Anaplastic and Poorly Differentiated Thyroid Cancer

Gabriele Ricci*[1], Angelo Serao[1], Carla Di Cosimo[1], Roberto Baldelli[2], Paolo Zuppi[2] and Pierluigi Marini[1]

[1]Division of General and Emergency Surgery, Department Emergency and Acceptance, Italy

[2]Division of Endocrinology, San Camillo-Forlanini Hospital, Italy

***Corresponding author:** Gabriele Ricci, Department Emergency and Acceptance, Division of General and Emergency Surgery, C.ne Gianicolense 87, 00152, Rome, Italy, Tel: 390658703413, Fax: 390658704589, Email: gabrielericci79@yahoo.com

Published Date: September 20, 2017

ANAPLASTIC THYROID CANCER

Epidemiology

Malignant thyroid tumors include, on the one hand scarcely aggressive and rarely lethal forms such as differentiated tumors, and on the other anaplastic carcinoma, which is one of the most aggressive tumors, with a mortality rate close to 100%. Fortunately, anaplastic cancer accounts for less than 2% of all thyroid malignancies, and contrary to differentiated tumors, its incidence in industrialized countries is steadily decreasing in the last decades [1]. The reasons for this decline are not entirely clear, some authors point to the new diagnostic techniques that allow the reclassification of some tumors previously exchanged for anaplastic carcinomas in lymphomas and medullary cancer. An equally important role is attributed to increased iodine intake with diet and improved economic status: in fact,the incidence of anaplastic carcinoma is double in areas of endemic goiters [2]. However, a recent Swedish study has shown that the incidence of anaplastic carcinoma does not vary by adding iodine to the diet [3], while the increasing use of total thyroidectomy as a therapeutic choice of thyroid pathology seems crucial, and on the other hand early detection of differentiated tumors, which reduce the risk of a potentially well-differentiated tumor transformation in anaplastic tumor [4].

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

Although anaplastic carcinoma represents a small percentage of thyroid malignancies, it is responsible for more than 50% of the deaths attributable to thyroid cancer [5].

The prognosis of anaplastic carcinomas is bad: in the case series reported in the literature, median survival from diagnosis ranging from 4 to 12 months [6]. Patients with a survival of more than two years are so rare that probably the anecdotal cases with long-term survival reported in the literature received a wrong histopathological diagnosis. In a retrospective study, 516 patients reported a 6-month mortality rate from the diagnosis of 68.4%, and a one-year mortality rate of 80.7% [5].

Anaplastic thyroid carcinoma shows a peak in the sixth and seventh decades of life (mean 64 years), although sporadic cases of patients under the age of 40 years have been reported [7]. There is a slight predominance of female sex, with a male to female ratio of 1: 1.5.

Clinical Presentation

The incidental diagnosis of anaplastic carcinoma after surgical therapy for nodular tireopathy is rare. Unlike differentiated cancer, anaplastic cancer has a clinical course that often suggests the diagnosis of cancer. Patients can be schematically divided into four groups: 1. patients with different thyroid cancer history treated several years earlier, who after a long period of clinical stability notice sudden changes; 2. long-term patients with benign goitre therapy, who notice a rapid growth of the goiter; 3. patients with acute "*de novo*"massive cervical mass in rapid growth; 4. presence of a distant metastatic localization as first evidence of an anaplastic thyroid carcinoma.

The presence of a rapidly growing cervical mass, hard and firm in surrounding tissues, is the symptom of presentation in 97% of patients [8]. Commonly patients complain of swelling and compression of the neck. The average size of the cervical mass at the time of diagnosis is 8cm (range 3 to 20cm). It is not uncommon for mass to double volume over a week. Hemorrhage within the neoplasm suddenly increases the size of the mass and the related symptoms. Symptoms of compression and invasion of surrounding structures are found in most patients: rhinitis, dyspnoea, dysphagia, cough, cervical pain. At the time of diagnosis patients present a compression or infiltration of at least one recurrent nerve in more than 30% of cases, and in more than 40% of cases there are metastases in the cervical nodes. Distant metastases are also very frequent and involve more than 50% of patients at diagnosis, while another 25% will be affected by distant metastasis during the disease (5.8). The lung is the most frequent metastatic site (80%), followed by bones (6-15%) and brain (5-13%), common are also adrenal metastases and intra-abdominal lymph nodes.

The local extent of the disease is the most important prognostic factor in thyroid anaplastic carcinoma [5,9,10].

