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Original research

The role of surgery in the treatment of thyroid anaplastic carcinoma in the elderly

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ABSTRACT

Introduction: Anaplastic thyroid carcinoma (ATC) is characterized by local invasiveness, risk of recurrence and very poor prognosis. **Methods**: We retrospectively analysed the multimodality treatment of ATC in 79 patients considering the impact of surgery on survival. **Results**: Patients were divided in two age groups A and B (cut-off 75 years) and in two size subgroups (cut-off 5 cm). Surgery was performed in 78.5% patients of group A and 32.4% of B ($p < 0.05$). Radiation respectively in 73.8% and 43.2% ($p < 0.05$). Tracheostomy and endoprosthesis were used in 45.2% and 16.6% in group A and in 43.2% and 35.1% in group B. The use of tracheostomy was significantly higher ($p < 0.05$) in larger tumours. In group B comparing operated and not operated patients significant difference in survival was observed for larger tumours ($p = 0.043$). In Kaplan Meir analysis significant difference in survival was observed comparing surgical and no surgical patients of all four subgroups. Surgery plus radiotherapy offered a significant better outcome in smaller tumours ($p = 0.017$). Considering the effect of the single treatment, compared to no treatment at all, survival is significantly improved by surgery for smaller and larger tumours respectively with 4.42 ($p = 0.001$) and with 3.5 months ($p = 0.0001$) and by radiotherapy respectively with 3.44 and with 3.28 months ($p = 0.047$ and $p = 0.0001$). **Conclusion**: In elderly patients with ATC, although poor prognosis, surgery is still fundamental in the multimodality treatment with significant advantage in selected patients. Nevertheless most of elderly patients with large tumours are suitable only for palliative management.

1. Introduction

Anaplastic thyroid carcinoma (ATC) is a rare condition representing only 1.5% of all thyroid cancers. General incidence of thyroid cancer is increasing worldwide and specifically in Umbria region, Italy, where, compared to the national data, it counts in the local cancer register as the height cancer for incidence [1]. The 5-years survival rate is 94% for differentiated tumours (DTC) but in case of ATC it decreases to 5.6–11.4%, with a median life expectancy of about 4–9 months and only 10%–15% of patients alive at two years in sharp contrast to what observed in DTC [2,3]. The peak of incidence is in the sixth and seventh decades, with significant observation also in very elderly patients over 75-years-old [1]. Females are mostly affected with a ratio of 5 to 1 compared to males [1].

A large portion of ATCs are diagnosed in patients with history of longstanding goitre or incompletely treated papillary or follicular thyroid carcinomas, supposing a derivation from a terminal dedifferentiation of differentiated carcinoma. In fact papillary structure or follicular components are revealed in focal areas of the tumour among the classical histopathologic patterns of ATC (squamoid, spindle cell and giant cell) [4]. As in follicular thyroid carcinomas *RAS* molecular mutations are seldom observed in ATC [5].

At the time of first clinical observation patients with ATC usually present a rapidly enlarging anterior neck mass, with compressive symptoms such as dyspnoea, dysphagia and vocal cord paralysis. Surrounding structures are invaded in almost 70% of the patients as

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observed in large series: muscles (65%), trachea (46%), oesophagus (44%), laryngeal nerve (27%) and larynx (13%). Lymph node metastases are observed in almost 40% of the patients. Distant metastases are observed in up to 50% of cases at the time of diagnosis. The most frequent site of distant metastasis is the lung, followed by bone, skin and brain [4,6]. Death is often caused by tracheal and oesophageal invasion and obstruction, as well as by consequences of metastatic disease.

Multimodality treatment advocated by many authors vs no treatment at all, is proposed to control symptoms with palliative intent and as an attempt to increase survival [4,6]. Distinguishing treatment effects from clinical course itself is difficult and it represents the main criticism in the acceptance of multimodality approach as a gold standard of treatment [7].

Aim of the present study is the analysis of the impact of surgical in ATC treatment compared to palliative procedures in elderly patients over 75 years-old.

2. Patients and methods

2.1. Patients

We retrospectively reviewed 79 consecutive patients with ATC referred to the Unit of Endocrine Surgery, S. Maria University Hospital, Terni, University of Perugia between 1996 and 2013.

