAL: A REVIEW OVER THE LAST 50 YEARS AND A CONFRONTATION BETWEEN HISTORICAL TREATMENTS AND NEW THERAPEUTIC MODALITIES

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ABSTRACT IN ITALIAN

Introduzione: Il cancro anaplastico della tiroide (ATC) è una rara neoplasia a prognosi infausta a breve distanza dalla diagnosi. La gestione dell'ATC è ancora oggetto di discussione.

Obiettivo: Confrontare la sopravvivenza specifica per ATC in una coorte storica (1967-2014) ed una coorte attuale (2015-2022), alla luce delle modifiche terapeutiche recenti.

Metodi: Sono stati selezionati tutti i pazienti con ATC diagnosticati e trattati presso la Chirurgia Endocrina dell'Ospedale San Martino dal 1967 al 2022. Il *cut-off point* per le coorti è stato inserito nel 2015, anno di introduzione della chemioterapia mirata per ATC. Sono state eseguite analisi univariate, multivariate e stratificate per coorte.

Risultati: Sono stati inclusi 64 pazienti. La sopravvivenza mediana è stata di 3.7 mesi e la probabilità di sopravvivenza a 1 anno era del 17.9%. La distribuzione di ATC su gozzo preesistente o di prima diagnosi era identica (p=0.517). Il genere femminile era associato ad una sopravvivenza specifica più lunga (HR=0.52; 95%CI= 0.28-0.95; p= 0.035) e la terapia adiuvante ha evidenziato un beneficio sulla sopravvivenza specifica per ATC tra i pazienti della coorte storica (HR=0.47; 95% CI=0.23-0.98; p=0.045). Lo stadio TNM più avanzato è associato ad una diminuzione della sopravvivenza (p<0.001). Non sono state osservate differenze statisticamente significative per la sopravvivenza specifica tra le coorti (p=0.143). Non è stato possibile determinare le associazioni con la sopravvivenza per l'attuale coorte, a causa della rarità della malattia.

Conclusioni: I nostri risultati suggeriscono un ruolo della terapia adiuvante post-chirurgia nel migliorare della sopravvivenza specifica per ATC; la chirurgia potrebbe fornire quindi un sottostante beneficio. Il potere statistico del nostro studio non ci ha permesso di investigare l'impatto della terapia mirata. Sono necessari ulteriori studi per chiarire il contributo prognostico delle nuove modalità per il trattamento dell'ATC.

ABSTRACT IN ENGLISH

Introduction: Anaplastic thyroid cancer (ATC) is a rare aggressive malignancy with a poor prognosis. The management of ATC is still under debate due to lack of data, scarce literature, and absence of prospective studies. **Objective:** To compare ATC-specific survival between a historical cohort (1967-2014) and a current cohort (2015-2022). **Methods:** All patients with ATC diagnosed and treated at the Endocrine Surgery Unit of San Martino Hospital from 1967 to 2022 were enrolled. Patients were divided into two cohorts using the introduction of targeted therapy for ATC in 2015 as the cut-off point. Univariate, multivariate and analysis stratified by cohort were performed. **Results:** The final sample consisted of 64 patients. The overall median survival was 3.7 months, and the 1-year survival probability was 17.9%. The distribution of ATC diagnosed in a pre-existing goiter and as a first diagnosis was even (p=0.517). Overall, female gender was associated with longer specific survival (HR=0.52; 95%CI=0.28-0.95; p=0.035). Adjuvant therapy was beneficial on survival among patients from the historical cohort (HR=0.47; 95% CI=0.23-0.98; p=0.045). Advanced TNM stages were associated with decreased ATC-specific survival for patients as a whole (p< 0.001). No differences for ATC-specific survival were observed between the cohorts on adjusted analysis (p=0.143). It was not possible to determine associations with survival for the current cohort due to the poor outcome, particularly about the use of targeted therapy. **Conclusions:** Our findings suggest a role of adjuvant therapy on improving ATC-specific survival, and surgery might have a subjacent benefit. This role is nevertheless of very limited clinical value. The statistical power of the study did not allow us to investigate the impact of targeted therapy on survival. Further studies are needed to clarify the contribution of the new treatments and to elucidate predictors of survival.

1. INTRODUCTION

The present thesis was performed to obtain the medical degree (M.D.) from the *Università Degli Studi di Genova*. The study developed was a cohort of patients with Anaplastic Thyroid Cancer (ATC) diagnosed and treated from 1967 to 2022 at the Endocrine Surgery Unit of San Martino Hospital with the objective to compare ATC-specific survival between two different periods: 1967-2014 and 2015-2022. The total sample was divided in two cohorts to better understand the potential differences regarding the treatment of ATC over 50 years of follow-up, particularly after the introduction of targeted therapy for management of ATC in 2015.

The introduction below is an overview about the thyroid gland, the epidemiological aspects for thyroid cancer, and encloses with considerations focused on ATC. Thereafter, the objective and the hypothesis of the study are presented separately. In methodology, the analysis plan for carrying out the study is explained. For the next section, the results are exposed. The last sections, discussion and the conclusions, finalize the thesis with considerations about the findings, and reply the objective of the study.

1.1 Thyroid Gland

The thyroid is an endocrine gland consisted of two lobes connected by the isthmus, a thin band of tissue. The thyroid gland typically is localized posterior to the sternohyoid and sternothyroid strap muscles and the lobes are situated adjacent to the thyroid cartilage in the deep cervical fascia. The adult thyroid is reddish-brown in color, rubbery in texture and it weighs approximately 20 g, depending on the body weight and iodine intake (1, 2).

The arterial supply of the thyroid gland is abundant, and derives from the superior and the inferior thyroid arteries. The superior thyroid arteries originate from the external carotid arteries, and divide into anterior and posterior branches at the apices of the thyroid lobes whereas the inferior thyroid arteries are branches from the thyrocervical trunks of the subclavian arteries (2). Branches of the inferior and superior arteries also supply the parathyroid glands. The direction of the inferior thyroid artery as it enters the thyroid gland is an important landmark used for the identification of the recurrent laryngeal nerve (1, 2).

For the surgeon, the two most important nerves associated with the thyroid gland are the recurrent laryngeal nerve and the external branch of the superior laryngeal nerve. Both are the nerves responsible for the function of the larynx and each of them is paired, with a right and left side. Injury to one recurrent laryngeal nerve leads to a paralysis of the

ipsilateral vocal cord which results in a normal but weak voice if the paralysis be in the paramedian position, and in hoarse voice with an ineffective cough if the paralysis be in the abducted position. Bilateral recurrent laryngeal nerve injury may lead to airway obstruction, necessitating emergency tracheostomy, or loss of voice. The injury to the superior laryngeal nerve may result in aspiration. It is critical that these structures should be better preserved during a thyroidectomy (1, 2).

The thyroid hormones, Tetraiodothyronine (T4) and Triiodothyronine (T3), affect almost every system in the body. They are important for fetal brain development and skeletal maturation, the stimulation of Na/K ATPase in various tissues, the maintaining the normal hypoxic and hypercapnic respiratory drive in the respiratory center of brain, the gastrointestinal motility, the increase of bone and protein turnover, the speed of muscle contraction and relaxion, and the increase of glycogenolysis, hepatic gluconeogenesis, intestinal glucose absorption as well as cholesterol synthesis and degradation (1).

The regulation of the thyroid hormones production is tightly controlled by the hypothalamic-pituitary-thyroid axis. Low circulating levels of T4 and T3 stimulate the hypothalamus to release thyrotropin-releasing hormone, which in turn stimulates the release of TSH from the anterior pituitary. TSH stimulates the formation of thyroid hormones by binding to its receptor on the thyroid follicular cells, leading to both increased transport of iodine as well as transport and release of T4 and T3 from the colloid into the bloodstream. Conversely, elevated circulating thyroid hormone levels lead to a negative feedback loop, with downregulation of thyrotropin-releasing hormone and TSH from the hypothalamus and pituitary, respectively (2).

Nonetheless, the thyroid gland is also capable of autoregulation which allows it to modify its function independent of TSH, as an adaptation to low iodide intake or to iodine excess. In situations of low iodide intake, the gland preferentially synthesizes T3 rather than T4, increasing the efficiency of secreted hormone. On the other hand, in a scenario of iodide excess, the synthesis and secretion of thyroid hormones are inhibited (1).

1.2 Thyroid Cancer

Thyroid cancer is the most common endocrine malignancy (3) that is, generally, classified into papillary carcinoma, follicular carcinoma, medullary carcinoma and anaplastic carcinoma (1, 2). Well-differentiated thyroid carcinomas include papillary carcinoma, follicular carcinoma and Hürtle cell carcinoma (a subtype of follicular thyroid

cancer (1), and all those tumors arise from the thyroid follicular epithelial cells. Poorly differentiated carcinoma and anaplastic (undifferentiated) carcinoma also derive from follicular cells but are more clinically aggressive compared to well-differentiated thyroid carcinomas due to their loss of differentiation. Medullary carcinoma, unlike the other tumors described, arise from the neuroendocrine parafollicular C cells (2, 4).