Sugitani developed a prognostic index based on the combination of the major risk factors: acute symptoms, tumor greater than 5 cm, presence of distant metastasis and white blood cells

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

above 10,000/mm^3. In the case series reported, patients with prognostic index 4 died within three months of diagnosis, those with prognostic index 3 died within six months, while 62% of those with prognostic index 1 survive at 6 months [10]. A retrospective analysis of the National Cancer Institute's Surveillance Epidemiology and End Results (**SEER**) database by Kebebew identified 516 patients with anaplastic thyroid carcinoma between 1973 and 2000 [5]. Age (under 60 years), extent of the disease (local, regional or distant metastases) and combined surgical resection with radiotherapy were identified as independent prognostic factors at multivariate analysis. The author reports an improvement of 28.3% of tumor-specific mortality in patients less than 60 years old, and an improvement of 44.9% in one-year tumor-specific mortality among patients with intrathyroidal carcinoma compared to patients with distant metastases. The prognosis of patients with incidental anaplastic carcinoma (small foci of anaplastic carcinoma within a well differentiated tumor) is still unclear, although it seems to be better than classic anaplastic carcinoma. Sugino reported survival rates of 73% at one year and 46% at two years in patients with incidental anaplastic carcinoma [11].

Pathology

Histologically, three different subtypes of anaplastic carcinoma have been described [12]: fused cell carcinoma (40-53%), giant cell carcinoma (38-50%) and desmoid or mixed carcinoma (19-22%). They show the same clinical behavior and the same prognosis. All variants appear macroscopically as a firm mass that deforms the glandular profile and are histologically characterized by a high pleomorphism, the presence of large necrotic and hemorrhagic areas, a high mitotic index, and a marked vascular invasion. The fused cell variant is characterized by a sarcomatoid-like fascicular architecture. The giant cell variant has a greater pleomorphism, characterized by voluminous, polygonal or globular cells with atypical and hyperchromic nuclei. Squamous carcinoma is characterized by the presence of large cell nests that resemble a squamous carcinoma and may contain some keratin beads. Small cell carcinomas in the past have been a source of confusion and diagnostic mistakes. Today, such lesions have been reclassified as lymphoma or poorly differentiated thyroid medullary carcinomas. This distinction is very important because these two histotypes have a better prognosis than anaplastic carcinoma. Probably sporadic long-term survival cases reported in the literature depend on lack of recognition of these forms. In a study of 82 patients with anaplastic cancer treated at the Mayo Clinic, survival of more than 5 years for 3 patients was reported. A recent reassessment of histological preparations has shown that erroneous diagnosis was reported in these patients: the first two patients had a thyroid lymphoma and the third patient had a poorly differentiated medullary thyroid carcinoma [12,13]. Lymphomas are characterized by small, relatively uniform round cells and show scarce pleomorphism compared to anaplastic carcinoma. The immunohistochemical markers for lymphoid cells and electronic microscopy can confirm the diagnosis. Poorly differentiated medullary carcinomas may resemble giant cell or fused cellular anaplastic cell subtypes but are recognized based on immunohistochemical positivity for neuron-specific enolase, chromogranin,

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

calcitonin and CEA. At electronic microscopy typical intracytoplasmic secretory granules are also visible.

Pathogenesis

The pathogenesis of anaplastic thyroid tumors is not completely clear. Some authors consider these tumors as"*de novo*"cancer, other authors suggest that they develop from the dedifferentiation of a previous differentiated carcinoma. Anaplastic carcinoma has a greater incidence in patients with a long history of goiter or with a history of follicular or papillary carcinomas treated inadequately. DeMeter has documented the presence of previous thyroid (benign or malignant) pathologies in 76% of patients with anaplastic carcinoma, in particular 47% of patients had a previous or concomitant differentiated tumor [4].

The presence of well-differentiated histologic foci of carcinoma in association with anaplastic carcinoma is well documented and was found in 23% to 100% of cases [6]. Although there may be any type of differentiated carcinoma, papillary cancer represents the most common histotype associated with anaplastic carcinoma. Among the papillary tumors, more aggressive forms (columnar cell variant) or poorly differentiated carcinomas are the most common, supporting the theory of a well differentiated carcinoma transformation through intermediate forms. Ibanez analyzed sections of the entire removed organ found the presence of differentiated carcinomas in all cases of anaplastic carcinoma of the thyroid examined [14], while the failure to find foci of carcinoma differentiated in the anaplastic carcinomas piece would be attributed to an inadequate number of examined sections, or exuberant growth of anaplastic cells which hides the presence of papillary cells.

Comparative genomic hybridization analysis of anaplastic carcinomas and coexisting papillary or follicular carcinomas demonstrate similar cytogenetic patterns, suggesting that anaplastic carcinomas may originate from differentiated thyroid tumors [15]. Cytophotometric studies, however, showed that only a part of the differentiated carcinoma associated with anaplastic anomalies share the aneuploidy of anaplastic elements, suggesting the "*de novo*" emergence of anaplastic thyroid carcinomas [16].