Accurate staging was carried out with laryngoscopy, neck ultrasonography, bone scan and computed tomography (CT) of head, neck, mediastinum, thorax, and abdomen to determine the extent of infiltration by the tumour. Follow-up was performed after discharge in the outpatient department, by the same diagnostic investigations and the overall survival was considered in months.

Multidisciplinary evaluation of patients affected by ATC was carried out in each case. Patients were allocated to surgery, radiotherapy, chemotherapy, or a combination of treatment or even just to palliative procedures according to the pre-operative evaluation and staging and later on considering final histology and clinical course. No demographic data were considered relevant to allocate of principle patients to the different treatment groups. The protocol was mainly dependent on clinical criteria and on the necessity of symptoms control and tumour treatment.

2.2. Surgery

All the surgical procedures were carried out in the endocrine surgery unit (AFOI, Area Funzionale Omogenea Interaziendale) of Umbria region, by the same surgical team, with standard surgical technique according to the protocol in use for the treatment of ATC. The surgical procedure was identified as total thyroidectomy, lobectomy or debulking. Total thyroidectomy denotes the removal of both lobes and the isthmus. Lobectomy considers resection of one entire lobe and of the isthmus. Debulking is defined as a tumours reduction of more than 90%. Total thyroidectomy was indicated in loco-regional resectable disease. In case of invasive extended tumours thyroidectomy less than total or just debulking procedures were chosen in order to provide a biopsy and symptoms relief. The dissection was operated aiming preliminary superior and inferior laryngeal nerves identification, the inferior was followed till the larynx when technically feasible. In all patients a Jackson Pratt drainage was used and removed according to the clinical course.

2.3. Management of airways obstruction

Tracheostomy and endoprosthesis were used in combination with surgery or alone as primary treatment in the management of airways obstruction by large ATC compressing or infiltrating the trachea. The indication for both treatments was given considering emergency situation with severe dyspnoea, specific intraoperative findings with the necessity of airways control or cases in which patients were not suitable for surgical resection but only for symptoms relief or even as airways protection after radical surgery.

2.4. Radiotherapy

The treatment included adoption of radiotherapy and chemotherapy usually in a postoperative adjuvant combined modality or primarily with palliative intent. Postoperative radiotherapy administers high doses, using a hyperfractionated accelerated regimen delivered by linear accelerators (4–25 MV photon or 9–17 MeV electron). The radiation dose prescribed was greater than 40 Gy in radical radiotherapy. The median and most frequently prescribed dose was 60 Gy. Radiation total dose was 40 Gy or less in the palliative radiotherapy group.

2.5. Chemotherapy

Chemotherapy included the combination of doxorubicin (50–60 mg/m^2/d) and cisplatin (100 mg/m^2/d) as standard treatment. More recently paclitaxel plus carboplatin and sorafenib were used in selective not responsive cases.

Table 1
Groups division related to the different treatment and general survival.

Group	Subgroup	n	Surgery (n/total)	No surgery (n/total)	Tracheostomy (n/total)	Endoprosthesis (n/total)	Radiotherapy (n/total)	Mean survival (months)	*p*-value (N.S.>0.05 *<0.05)	
A (< 75 years)	< 5cm	30	25/30 (83.3%)	5/30 (16.7%)	11/30 (36.6%)	7/30 (23.3%)	22/30 (73.3%)	6.7	N.S.	*
	>5 cm	12	8/12 (66.6%)	4/12 (23.4%)	8/12 (66.6%)	0/12 (0%)	9/12 (75%)	4.6		
B (> 75 years)	< 5cm	14	7/14 (50%)	7/14 (50%)	3/14 (21.4%)	6/14 (42.8%)	8/14 (57.1%)	4.4	N.S.	N.S.
	>5 cm	23	5/23 (21.7%)	18/23 (78.3)	13/23 (56.5%)	7/23 (30.43%)	8/23 (34.7%)	3		

2.6. Statistical methods

We used Student's *t* test for analysis of variance between groups. Survival curves were generated using the Kaplan–Meier method, and the log-rank test was used for univariate analysis. For multivariate survival analysis, a Cox proportional hazards model was used. A *p*-value <0.05 was considered statistically significant. All of the data were analysed using *XL*STAT (Addinsoft, New York, NY, USA).