Papillary carcinoma accounts for 80% of all thyroid malignancies in iodine-sufficient areas, and it is the predominant thyroid cancer in children and individuals exposed to external radiation. Follicular carcinomas comprise as 10% of thyroid cancers and occur more commonly in iodine deficient areas. Most medullary carcinomas occur sporadically, and accounts for about 5% of thyroid malignancies (1). The anaplastic carcinoma is found in 1-4% of all thyroid cancers but accounts for 40-50% of thyroid cancer mortality (3-5). As the topic of this study, the anaplastic thyroid cancer will be separately discussed below.

The etiology of thyroid carcinoma is not well understood. The only known established risk factor is ionizing radiation, especially when expose is in childhood. Although, there is an evidence that other factors may play a role, such as excess body weight, greater height, hormonal exposures, and certain environmental pollutants (6).

Thyroid cancer is responsible for 586,000 cases worldwide, ranking in 9th place for incidence in 2020 (4). The global incidence rate in women is 3-fold higher than that in men, leading the thyroid cancer to represent 1 in every 20 cancers among women. Mortality rates from the disease are much lower, compared to the incidence rates, being estimated 44,000 deaths in both sexes combined (6).

The rises in incidence rates, since 1980, and comparatively stable or even declining mortality rates have been observed in much of the world. The rapid increase of thyroid cancer, particularly papillary thyroid cancer, has been largely attributed to the progressively available and sensitive use of ultrasonography and other imaging modalities. The precocious detection and diagnosis consecutively led to a forward therapy which in turns lead to decrease or stable in mortality rates (6).

1.3 Anaplastic Thyroid Cancer

Anaplastic thyroid cancer (ATC) is a rare aggressive malignancy with a dismal prognosis. While well-differentiated thyroid cancers account for majority of thyroid tumors, ATCs comprise 1-4% of the overall cases but it is responsible for 40-50% of total thyroid cancer-related deaths. Due to its aggressive nature, the overall survival of patients with ATC is estimated in less than 12 months (historically, about 5 months) and an one-year overall survival of 20%, in contrast of the good prognosis with > 98% five-years survival among well-differentiated thyroid cancers (3, 5, 7).

The patterns of thyroid carcinoma have been changing over the time, in favor of an increasing in the incidence of papillary thyroid cancer (which has been postulated to be related to the raise of dietary iodine intake). This trend has the potential to decrease the percentage accounted for ATC in several countries, leading to a more favorable prognosis for patients with thyroid cancer (5, 8). However, for the patients with ATC, the medical approaches remain intensive due to the sudden onset and aggressive course of ATC that necessitate immediate and coordinated involvement of surgeons, radiation and oncologists, endocrinologists and palliative care teams (5).

The risk factors for ATC are uncertain. An association of goiter with ATC was previously observed but the evidences are limited to clarify if goiter is a risk factor for ATC. Measures of adiposity and risk of thyroid cancer were already exploited, and obesity may be implicated as a risk for ATC as for other thyroid cancers. The view that a small subset of differentiated thyroid cancer might transformer to ATC is supported. ATC arises from a preexisting differentiated thyroid cancer via the accumulation of additional somatic genetic mutations, including TP53 and TERT. Nevertheless, these findings need to be confirmed (5).

Commonly, ATC presents as one or more rapidly growing neck lesion, involving thyroid, cervical lymph nodes, and in certain circumstances infiltrating soft tissue, nerve structures, esophagus, and trachea. The potential tracheal implication leads the evaluation for securing the airway an essential step in assessing patients with suspected or confirmed ATC. Additionally, screening for distant metastasis is critical in managing these patients (3).

All ATCs are stage IV, defined as follow according to TNM (Tumor-Lymph node-Metastasis) classification:

- Stage IVA: T1-T3a, N0, M0
    - Stage IVA lesions comprise a disease still intrathyroidal (T1-T3a), not definitely spread to lymph nodes (N0) without distant metastases (M0).
- Stage IVB: T3b-T4, ≥N1, M0
    - In Stage IVB, the primary tumor has gross extrathyroidal extension (T3b-T4) and/or is involving locoregional lymph nodes (≥N1) but not spread to distant sites (M0).
- Stage IVC: Any T, Any N, M1
    - Stage IVC patients have distant metastases.

Approximately 10% of patients with ATC present with stage IVA, whereas 40% have extrathyroidal invasion and/or lymph node metastases. The remainder of the patients presenting with metastatic disease. Nonetheless, airway assessment is an important element for every patient with ATC, independently of TNM stage, due to the potential of presence of recurrent laryngeal nerve invasion, tumor mass affecting the pharynx, larynx, trachea and/or esophagus, and transluminal invasion of any of these structures, particularly tracheal lumen (5).

The recommendations for the ATC management are limited because of lack of data, scarce studies, and not available randomized clinical trials in ATC. Consequently, at present, there is no definitive or standardized treatment for ATC in order to improve survival (5, 9), despite of recent evidences that patients who have surgical intervention for ATC have a significantly longer median overall survival than non-operated ATC patients (5, 7, 10). Nevertheless, surgical resection, when achievable, is strongly recommended for patients with IVA/IVB ATC followed by an adjuvant therapy, preferably external beam high-dose radiation or chemoradiation. A subset of IVC ATC patients are also candidates for a surgery when a locoregional disease control for palliation or to prevent future complications, such as tracheal invasion/obstruction, are required (5). Radical resection (laryngectomy, oesophagectomy, tracheal resection and/or resection of great vessels) is generally not indicated given the poor prognosis of ATC patients (5).

Total thyroidectomy with lymph node dissection is the most common type of surgery for patients with ATC, and a total thyroidectomy with negative margins is

implicated on improving survival, notably, if the surgical approach is followed by a high-dose radiation therapy. Prophylactic central or lateral neck node dissection is not indicated (5).

Additionally to the current therapeutic regimes, targeted approaches emerged as treatment options for ATC patients (7, 9). The $BRAF^{V600E}$ is the most commonly actionable mutation seen in ATC patients (in 50-70% of cases), and the use of BRAF-directed therapy may be recommended in stage IVC BRAF-mutated patients (5). In patients without a somatic mutation, the use of personalized targeted therapy is not supported for any class of systemic targeted drugs (5).

Immunotherapy is also presently under investigation since it was demonstrated that ATC shows the immune infiltration as a hallmark of the disease. In ATC, $BRAF^{V600E}$ mutation is strongly associated with the expression of PD-L1, a landmark of tumor-immune cell interaction (5, 7). Although, at the moment, any immunotherapy approach was FDA approved specifically for the treatment of ATC patients (5).

Besides the available tools for the treatment of ATC, the survival for patients with ATC remains poor. The promising new modalities may result in expanding treatment routes for ATC, if the beneficial of these therapies be confirmed. This study was developed not only for knowing the casuistry of the Endocrine Surgery Unit of San Martino Hospital but also for comparing the impact on survival of conventional approaches with new strategies for ATC patients over the time.

2. OBJECTIVE

The objective of this study was to compare the outcome (ATC-specific survival) of patients diagnosed with ATC and treated at the Endocrine Surgery Unit of San Martino Hospital between a historical group of patients (diagnosed and treated within 1967-2014) and a current group of ATC patients (diagnosed and treated within 2015-2022).

3. HYPOTHESIS

The null hypothesis (H0) and the alternative hypothesis (Ha) of the study were defined as:

H0: There is no survival differences between the treatments for the two groups

Ha: There is survival differences between the treatments for the two groups

4. METHODS

4.1 Type of Study

The study is a cohort study in which the patients who constitute the population were diagnosed and treated at the Endocrine Surgery Unit of San Martino Hospital in Genoa from 1967 to 2022.

4.2 Study Population

The study population was defined as patients with ATC that were diagnosed and treated at the Endocrine Surgery Department in collaboration with endocrinologists, pathologists, and oncologists/radiation team of San Martino Hospital during 1967-2022.

The total sample was divided in two cohorts to better understand the potential differences regarding the treatment of ATC during the period from 1967 to 2022. The cutoff point between the two cohorts was chosen as the introduction of targeted therapy for ATC in 2015. Based on this, the two cohorts were defined as:

- Historical cohort: ATC patients diagnosed and treated during 1967-2014
- Current cohort: ATC patients diagnosed and treated during 2015-2022

The diagnosis of ATC was pathologically confirmed for all patients of the sample.

4.3 Measurements

The ATC-specific survival was the outcome of the study.

The ATC-specific survival was considered as the time elapsed between the date of the diagnosis of ATC for not operated patients or the date of the surgery for operated ATC patients and death, measured in months, from 01/01/1967 to 31/12/2022. The end of the follow-up was on the 30/04/2023. Patients without date of death until the end of the follow-up were considered alive.

The exposure of the study was the treatment. For operated patients, we considered surgery as isolated, as neoadjuvant approach and as adjuvant approach. For not operated patients, we considered the systemic therapy. Adjuvant therapy and systemic therapy were evaluated in combination of different treatments (multimodal approach) and as a singly strategy.

4.4 Data Source and Variables

Three different sources were used to accrue the patients. The historical cohort was obtained, basically, through pre-filled questionnaires that were completed when the patient was admitted at the Endocrine Surgery Unit of San Martino Hospital. Few patients from the historical cohort and all patients from the current cohort were allocated from databases of the Endocrine Surgery Unit and of the Endocrinology Unit of San Martino Hospital.

The variables studied were grouped as follow:

- Demographic characteristics: gender and age (categorized as <70 and ≥70 years);
- Clinical characteristics: time for pre-existing goiter (in months), first symptom (defined as swelling, dysphonia, dysphagia, dyspnea, local pain, slimming, and other) duration of first symptom (in months), thyroid palpation (defined as no alteration, single nodule, multinodular, diffuse thyroid enlargement, and other), cervical lymph node palpation (defined as absent, homolateral or bilateral), extra-thyroidal disease (defined as absent, present, neoplastic disease or non-neoplastic disease);
- Tumoral characteristics: ATC (classified as pure, within a pre-existing goiter or incidental), somatic mutations (classified as not investigated, investigated, mutated or wild), tumoral stage (IVA, IV, and IVC), local invasion (absent or present), and distant metastases (absent or present);
- Treatment: previous surgical therapy (classified as no, linfonodal biopsy, enucleation, and other), not surgical previous therapy (classified as no, radiotherapy, chemotherapy, targeted therapy, and other), surgery (classified as total thyroidectomy, total thyroidectomy with homolateral lymphadenectomy, total thyroidectomy with bilateral lymphadenectomy, subtotal thyroidectomy, near-total thyroidectomy, debulking, tracheostomy, lobectomy, and other), adjuvant therapy or therapy for not operated (classified as radicalization, radiometabolic therapy, radiotherapy, chemotherapy, targeted therapy, thyroid replacement therapy, tracheostomy, and other).

4.5 Inclusion criteria

Pathological confirmation of ATC was mandatory for inclusion of patients in the sample.

4.6 Exclusion criteria

The exclusion criterion for enrollment was not having an available pathologic confirmation of ATC, and for the analysis, not having enough information for statistical measures.

4.7 Statistical Analysis

Qualitative variables were presented through absolute and relative frequencies. Quantitative variables were showed as mean, median, standard deviation, interquartile range, and minimum-maximum values. Associations between qualitative variables were performed using Pearson's chi-square test or Fisher's exact test. For comparison between two groups was used Student's test.

For the survival analysis, the Kaplan-Meier method was performed for the survival curves compared through the log-rank test. Univariate and multivariate Cox proportional hazard models were used to estimate hazard ratio (HR) and 95% confidence interval (95% CI) for the association between ATC-specific survival and the studied variables for the total sample, for the historical cohort, and for the current cohort. Stratified analyses were performed by cohort. The significance level adopted was 5%.

Analyzes were performed using SPSS for Windows v.25 statistical software.

5. RESULTS

We identified 71 patients with ATC diagnosed and treated from 01/01/1967 until 31/12/2022 at Endocrine Surgery Unit of San Martino Hospital. Seven patients were excluded from the final sample due to missing data for statistical analysis. Therefore, 64 patients were followed-up, and 61 deaths (95.3%) were observed at the end of the follow-up (on the 30/04/2023).

Forty-seven patients comprised the historical cohort, and 17 patients encompassed the current cohort. The historical cohort covered 73.4% of the final sample.

Patients from the historical cohort were younger (p= 0.029), presented mainly swelling as the first symptom of the ATC, with a median duration of 3 months, and showed mostly a multinodular thyroid without palpable lymphadenopathy at the time of the diagnosis. Only 7 patients out of the total were subject to a neoadjuvant approach (6 patients were undergone to a surgical pre-operative approach and 1 patient was performed a non-surgical modality of therapy). Seventeen patients (37,8%) were subjected to an

adjuvant treatment in which radiotherapy followed by chemotherapy was the post-operative modality mostly performed among the patients from the historical cohort. [Table 1]

Patients from the current cohort were more likely to be diagnosed with distant metastasis (p= 0.022), more investigated for somatic mutations (p<0.001), and more frequently treated with systemic therapy isolated (p= 0.007) – particularly targeted therapy (p= 0.003) – than patients from the historical cohort. [Table 1]

Forty-four patients from the historical cohort were undergone to a surgical intervention in contrast with 11 patients from the current cohort (93.6% *versus* 64.7%) [Table 1 and Figure 1], and this association was statistically significant (p= 0.008). No patient from the current cohort was submitted to a debulking approach while it was the type of surgery mostly performed among patients from the historical cohort (p= 0.002), followed by a total thyroidectomy or a total thyroidectomy with homolateral lymphadenectomy. [Table 1]

No statistical association was observed between sex distribution by cohort (p=0.826) [Table 1] but the female gender was more frequent in both cohorts.

Characteristics of all patients are reported in Table 1 and additional Table 1 [Table 1a].

Table 1. Characteristics of patients with Anaplastic Thyroid Cancer, San Martino Hospital, Genoa 1967-2022.

Characteristics		***Current***	***Historical***	***p-value***
		n = 17 (%)	**n = 47 (%)**	
Sex	Male	6 (35.3)	18 (38.3)	0.826[1]
	Female	11 (64.7)	29 (61.7)	
Age (years)	Mean (SD)	74.3 (11.8)	66.6 (12.3)	0.029[3]
	Median (IQR)	79 (62-84)	67 (60-77)	
	Min- Max *	54-88	40-87	
Anaplastic	Pure	4 (33.3)	17 (45.9)	0.517[1]
	Pre-existing goiter	7 (58.3)	19 (51.4)	
	Incidental	1 (8.3)	1 (2.7)	

Time for pre-existing goiter (*months*)	Mean (SD)		29.8 (25.3)	NA
	Median (IQR)		24 (10-36)	
	Min-Max *		1-84	
First Symptom				
Swelling	No		1 (3.4)	NA
	Yes		28 (96.6)	
Dysphonia	No	0	19 (65.5)	0.367[2]
	Yes	1 (100)	10 (34.5)	
Dysphagia	No	0	20 (69.0)	0.333[2]
	Yes	1 (100)	9 (31.0)	
Dyspnea	No	0	15 (51.7)	0.999[2]
	Yes	1 (100)	14 (48.3)	
Local pain	No		21 (70.0)	NA
	Yes		9 (30.0)	
Slimming	No		28 (96.6)	NA
	Yes		1 (3.4)	
Other symptom	No		27 (93.1)	NA
	Yes		2 (6.9)	
Duration of the first symptom (*months*)	Mean (SD)		19.0 (38.3)	NA
	Median (IQR)		3 (1-17)	
	Min-Max *		0-180	
Thyroid palpation	Single nodule		9 (32.1)	NA
	Multinodular		13 (46.4)	
	Diffuse thyroid enlargment		6 (21.4)	
Cervical lymph nodes enlargment	No	0	18 (62.1)	0.400[2]
	Yes, homolateral	1 (100)	7 (24.1)	
	Yes, bilateral	0	4 (13.8)	
Previous surgical therapies	No	16 (100)	32 (84.2)	0.163[2]
	Yes	0	6 (15.8)	
Lymph node biopsy	No	16 (100)	34 (89.5)	0.306[2]
	Yes	0	4 (10.5)	

Enucleation	No	16 (100)	36 (94.7)	0.999[2]
	Yes	0	2 (5.3)	
Other therapy	No	16 (100)	36 (94.7)	0.999[2]
	Yes	0	2 (5.3)	
Not surgical previous therapy	No	15 (93.8)	38 (97.4)	0.501[2]
	Yes	1 (6.3)	1 (2.6)	
Radiotherapy	No	15 (93.8)	38 (97.4)	0.501[2]
	Yes	1 (6.3)	1 (2.6)	
Chemotherapy	No	16 (100)	38 (97.4)	0.999[2]
	Yes	0	1 (2.6)	
Somatic mutations	Not, investigated	0	38 (88.4)	<0.001[2]
	Yes, investigated	17 (100)	5 (11.6)	
*TP*53	Mutated	5 (31.3)	2 (40.0)	0.999[2]
	Wild	11 (68.8)	3 (60.0)	
TERT	Mutated	1 (7.1)	0	0.999[2]
	Wild	13 (92.9)	5 (100)	
BRAF	Mutated	2 (14.3)	0	0.999[2]
	Negative	12 (85.7)	5 (100)	
RAS	Mutated	2 (14.3)	0	0.999[2]
	Wild	12 (85.7)	5 (100)	
Other mutations	Mutated	9 (56.3)	1 (20.0)	0.311[2]
	Wild	7 (43.8)	4 (80.0)	
Extra thyroidal disease	No	15 (93.8)	42 (93.3)	0.999[2]
	Neoplastic disease	1 (6.3)	3 (6.7)	
Surgery	No	6 (35.3)	3 (6.4)	0.008[2]
	Yes	11 (64.7)	44 (93.6)	
Biopsy	No	14 (82.4)	44 (93.6)	0.329[2]
	Yes	3 (17.6)	3 (6.4)	
Total thyroidectomy	No	14 (82.4)	38 (80.9)	0.999[2]
	Yes	3 (17.6)	9 (19.1)	