3. Results

The cases included 79 patients, 44 females (55.7%) and 35 males (44.3%), with a mean age of 72.6 (±8.7) years. For statistical comparison patients were divided in two groups: group A including patients younger than 75 years-old ($n = 42$) and group B patients older than 75 years-old ($n = 37$). In each group patients were divided into two subgroups: tumours less than 5 cm in main size and those larger than 5 cm respectively 30 and 12 patients in group A and 14 and 23 in group B.

The rate of the different treatment adopted in each group are summarized in Table 1. We evaluated use of surgery, radiotherapy, tracheostomy/endoprosthesis and survival in the different groups.

Thirty-three patients (78.5%) underwent surgery in group A respectively 25 out of 30 (83.3%) with tumours less than 5 cm and 8 out of 12 (66.6%) with tumours larger than 5 cm.

Twelve patients (32.4%) underwent surgery in group B with 7 out of 14 (50%) and 5 out of 23 (21.7%) respectively for the subgroups of tumour size. The difference between group A vs B and the relative subgroups were significant ($p < 0.05$). The surgical procedures adopted in the different groups are summarized in Table 2. A significant difference ($p < 0.05$) was observed in the indication and feasibility of total thyroidectomy in younger patients with smaller tumours compared to the other groups. Debulking resection was limited to rare cases ($n = 3$) and even lobectomy was limited to few case ($n = 5$) and never applicable in old patients with large tumours. All patients not undergone surgery, 9 of group A plus 25 of group B, presented contraindications to operation including: advanced stage with metastases (respectively $n = 2$ and $n = 12$), severe clinical conditions with poor prognosis for which patients were not suitable for surgery (respectively $n = 2$ and $n = 7$) and not resectable tumours for too extensive local invasiveness (respectively $n = 3$ and $n = 8$).

The rate of radiated patients of 73.8% in group A was significantly higher ($p < 0.05$) than the rate of 43.2% observed in group B, having only 34.7% of older patients with tumours larger than 5 cm referred to radiotherapy. In terms of palliative treatment tracheostomy and endoprosthesis were used respectively in 45.2% and 16.6% in group A and in 43.2% and 35.1% in group B. In both group A and B the use of tracheostomy was significantly higher ($p < 0.05$) in tumours larger than 5 cm. Adequate control of symptoms was obtained in almost all symptomatic patients treated both with curative and palliative intent.

The mean survival in all 79 patients was 5.35 (±3.2) months. The mean survival rate observed was 6.7 (±2.09) and 4.6 (±1.89) months in patients of group A respectively for tumours smaller and larger than 5 cm and respectively, 4.4 (±2.5) and 3 (±2.67) months in patients of group B. Considering operated and not operated patients in each subgroup the only significant difference was observed comparing the subgroups of smaller tumours of group A and larger of B (respectively $p = 0.048$ and $p = 0.043$) (Fig. 1). In Kaplan Meir analysis, significant difference in survival was observed comparing surgical and no surgical patients of all four subgroups, having in tumours smaller and larger than 5 cm, respectively $p < 0.001$ and $p < 0.005$ (Fig. 2B) and D)). When observing older patients of group B alone, a significant difference was evident comparing operated vs not operated patients in tumours larger than 5 cm ($p < 0.05$) but not those in with tumours less than 5 cm (Fig. 2A) and C)). Multidisciplinary treatment combining surgery to radiotherapy offered a significant better outcome in tumours smaller than 5 cm compared to larger ones, respectively 7.73 and 6.20 months ($p = 0.017$). Considering the effect of the single treatment, survival is significantly improved by surgery for smaller tumours with 4.42 ($p = 0.001$) and for larger ones with 3.5 months ($p = 0.0001$) and by radiotherapy respectively with 3.44 and with 3.28 months ($p = 0.047$ and $p = 0.0001$), compared to no treatment at all which shows survival of 2.90 and 1.86 months, respectively for smaller and larger tumours.

Table 2
Type of surgical resection in the different groups.

Group	Total thyroidectomy	Lobectomy	Debulking
A < 5 cm	23	2	/
A > 5 cm	4	2	2
B < 5 cm	6	1	/
B > 5 cm	4	/	1

4. Discussion

In patients with ATC, the effects of surgery, radiotherapy and chemotherapy on local control or on improvement of survival are unclear. Although some studies have shown no survival benefit from resection, radiation therapy, or chemotherapy, other authors suggested that multimodality therapy may be beneficial in some patients with ATC [4–10]. A major confounding factor in determining the effect of treatment on outcome might be related to the evidence that patients who usually undergo surgical resection and radiation treatment often present less extensive disease at first observation.

ATC typically has its peak of incidence in the sixth and seventh decades and it is associated to very poor prognosis presenting usually local invasive disease and distant metastases at the time of diagnosis. The rate of very old patients with ATC is progressively increasing [1] and this suggests a specific investigation on which is the impact of the treatment on these fragile patients with higher comorbidity and especially if it is useful to treat or better just to palliate them, if no benefit in survival is observed.

It is generally accepted that in patients with ATC, usually treatment is palliative rather than therapeutic and is based on a multimodality approach which is the only chance to improve survival and quality of life [4].

Multidisciplinary evaluation of patients affected by ATC is necessary in each case. Patients undergo surgery, radiotherapy, chemotherapy, or a combination of treatment considering oncologic stage at first diagnosis, symptoms at clinical presentation and clinical course. Excluding emergency procedures to treat life threatening conditions such acute dyspnoea for tracheal compression, all the other patients are treated with palliative intent in order to control symptoms or with curative intent in limited invasive tumours. In our setting all cases received a multidisciplinary evaluation with standard application of the different treatment protocols.

Surgery is usually the first approach used to reduce the tumour burden and improve at least compressive complications on airways although, up to one-third of patients at the time of clinical presentation results unsuitable for radical surgery and they usually undergo subtotal resection with palliative intent [4–7].

We observed a very low rate of radiated elderly patients in group B and this is associated to reduced palliative effects, usually

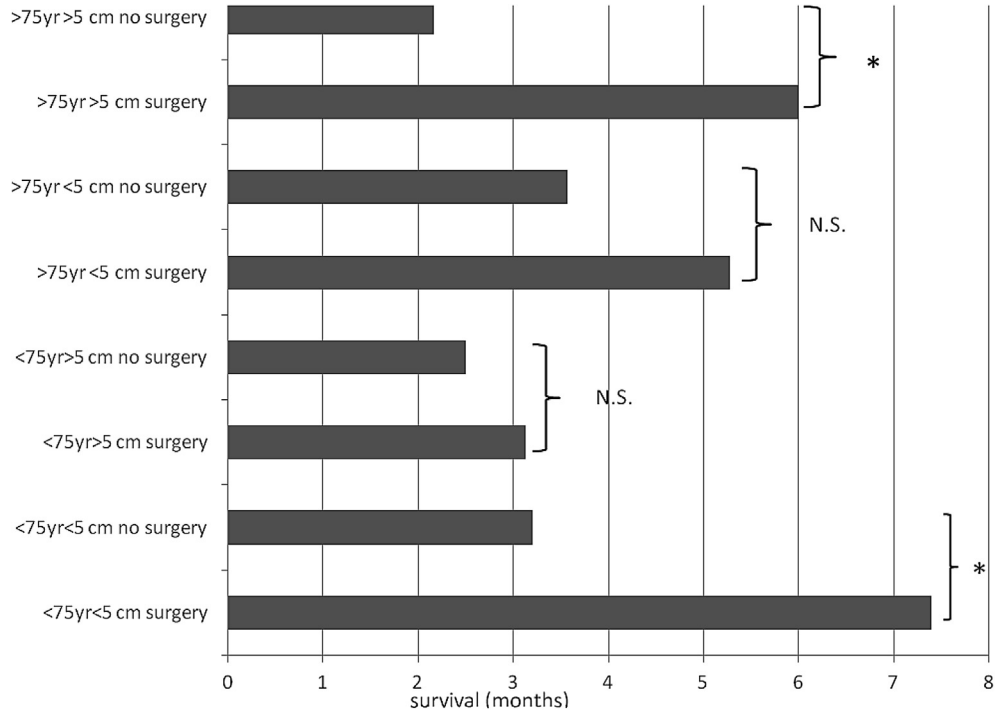

Fig. 1. Survival related to group treatment. * denotes $p < 0.05$, N.S. denotes no significant difference.