Total thyroidectomy with homolateral lymphadenectomy	No	13 (76.5)	38 (80.9)	0.732[2]
	Yes	4 (23.5)	9 (19.1)	
Subtotal thyroidectomy	No	17 (100)	44 (93.6)	0.559[2]
	Yes	0	3 (6.4)	
Debulking	No	17 (100)	29 (61.7)	0.002[2]
	Yes	0	18 (38.3)	
Tracheostomy	No	16 (94.1)	43 (91.5)	0.999[2]
	Yes	1 (5.9)	4 (8.5)	
Lobectomy	No	16 (94.1)	45 (95.7)	0.999[2]
	Yes	1 (5.9)	2 (4.3)	
Other surgery	No	16 (94.1)	44 (93.6)	0.999[2]
	Yes	1 (5.9)	3 (6.4)	
Adjuvant therapy or therapy or for not operated	No	3 (20.0)	28 (62.2)	0.007[2]
	Yes	12 (80.0)	17 (37.8)	
Radicalization	No	14 (93.3)	44 (97.8)	0.441[2]
	Yes	1 (6.7)	1 (2.2)	
Radiometabolic therapy	No	15 (00)	44 (97.8)	0.999[2]
	Yes	0	1 (2.2)	
Radiotherapy	No	9 (60.0)	32 (71.1)	0.525[2]
	Yes	6 (40.0)	13 (28.9)	
Chemotherapy	No	15 (100)	37 (82.2)	0.182[2]
	Yes	0	8 (17.8)	
Targeted therapy	No	8 (53.3)	41 (91.1)	0.003[2]
	Yes	7 (46.7)	4 (8.9)	
Thyroid replacement therapy	No	15 (100)	43 (95.6)	0.999[2]
	Yes	0	2 (4.4)	
Tracheostomy	No	15 (100)	42 (93.3)	0.566[2]
	Yes	0	3 (6.7)	
Other surgery	No	13 (86.7)	41 (91.1)	0.634[2]
	Yes	2 (13.3)	4 (8.9)	

Local invasion	No	2 (12.5)	15 (33.3)	0.193
	Yes	14 (87.5)	30 (66.7)	
Tumoral stage	IVA	2 (11.8)	5 (11.1)	0.057[2]
	IVB	4 (23.5)	25 (55.6)	
	IVC	11 (64.7)	15 (33.3)	
Distant metastases	No	6 (35.3)	31 (68.9)	0.022[2]
	Yes	11 (64.7)	14 (31.1)	

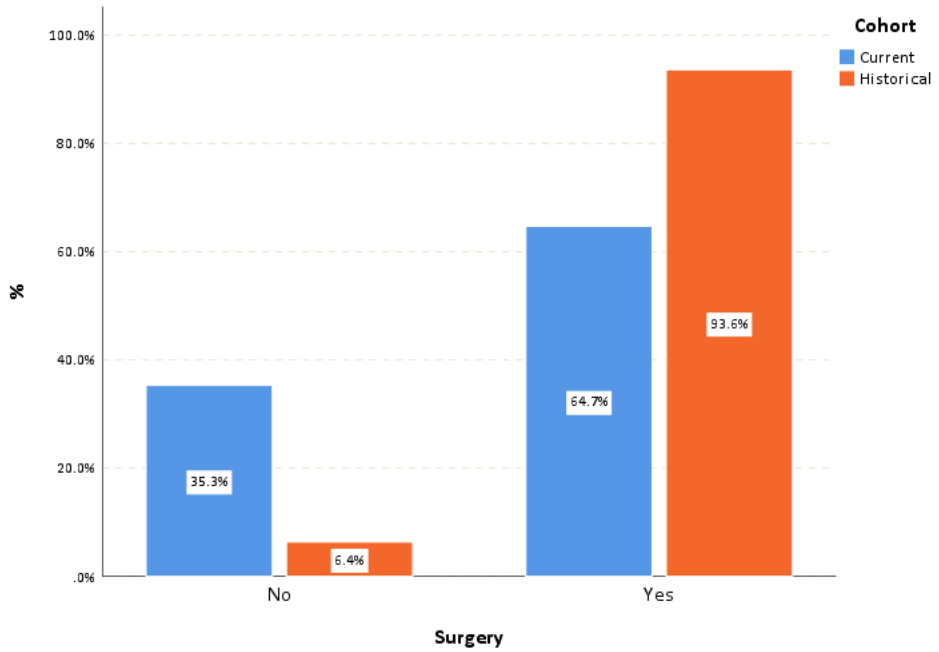
SD: standard deviation; IQR: Interquartile range; NA: not available; Min-Max *: Minimum-maximum
. [1] Chi-square test; [2] Fisher's exact test; [3] t-Student test.

Table 1a. Characteristics of patients with Anaplastic Thyroid Cancer by age, San Martino Hospital, Genoa 1967-2022.

Characteristic		***Current***	***Historical***	***Total***	**p-value**
		n = 17 (%)	**n = 47 (%)**	**n = 64 (%)**	
Age (years)	Mean (SD)	74.3 (11.8)	66.6 (12.3)	68.6 (12.6)	0.029[1]
	Median (IQR)	79 (62-84)	67 (60-77)	68.5 (60-81)	
	Min-Max *	54-88	40-87	40-88	

[1] t-Student test; Min-Max *: Minimum-maximum

Figure 1. Surgery according to cohort of patients with Anaplastic Thyroid Cancer, San Martino Hospital, Genoa 1967-2022.



The median survival of all ATC patients was 3.7 months, and the 1-year survival probability was 17.9%. Women lived statistically longer than men (median: 6 months *versus* 2.2 months; p=0.015) [Table 2 and Figure 4] with more probabilities of survival in 1 and 3 years (25% and 20% *versus* 5% and 0%, respectively). [Table 2]

Table 2. Characteristics of patients with Anaplastic Thyroid Cancer by mortality and probability of survival in 1-year and 3-years, San Martino Hospital, Genoa 1967-2022.

Characteristics	***Deaths/Total***	***Mean (SE) (months)***	***Median (months)***	***Probability of survival***		***p-value[1]***
				1-year	**3-years**	
All cases	61/64	21.9 (7.1)	3.7	17.9%	13.0%	
Cohort						0.154
Current	15/17	6.7 (2.8)	2.2	15.7%	7.8%	
Historical	46/47	24.4 (8.4)	5.1	19.1%	14.9%	

Sex						0.015
Male	23/24	4.7 (1.0)	2.2	5.0%	0%	
Female	38/40	31.1 (10.7)	6.0	25.0%	20.0%	
Age (*years*)						0.572
<70	33/34	21.3 (8.9)	4.2	22.0%	15.7%	
≥70	28/30	18.9 (8.0)	3.2	13.3%	10.0%	
Anaplastic						0.232
Pure	20/21	21.1 (9.5)	2.5	19.0%	19.0%	
Pre-existing goiter	25/26	18.5 (10.8)	3.8	16.8%	8.4%	
Incidental	1/2	125.5	125.5	100%	100%	
Surgery						0.102
No	9/9	3.7 (1.2)	2.2	0%	0%	
Yes	52/55	24.9 (8.2)	5.1	20.9%	15.2%	
Surgery and Adjuvant therapy or therapy for not operated						0.433
No surgery/Yes therapy	7/7	4.4 (1.4)	2.6	0%	0%	
Surgery/No adjuvant therapy	29/29	20.5 (9.9)	3.2	17.2%	13.8%	
Surgery/Yes adjuvant therapy	20/22	18.8 (7.8)	7.8	24.8%	14.9%	
Type of surgery						
Debulking						0.128
No	43/46	25.7 (9.6)	6.0	18.3%	16.0%	
Yes	18/18	12.3 (7.5)	2.1	16.7%	5.6%	

Total thyroidectomy						0.772
No	50/52	22.0 (7.9)	3.5	18.2%	12.1%	
Yes	11/12	13.7 (6.1)	5.1	16.7%	16.7%	
Total thyroidectomy with homolateral lymphadenectomy						0.590
No	49/51	16.9 (5.2)	3.5	17.6%	11.8%	
Yes	12/13	32.4 (23.7)	6.0	19.2%	19.2%	
Adjunt theraphy or therapy for not operated (multimodal approach)	0.465					0.465
No	31/31	19.3 (9.3)	2.5	16.1%	12.9%	
Yes	27/29	15.2(5.9)	6.8	18.6%	11.1%	
Adjunt theraphy or therapy for not operated (singly approach)						
Radiotherapy						0.322
No	40/41	19.6 (8.1)	2.6	15.8%	13.1%	
Yes	18/19	11.7 (3.3)	8.0	21.1%	10.5%	
Chemotherapy						0.278
No	50/52	19.2 (7.2)	3.2	16.3%	12.2%	
Yes	8/8	14.9 (5.5)	9.5	25.0%	12.5%	
Targeted therapy						0.664
No	47/49	21.2 (7.5)	3.7	19.3%	15.0%	
Yes	11/11	5.6 (1.2)	3.5	9.1%	0%	

For both unadjusted and adjusted analyses, increased ATC-specific survival was showed only for females among all variables studied for ATC patients as a whole (multivariate analysis: HR= 0.52; 95% CI= 0.28-0.95; *p*= 0.035), whilst advancing TNM stages was associated with decreased ATC-specific survival for the total population (multivariate analysis: for stage IVB: HR= 5.97; 95% CI= 1.77-20.20; *p*= 0.004; for stage IVC: HR= 12.95; 95% CI= 3.41-49.19; *p*< 0.001). Analyses were adjusted for cohort. [Table 3]

Table 3. Prognostic factors associated with ATC-specific survival for patients with Anaplastic Thyroid Cancer by unadjusted and adjusted analysis, San Martino Hospital, Genoa 1967-2022.

Characteristics		***Unadjusted***		***Adjusted***	
		HR (95%CI)	***p*-value**	**HR (95%CI)**	***p-value***
Cohort	Current	1		1	
	Historical	0.65 (0.36-1.18)	0.157	0.56 (0.26-1.22)	0.143
Sex	Male	1		1	
	Female	0.51 (0.29-0.89)	0.017	0.52 (0.28-0.95)	0.035
Age (*years*)	<70	1			
	≥70	1.16 (0.70-1.93)	0.572		
Anaplastic	Pure	1			
	Pre-existing goiter	0.96 (0.53-1.76)	0.903		
	Incidental	0.20 (0.03-1.53)	0.123		
Surgery	No	1			
	Yes	0.55 (0.27-1.14)	0.107		
Surgery and Adjuvant therapy or	No surgery /Yes therapy	1		1	

therapy for not operated	Surgery/No adjuvant therapy	0.75 (0.32-1.75)	0.503	2.39 (0.86-6.63)	0.096
	Surgery/Yes adjuvant therapy	0.58 (0.24-1.39)	0.225	1.13 (0.46-2.81)	0.786
Adjuvant therapy or therapy for not operated	No	1			
	Yes	0.82 (0.48-1.39)	0.466		
Type of Surgery					
Debulking	No	1			
	Yes	1.53 (0.88-2.67)	0.131		
Total thyroidectomy	No	1			
	Yes	0.91 (0.47-1.75)	0.773		
Total thyroidectomy with homolateral lymphadenectomy	No	1			
	Yes	0.84 (0.43-1.61)	0.591		
Adjunt theraphy or therapy for not operated (singly approach)					
Radiotherapy	No	1			
	Yes	0.75 (0.43-1.33)	0.324		
Chemotherapy	No	1			
	Yes	0.66 (0.31-1.41)	0.282		
Targeted therapy	No	1			
	Yes	1.16 (0.59-2.27)	0.665		
Tumoral stage	IVA	1		1	
	IVB	3.12 (1.16-8.37)	0.024	5.97 (1.77-20.20)	0.004
	IVC	6.45 (2.26-18.35)	<0.001	12.95(3.41-49.19)	<0.001

Somatic mutations					
*TP*53	Mutated	1.05 (0.39-2.82)	0.918		
	Wild	1			
Other mutations	Mutated	0.76 (0.29-1.97)	0.565		
	Wild	1			

HR: hazard ratio; 95%CI: 95% confident interval.

Adjusted for cohort.

When the analyses were stratified by cohort, an association between adjuvant therapy and improved ATC-specific survival was found for patients from the historical cohort on multivariate analysis (HR= 0.47; 95% CI= 0.23-0.98; *p*= 0.045). For these patients, even as all ATC patients, the ATC-specific survival was reduced with the TNM stages progress on both analyses (multivariate analysis: for stage IVB: HR= 7.74; 95% CI= 1.78-33.63; *p*= 0.006; for stage IVC: HR= 20.77; 95% CI= 4.40-106.83; *p*< 0.001. [Table 4] Analyses for Table 4 were adjusted for sex. It was not possible to determine associations with survival for the current cohort. [Table 5]

Table 4. Prognostic factors associated with ATC-specific survival for patients with Anaplastic Thyroid Cancer from historical cohort, San Martino Hospital, Genoa 1967-2014.

Characteristics		***Unadjusted***		***Adjusted***	
		HR (95%CI)	***p-value***	**HR (95%CI)**	***p-value***
Sex	Male	1	0.028	1	0.200
	Female	0.48 (0.25-0.92)		0.62 (0.30-1.29)	
Age (*years*)	<70	1	0.938		
	≥70	1.02 (0.56-1.87)			
Anaplastic	Pure	1			
	Pre-existing goiter	0.93 (0.47-1.85)	0.834		
	Incidental	0.38 (0.05-2.91)	0.352		

Surgery	No	1			
	Yes	0.97 (0.30-3.15)	0.953		
Surgery and Adjuvant therapy or therapy for not operated	No surgery/Yes therapy	1			
	Surgery/No adjuvant therapy	1.48 (0.35-6.35)	0.595		
	Surgery/Yes adjuvant therapy	1.29 (0.29-5.70)	0.737		
Adjuvant therapy (multimodal)	No	1		1	
	Yes	0.82 (0.44-1.51)	0.517	0.47 (0.23-0.98)	0.045
Type of Surgery					
Debulking	No	1	0.042		
	Yes	1.87 (1.02-3.41)			
Total thyroidectomy	No	1	0.832		
	Yes	1.08 (0.52-2.27)			
Total thyroidectomy with homolateral lymphadenectomy	No	1	0.668		
	Yes	0.85 (0.39-1.82)			
Adjuvant therapy or therapy for not operated (singly)					
Radiotherapy	No	1	0.743		
	Yes	0.90 (0.46-1.74)			
Chemotherapy	No	1	0.378		
	Yes	0.71 (0.32-1.53)			
Targeted therapy	No	1	0.952		
	Yes	0.97 (0.34-2.74)			
Tumoral stage	IVA	1		1	
	IVB	3.22 (1.07-9.69)	0.038	7.74 (1.78-33.63)	0.006
	IVC	8.29(2.46-28.02)	0.001	20.77(4.04-106.83)	<0.001
Somatic Mutations					
*TP*53	Mutated	2.92(0.26-32.93)	0.385		
	Wild	1			

Other mutations	Mutated	0.02 (0-187.22)	0.414		
	Wild	1			

HR: hazard ratio; 95% CI: 95% confident interval.

Adjusted for sex.

Table 5. Prognostic factors associated with ATC-specific survival for patients with Anaplastic Thyroid Cancer from current cohort, San Martino Hospital, Genoa 2015-2022.

Characteristics		***Unadjusted***	
		HR (95%CI)	***p-value***
Sex	Male	1	0.200
	Female	0.48 (0.15-1.48)	
Age (*years*)	<70	1	
	≥70	1.52 (0.52-4.47)	0.449
Anaplastic	Pure	1	
	Pre-existing goiter	1.19 (0.33-4.32)	0.790
	Incidental	-	
Surgery	No	1	0.145
	Yes	0.41 (0.12-1.36)	
Type of Surgery			
Total thyroidectomy	No	1	0.539
	Yes	0.62 (0.14-2.86)	
Total thyroidectomy with homolateral lymphadenectomy	No	1	0.569
	Yes	0.68 (0.18-2.54)	
Adjunt theraphy or therapy for not operated (singly)			
Radiotherapy	No	1	0.130
	Yes	0.36 (0.09-1.35)	
Targeted therapy	No	1	0.620
	Yes	0.76 (0.25-2.28)	

Tumoral stage	IVA	1	
	IVB	4.65(0.44-49.39)	0.202
	IVC	2.85(0.35-23.24)	0.327
Somatic mutations			
*TP*53	Mutated	0.86(0.27-2.76)	0.793
	Wild	1	
Other mutations	Mutated	0.85 (0.30-2.44)	0.762
	Wild	1	

HR: hazard ratio; 95% CI: 95% confident interval.