coming after radiation, leaving surgery and airways controlling procedures as the only possible treatments in very aggressive tumours. Palliative procedures in association to surgery or as primary treatment included tracheostomy and endoprosthesis insertion. Tracheostomy was carried out in half of patients as primary treatment not associated to surgery and was prevalent in smaller tumours. Use of endoprosthesis was limited to 25% of patients and was not associated to surgery in the 70% of cases and mostly indicated in patients with large tumours. Both palliative options of tracheostomy and endoprosthesis were significantly more used in patients of all ages, when the tumour was larger than 5 cm. This confirms a specific role of the palliative treatment as first option for most of the elderly patients with large tumours. In fact those patients not suitable for surgery alone or in association to radiotherapy, except for few terminal cases, are anyway approached with tracheostomy and endoprosthesis and referred to medical palliative care. Surgery represents an important option when radiotherapy is not applicable, but in our series even surgery in elderly patients is less adopted compared to younger ones. In fact the rate of surgical respectability decreases with increasing age and size.

For limited disease, in with no local neither general contraindications, total thyroidectomy appears as the best option. Even in the elderly patients it is the only treatment in association to radiotherapy, when feasible, or to palliative procedures and even alone, to produce a significant increase in survival, although limited to very few case, compared to the mean mortality observed in this group.

Kebebew and al [7] found that only patient age at diagnosis and the presence of intrathyroidal ATC were independent predictors of lower cause-specific mortality. In the above study was found a 28.3% difference in the cause-specific mortality between patients older than 60 years and patients younger than 60 years and there was a 44.9% difference in the cause-specific mortality at 1-year follow-up between patients who had distant metastasis and patients who had intrathyroidal ATC [7]. Differently consistent clinical experience from the Mayo Clinic defined histologic type of cell, size of lesion (6 cm or larger), surgical treatment, local invasiveness and metastatic disease as potential predictors of poor survival [11].

We either experienced a significant relation between size of tumour and advanced age with poor survival and it is probably due to the limited indication to radical total thyroidectomy in case of larger tumours or to limited eligibility to surgery and radiotherapy for severe comorbidity in elderly patients, with prudential limitation of aggressive approaches, in consideration of the poor prognosis expected. In our series surgery as primary treatment was possible in 55% of all patients, in the younger ones respectively in 83% and 66.6% of small and larger tumours, whereas the correspondent rates for elderly patients were of 50% and 21%.

Surgical treatment is primarily indicated for relief of airway obstruction. Local control of disease is an important component of clinical management but in some experience total thyroidectomy and radical neck dissection may have no advantage over a less aggressive surgical approach [12,13].

In our experience total thyroidectomy can be recommended if cervical and mediastinal disease can be resected in cases of limited disease. Differently in case of invasive extended tumours at the time of diagnosis, debulking can be considered an adequate option providing as well a biopsy for pathological diagnosis and partially symptoms relief as previously shown by other authors [4].

We experienced that surgery as first step followed by chemoradiotherapy can significantly improve survival in patients with initial stage of ATC. Kebebew et al. in a subgroup analysis, reported that combined surgical resection and external beam radiation decreased the cause-specific mortality rate significantly in patients with regional and distant disease, but not in patients with only intrathyroidal ATC whose those younger than 60 years old appeared to have a better prognosis than older patients with distant metastases [7].