The median survival time was 5.1 months for patients from historical cohort in contrast with the median survival time of 2.2 months for patients from the current cohort. [Table 2] No statistically differences for ATC-specific survival was observed between the cohorts on adjusted analysis (multivariate analysis: p= 0.143) [Table 3], since 15 out of 17 patients from the current cohort died at the end of the follow-up, and 46 out of 47 patients died in the historical cohort. [Table 2] The median follow-up for the historical cohort was 5.06 months, and 2.23 months for the current cohort. [Table 6]

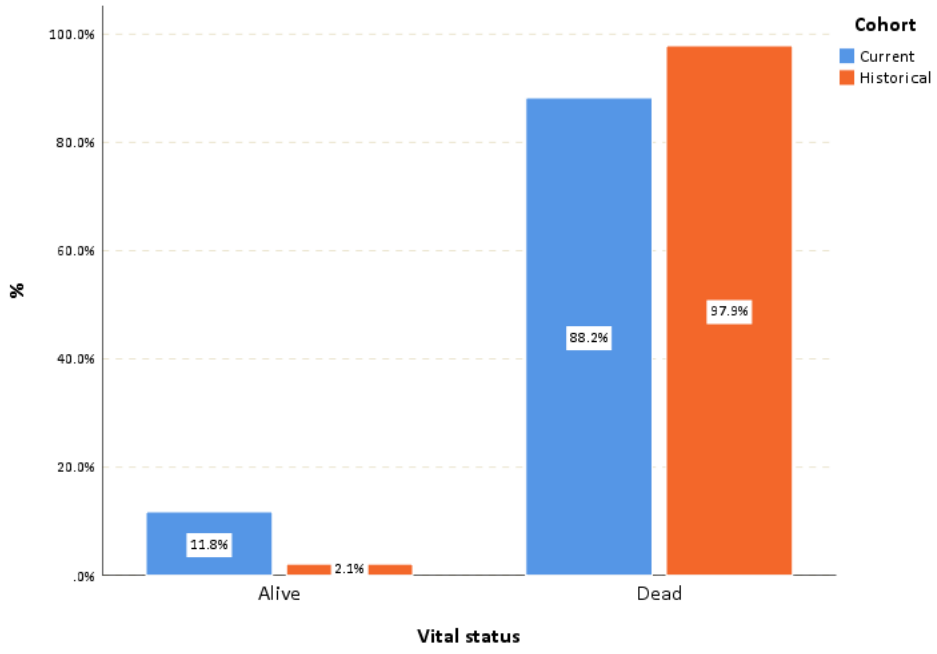
Table 6. Follow-up of patients with Anaplastic Thyroid Cancer by cohort, San Martino Hospital, Genoa 1967-2022.

Time of follow-up (*months*)	***Current Cohort***	***Historical Cohort***
Mean (SD)	5.88 (9.92)	22.30 (49.82)
Median (IQR)	2.23 (1.28-6.21)	5.06 (2.07-9.86)
Minimum-maximum	0.26-42.25	0.10-260.63

SD: standard deviation; IQR: Interquartile range.

The figure 2 shows the comparison between the status vital (dead *versus* alive) for all patients with ATC according to cohort.

Figure 2. Vital status according to cohort of patients with Anaplastic Thyroid Cancer, San Martino Hospital, Genoa 1967-2022.



Kaplan-Meier curves for ATC-specific survival according to cohort, sex, age, surgery, surgery *versus* adjuvant therapy and tumoral stage are, respectively, presented below.

Figure 3. Kaplan-Meier curves for ATC-specific survival according to cohort for patients with Anaplastic Thyroid Cancer, San Martino Hospital, Genoa 1967-2022.

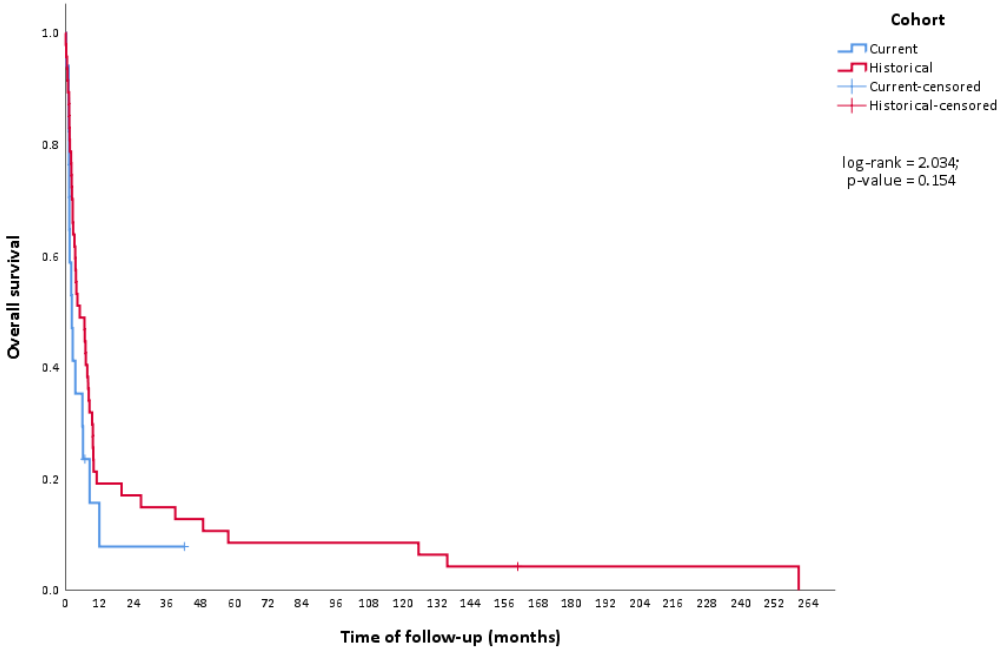


Figure 4. Kaplan-Meier curves for ATC-specific survival according to sex for patients with Anaplastic Thyroid Cancer, San Martino Hospital, Genoa 1967-2022.

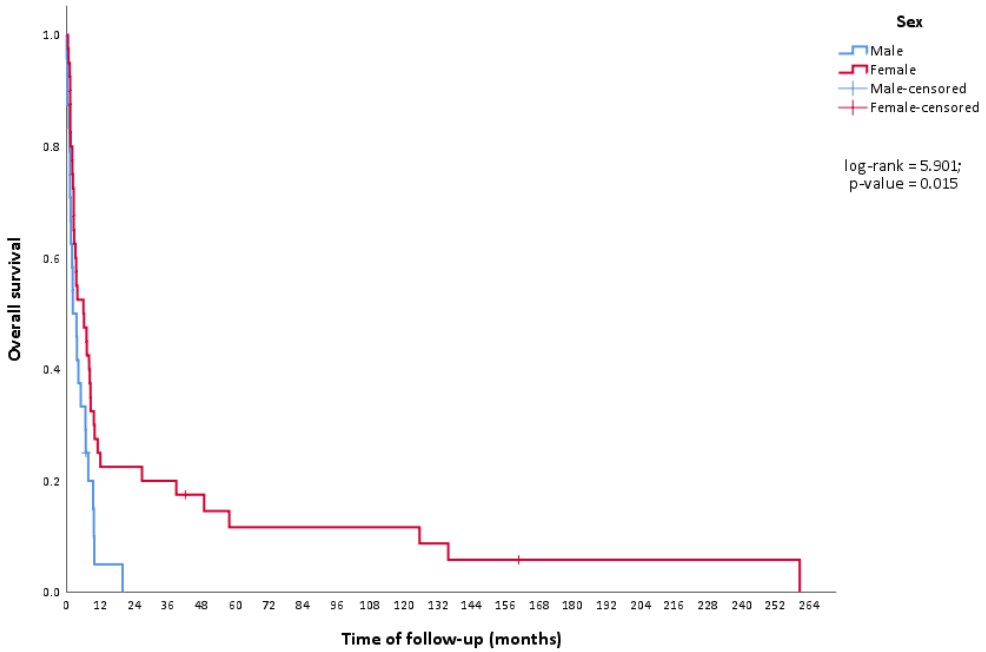


Figure 5. Kaplan-Meier curves for ATC-specific survival according to age for patients with Anaplastic Thyroid Cancer, San Martino Hospital, Genoa 1967-2022.

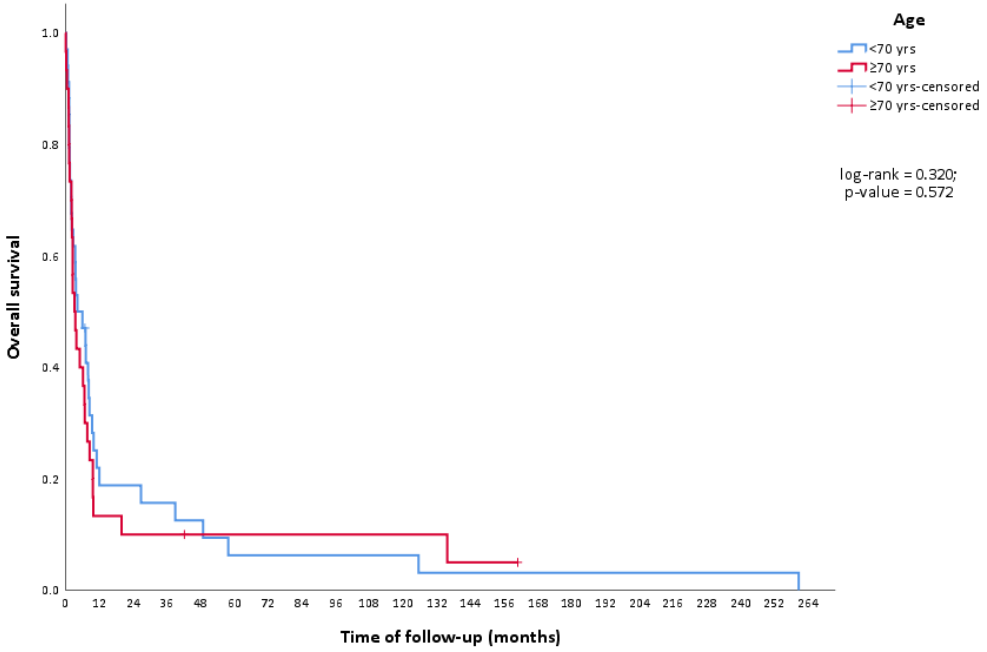


Figure 6. Kaplan-Meier curves for ATC-specific survival according to surgery for patients with Anaplastic Thyroid Cancer, San Martino Hospital, Genoa 1967-2022.