Usually patients with advanced disease present very poor prognosis, with an overall survival of about 3–6 months [7]. In our series patients with not metastatic but locally invasive disease, not suitable for primary surgical resection were referred to chemo-

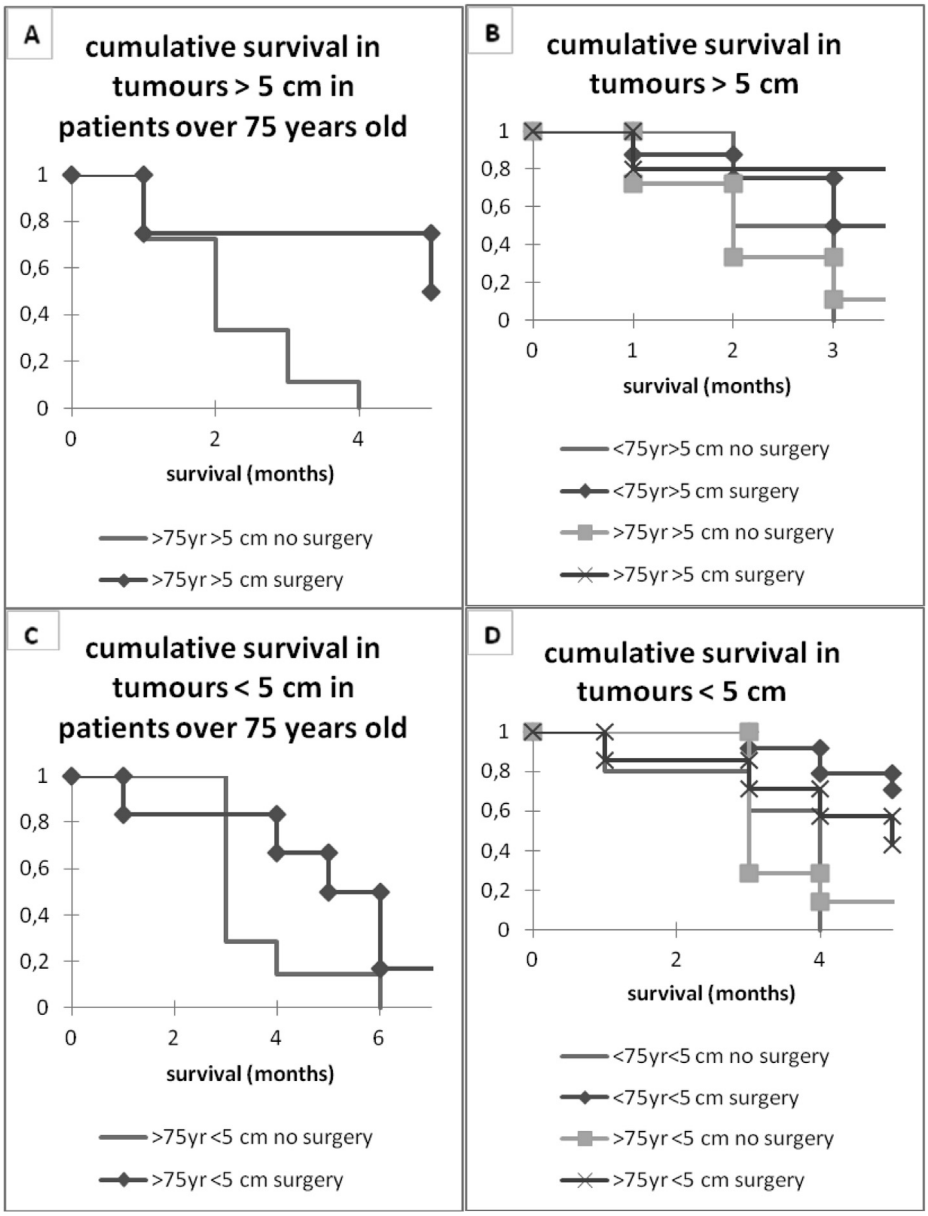

Fig. 2. Results of survival distribution with Kaplan Meier analysis comparing groups patients underwent or not to surgery. A) with Log-rank $p < 0.05$, significant, B) with Log-rank $p < 0.05$, significant, C) with Log-rank $p > 0.05$, not significant (NS), D) with Log-rank $p < 0.05$, significant.

radiotherapy, with some advantage in controlling symptoms as we showed in a previous publication from our group [14]. Radiotherapy in the past was used exclusively in postoperative setting to stabilize surgical excision whereas nowadays it can be either part of neoadjuvant treatment with higher hyperfractionated doses and can be indicated to control tumour local invasion, in delaying local recurrence and preventing thoracic outlet obstruction and metastatic progression [15].