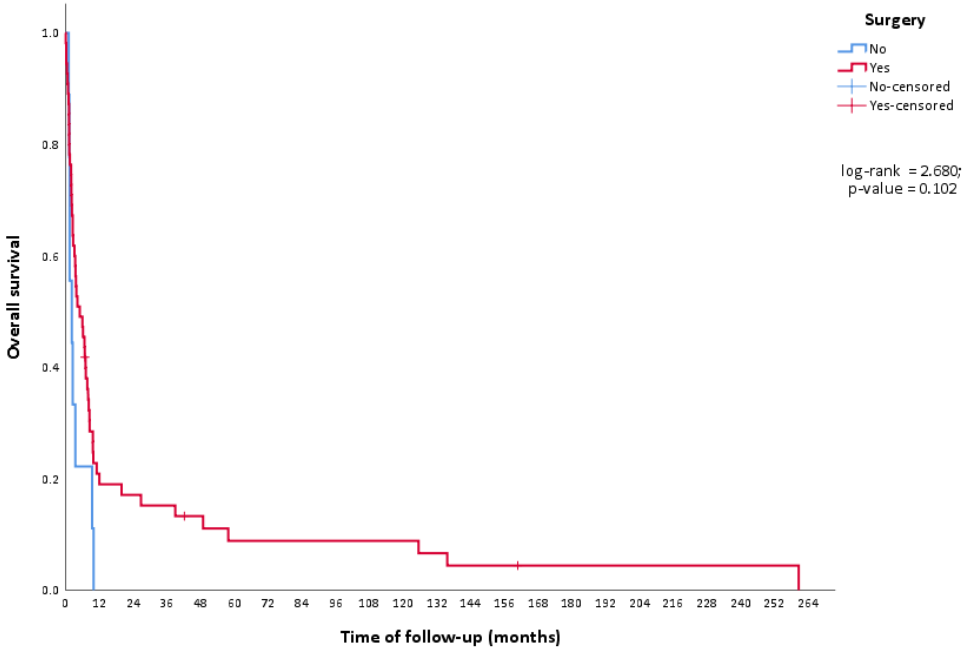


Figure 7. Kaplan-Meier curves for ATC-specific survival according to surgery *versus* adjuvant therapy for patients with Anaplastic Thyroid Cancer, San Martino Hospital, Genoa 1967-2022.

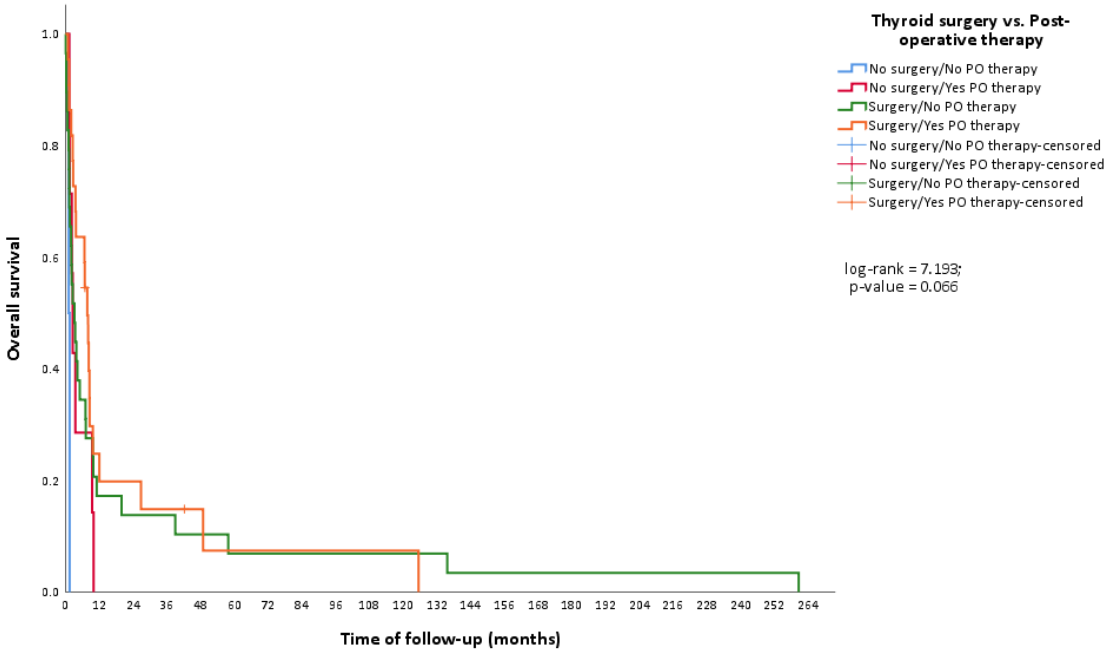
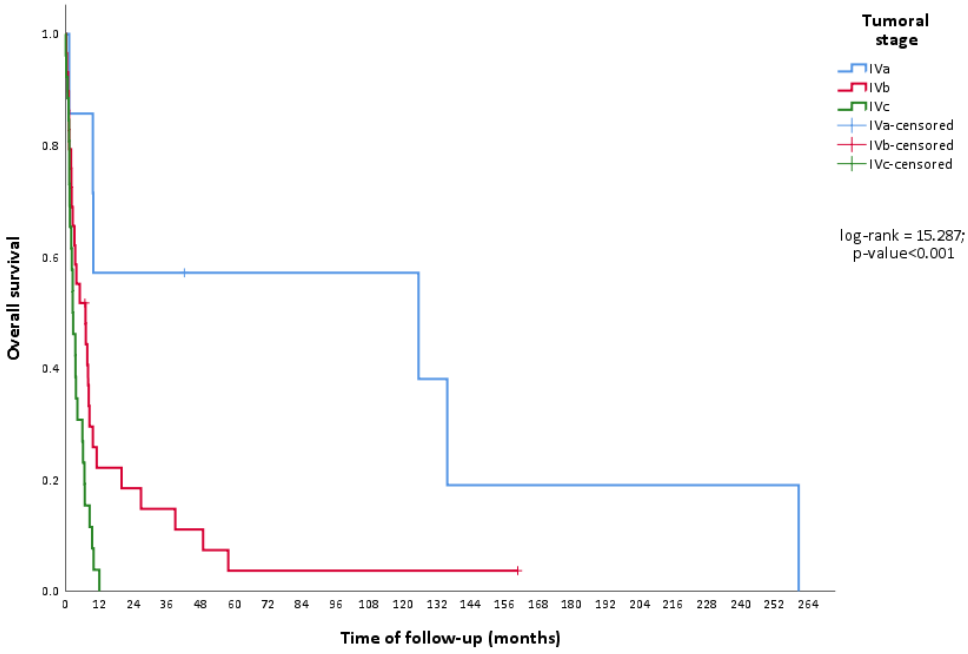


Figure 8. Kaplan-Meier curves for ATC-specific survival according to tumoral stage for patients with Anaplastic Thyroid Cancer, San Martino Hospital, Genoa 1967-2022.



6. DISCUSSION

In the present study, female gender was associated with improved ATC-specific survival for all patients, and the adjuvant therapy was beneficial on ATC-specific survival among patients from the historical cohort. Advancing TNM stages was associated with decreased ATC-specific survival both in overall analyses and in stratified analyses by cohort. This data reflects, obviously, the prognostic value of the TNM system.

The global incidence rate for thyroid cancers is higher in women (6), and ATC follows the same epidemiological pattern than well-differentiated thyroid cancers concerning gender. In terms of survival, the female gender was previously reported as a prognostic factor for ATC in few studies (11, 12, 13). However, gender was not unanimously considered as a strong independent predictor of survival (11, 12, 13). Although we excluded competing causes of death for both genders when we defined ATC-specific survival as the outcome of this study, and no statistical association between sex and TNM stages was observed in our series, the finding of the less favorable prognosis for men with ATC might reflect a survival disadvantage for the male gender intrinsically linked with the disease.

The American Joint Committee on Cancer Staging Manual for differentiated thyroid cancers and ATC (15) evolved the TNM concept from anatomic stages groups to prognostic stage groups since the very first editions, incorporating the impact on survival to the TNM classification, that is clear for ATC patients (15, 16). The higher the TNM stage, the more advanced the disease, and ATC is a rapidly progressive illness in which the prognostic stage of disease can change very fast (5). The TNM is a classification based on the mortality risk. Then, the progress on TNM stages for ATC naturally represents a higher risk of mortality (14).

The strength of recommendations for the treatment for ATC is mostly based on low-quality publications due to the rarity of the disease, and the consequent lack of prospective trials (5, 17). However, the completeness of the surgery with a prompt transition to adjuvant therapy are attainable strategies for a long-term survival, and are steps strongly recommended for ATC patients according to the most recent guidelines by the American Thyroid Association (5). The improvement of ATC-specific survival and adjuvant therapy in our historical cohort leads to the suggestion of a potential benefit of surgery to allow the use of a systemic therapy in these patients.

Surgery for ATC can rarely aim at complete resection, nevertheless the completeness of surgery has been implicated as a prognostic factor by many authors (4, 5, 10, 11, 12, 13, 14, 16, 17). Based on this, because of the prognosis is unaffected by incomplete resection (R2), debulking approach is not generally recommended for ATC. Nonetheless, evidences by a systematic review with 40 publications pertaining the treatment of ATC and a Mayo Clinic series over 50 years (10, 18) suggested that patients undergoing surgery had a significantly better survival than those not treated by surgical intervention, independently of the extend of surgery (7, 10, 18). The improved survival for operated patients might be related to a reduced risk of dying from local progression of the tumor, which is the most rapidly fatal manifestation of ATC (10).

Our results showed that 93.6% of the patients from the historical cohort underwent a surgical approach. Debulking was performed in 38.3% of these patients followed by total thyroidectomy and total thyroidectomy with homolateral lymphadenectomy which, jointly, comprised 76.5% of the surgical intervention for ATC patients between 1967 and 2014. Debulking is a term that involves many different surgical approaches ranging from a palliative/decompression treatment to a complete resection of all gross tumor with minimal residual disease adherent to vital structures (10). Therefore, it is difficult to determine the real extension of the debulking approach within the historical cohort. For the current cohort, 11 patients underwent surgery. Seven of them underwent a total thyroidectomy or total thyroidectomy with homolateral lymphadenectomy, representing 41.2% of the surgical approaches chosen for these patients. No patient underwent a debulking surgery. However, due to the limited number of patients in the most recent cohort, conclusions about a changing on surgical decision-making for ATC patients would be inaccurate based on our results.

According to guidelines for management of patients with ATC, the best results in terms of both local control and survival appear when the surgical intervention is followed by a post-operative therapy (5, 17). The multimodal therapy is usually the option for an adjuvant approach which includes radiation, chemoradiation and/or targeted therapy. Radiotherapy, preferably external beam high-dose radiation, is the mainstream of adjuvant therapy with strong recommendation following surgery for IVA/IVB good performance status patients, and it should begin no later than 6 weeks after the surgery (5). Local radiation also triggers systemic effects that induces responses outside the radiation field (19). In our study, we observed an association between improved ATC-specific survival

and adjuvant therapy among patients from the historical cohort. Analyses stratified by radiotherapy, chemotherapy and targeted therapy as singly modalities did not show association with better survival, demonstrating that, for the patients of our study, the approach associated with prolonged survival was multimodal, possibly due to a synergistic benefit from the addition of different therapeutic strategies. The impact of adjuvant therapy on survival, in our study may be partially explained by the increased importance of preventing distant dissemination after surgery (10).

Targeted therapy is a promising option for treatment of ATC patients (3, 5, 7). The ATC mutational status can be used to understand the pathogenesis of the tumor, and to guide the selection of systemic therapy targeted toward a personalized strategy (20). Nonetheless, the move to targeted therapy as first-line strategy for the management of ATC patients still requires higher quality evidences. At present, the use of BRAF-directed therapy for ATC patients harboring $BRAF^{V600E}$ mutation is recommended in stage IVC but not for stage IVB unresectable ATC $BRAF^{V600E}$-mutated patients for which the current standard treatment is chemoradiation (3, 5). All patients from the current cohort were investigated for somatic mutations. Nevertheless, multivariate analyses were unable to be performed due to the very limited cases. Unadjusted analysis, on the other hand, did not show association between ATC-specific survival and the use of targeted therapy within current cohort.

For both cohorts, historical and current, the distribution of pre-existing goiter was not different from the subset of patients diagnosed directly as ATC. Despite some evidences that ATC frequently occurs in a setting of previous benign thyroid disorder, particularly primarily benign goiter (3, 17), our finding suggests that the presence of previous goiter is not a prognostic factor for ATC. Nonetheless, further studies are needed to fully elucidate the role of begin pre-existing goiter for ATC.

Comparative analysis of tumoral characteristics between the two cohorts showed that 64.7% of the patients from the most recent cohort had distant metastases at the time of the diagnosis contrasting to 31.1% of the patients from the historical cohort (p= 0.022) [Table 1]. The FDG-PET CT scan is the most sensitive tool for documenting the extend of the disease, and it was introduced in 2001 (14), 34 years after the beginning of the enrollment for patients from the historical cohort. Therefore, mostly patients from the historical cohort could potentially not be correctly diagnosed concerning distant metastases in comparison to patients from the current cohort.

No difference for ATC-specific survival between the cohorts was observed in this study. Notwithstanding, the difference for the median survival time between the cohorts was considerable. Half of patients from the historical cohort lived 5.1 months in contrast with 2.2 months for half of patients from the current cohort, representing a 55.93% reduction for median ATC-specific survival. The follow-up for the historical cohort also was longer than for the current cohort (5.06 months *versus* 2.23 months), providing more opportunities to follow survivors in the historical cohort than in the current cohort. Otherwise, the prognostic significant of adjuvant therapy for ATC-specific survival is plausible into our series whereas the association between the post-operative therapy and better survival was found among patients from the historical cohort without differences for the frequency by gender and TNM stage, other prognostic factors for ATC-specific survival in our study. The subjacent impact on survival concerning surgery on ATC may be also considered, since adjuvant therapy, by definition, follows a surgical intervention, we can suggest that surgery finally prolongs survival, and this is a hypothesis that should be best ascertained in further studies.

Our results must be considered in the light of the uneven covariate distribution between the cohorts that might not be relied on produce valid associations. As a rare and rapidly fatal disease, the accrual of ATC patients is difficult, especially regarding to a single-institution study. The separation of the total sample into two cohorts provides inherent limitations to the analyses, and consequently, to the results. For example, age was previously implicated as an independent predictor of lower cause-specific mortality for ATC according to some publications (5, 12, 13, 17) but no association between age and ATC-specific survival was found in the present study likely due to small sample in the current cohort. Furthermore, the unbalanced number of patients into cohorts as well as the distinct periods of follow-up may lead to biased associations or no association between a real prognostic factor and survival. A selection bias toward surgery for patients with smaller tumors and less extensive local invasion might influence the results, and it sets in another limitation for this study. Finally, the statistical power of our study did not allow us neither to investigate the impact of neoadjuvant therapy on ATC-specific survival nor performing a confrontation between historical treatments and new therapeutic modalities, particularly due to reduced *n* regarding the current cohort.

7. CONCLUSIONS

ATC is one of the most aggressive malignancies in medicine with an almost uniformly rapid and fatal course. Understanding the characteristics of the patients with ATC and the behavior of the tumor are tools for choosing treatment strategies. In this context, a strength of the present study was the adoption of ATC-specific survival as the outcome instead of overall survival. ATC-specific survival should be the preferred outcome for observational studies since it reduces the impact of competing causes of death, and it was especially relevant concerning the association between female gender and better survival. Excluding other causes of death and differences on TNM stages by sex, our finding suggests that the survival detriment among men was intrinsically linked to ATC. The burden of TNM progression on ATC is a determinant of survival, and this aforementioned association was corroborated in our study not only for ATC patients as a whole but also for patients from the historical cohort. No statistical differences, in our series, between the occurrence of ATC as primary tumor and in a setting of pre-existing goiter puts forward the possibility that ATC and previous benign thyroid goiter could be independent diseases.

Our review over the last 50 year for the treatment of patients with ATC showed a beneficial ATC-specific survival for multimodal adjuvant therapy within the historical cohort. Although already evidenced in other studies, the survival improvement for ATC patients related to post-operative therapy requires high-quality studies, especially regarding targeted strategies. Our study could not add for comprehending the role of personalized therapy for ATC operated patients due to poor accrual in the current cohort. Nevertheless, our finding headlines the importance of investigating new modalities for the treatment of ATC in the adjuvant context. Furthermore, our result suggests the extend of surgical approach seems to be less important than the preventing distant dissemination attainable with adjuvant treatment. A preceding surgical intervention implies on ATC-specific survival as a subjacent condition for an adjuvant therapy, regardless of the extend of the surgery, presumably due to minimization of local progression of the tumor, the very first fatal manifestation of ATC.

Unfortunately, the literature about therapy for ATC is scarce not only because of ATC is a rare disease but also due to lack of randomized clinical trials. Even guidelines for the management of ATC, such as The National Comprehensive Cancer Network and The

American Association of Clinical Endocrinologists, dedicate few pages to treatment of patients with ATC. Taking into account that expanding the knowledge about ATC therapeutic strategies is essential for patients' survival, this study contributed not only for highlighting predictors of survival but also for suggesting survival benefits related to adjuvant therapy which, ultimately, might instigate required further studies concerning ATC treatment approaches.

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