Since ATC is a rapidly dividing tumour, hyper-fractionated radiotherapy minimizes the opportunity for tumour cells to recover between treatments.

Patients not suitable for surgery at the time of diagnosis usually may be referred to a combination of chemo/radiotherapy although toxicity seriously affect the clinical course [16–19]. In our series radiotherapy was adopted in association to surgery in two thirds of patients and it was mainly used in smaller tumour (almost 70%). We observed that radiotherapy alone offers a significant improve in survival compared to no treatment, especially for larger tumours but as above, its use received limited indication in elderly patients with larger tumours, limiting the treatment options just to airways obstruction palliation if surgery was as well contraindicated.

We experienced that surgery when applicable, was the essential element of patient management. Similarly other authors reported that nearly all long-term survivors with ATC have had surgery as part of their treatment [13]. Our results confirm that multidisciplinary treatment combining surgery to radiotherapy offers a significant better outcome especially in tumours smaller than 5 cm compared to larger ones. Nevertheless when dealing with elderly patients surgery alone or in association with tracheostomy/endoprosthesis and radiotherapy, in selected patients, also for larger tumours, gains a significant improvement in survival although the prognosis remains very poor.

The role of radical surgery was supported by Haigh et al. [20] examining a restricted group of long-term survivors treated with

surgery followed by RT/chemotherapy. More specifically, those patients who underwent a potentially curative resection had a median survival of 43 months compared to 3 months for those with a palliative resection. Swaak-Kragten et al. [15] observed that patients with R0/R1 resection undergone protocol of chemoradiation achieved a local complete response rate of 89%, compared to only 3% for not radiated patients without R0/R1 resection. Complete local response resulted in longer median survival (7 months vs 3 months) and improved 1-year overall survival (32% vs 9%). Levendag et al. [21] also supported the fundamental role of a curative resection for the success of treatment. The above experiences confirm our observation about the central role of surgery in the treatment of ATC, with increased chance for long-term survival in selected patients.

This approach, if a low incidence of perioperative complications is possible, might be justified for all ATC patients and even for elderly ones [19,22–24].

In our study a major confounding factor in determining the effect of treatment on outcome has been selection bias, because patients who undergo surgical resection alone or in association to radiation often have less extensive disease and minor comorbidity. Although it is impossible to control for such factors in a retrospective study, it appears clear than when applicable a multidisciplinary approach is mandatory in the treatment of ATC, considering the combination of surgery and radiotherapy the fundamental options to achieve symptoms control and attempt to improve survival. When examining a cohort of elderly patients, especially with large tumours and in presence of severe comorbidity, we must consider that, although significant difference in survival are potentially offered to patients by a surgical approach, in most of them a limited palliation with tracheostomy or endoprosthesis might be reasonable and it is actually the more used approach. Nevertheless is common opinion that further, multicentric studies are needed to confirm the real impact of surgery alone or as part of a multimodality treatment in ATC and to standardize the approach to elderly patients.

5. Conclusion

In summary, ATC is characterized by aggressive behaviour with a very poor prognosis especially in case of large tumours and elderly patients. Results coming from single modality therapies are usually unsatisfactory, therefore multimodality therapy has progressively become the treatment of choice. Although the prognosis remains very poor, in elderly selected patients, a combination of surgery plus radiotherapy offers a significant increased survival, being total radical thyroidectomy an essential element of the multimodality treatment. Nevertheless in the elderly in presence of large ATC, since limited eligibility to surgery and radiotherapy, tracheostomy and endoprosthesis, with palliative intent on airways, are the mostly adopted options.

Ethical approval

Ethical approval was requested and obtained from the “Università degli Studi di Perugia, Facoltà di Medicina e Chirurgia” ethical committee.

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Author contribution

Andrea Polistena: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also the drafted and editing of the manuscript.

Massimo Monacelli: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Roberta Lucchini: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Roberta Triola: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Claudia Conti: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Stefano Avenia: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Fabio Rondelli: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Walter Bugiantella: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Ivan Barillaro: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Alessandro Sanguinetti: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Nicola Avenia: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Conflict of interest

The Authors declare no conflict of interest or any financial support.

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