Recent studies have shown that mutation of the BRAF gene is the most common gene mutation found in papillary thyroid carcinoma. Various anaplastic tumors appear to be derived from papillary tumors with BRAF mutation following the loss of the p53 gene [17]. The loss of the p53 oncosuppressor gene or the presence of an abnormal p53 gene is implicated in the transformation of differentiated carcinoma into anaplastic. Re-expression of the p53 gene in these *in vitro*-cultured cell lines has been shown to reverse certain aspects of anaplastic transformation: chemosensitivity and radiosensitivity, response to TSH, cell proliferation inhibition, re-expression of thyroid peroxidase [18,19].

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

Diagnosis

The clinical suspicion of anaplastic thyroid cancer is confirmed by fine-needle aspiration biopsy of the thyroid, which has a 90% diagnostic accuracy [20,21]. Diagnostic failure may be attributed to withdrawal within necrotic, hemorrhagic or fibrotic areas. In doubtful cases percutaneous biopsy could be used to confirm the diagnosis. Open biopsy has been practically abandoned and it is reserved for those rare cases of dubious diagnosis after percutaneous needle biopsy.

Typically, anaplastic carcinoma is unable to capture radioiodine: scintigraphy investigations are therefore not indicated. Diagnostic investigations should include a CT of the neck, chest, and mediastinum to evaluate the extent of the disease and the invasion of the surrounding structures or the presence of lung metastases, and bone scintigraphy to evaluate the presence of bone metastases. Magnetic resonance imaging (**MRI**) can be helpful in determining the local involvement of bone and vascular structures [1]. Since anaplastic carcinoma is a rapidly growing tumor, the use of FDG-PET can be very useful for the diagnosis of metastatic sites [22].

Treatment

Neither surgical treatment, nor its extension, nor radiotherapy or chemotherapy has been shown individually to alter the course of the disease. These failures have led to the adoption of multimodal therapeutic plans in the therapy of anaplastic thyroid cancer: radiotherapy associated with surgery improves the local control of the disease, while the association of chemotherapy with radiotherapy increases the radio sensitivity of the anaplastic tumor [5,8]. Despite the high incidence of distant synchronous metastasis, death is generally related to the local extension of the disease and the resulting airway obstruction. The first aim of treatment is therefore to get the local control of the disease. Airway obstruction may occur due to external compression of the trachea (which is the most common mechanism) for intraluminal tumor extension, or paralysis of both vocal cords. Hotling noted a reduction in mean survival in patients undergoing prophylactic tracheostomy over those who did not undergo [23].

Prophylactic tracheostomy should therefore be abandoned as it may be difficult to perform, does not improve survival, is associated with high morbidity due to cicatrization problems, affects negatively the quality of life of patients and retards the use of radiotherapy. The use of tracheal stents has been proposed instead of tracheostomy for palliative purposes [24].

Numerous studies have documented an improvement in survival when radical resection of the tumor could be achieved [7,25-28]. Based on these studies, the American Association of Endocrine Surgeons (**AAES**) guidelines recommend the use of full mass surgical resection if cervical and mediastinal disease can be resected with limited morbidity [29,30]. Thus full resection of primitive tumor associated with neck dissection in presence of clinically evident lymph node metastases should be performed, but the en-bloc radical resection of contiguous vital structures such as larynx, pharynx or esophagus in order to obtain the complete removal of the tumor mass

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

should be avoided because it does not increase the survival causing only a serious deterioration in the quality of life of these patients [30,31].

Only a small minority of cases at the time of presentation can be undergoing potentially curative resection [11,25]. For this reason, some authors have used preoperative radiotherapy, achieving a higher percentage of complete tumor resections [26,32-34]. There is, however, no agreement on timing for radiotherapy. Other authors support that it is better to administrate radiotherapy after surgery in order to allow radiations to act on a small tumor residue [7,11, 25,27,35]. In a study conducted by Tennvall on patients treated with radio chemotherapy and then surgical therapy, in 83% of cases a potentially curative resection of the neoplasm (**R0**) was possible. Tennvall reported a 9% survival rate at more than 2 years [34]. Similar results were reported by Nilsson [26]. In particular, the author has shown that the introduction of new radiotherapy protocols has resulted in surgical resection of tumor from 22% of cases between 1973 and 1975, to 55% of cases between 1975 and 1993 , and to 92% of cases between 1994 and 1997.

Improved survival was achieved only when radical surgery has been followed by radio-chemotherapy [9,26]. Although anaplastic thyroid carcinoma is a relatively radiotherapy resistant tumor, some studies have shown local disease control in 68-80% of cases. Anaplastic cancer is a rapidly growing tumor, most authors use hyperfractionated radiotherapy protocols to minimize the multiplication of tumor cells at intervals between radiotherapy sessions. Current protocols use doses ranging from 30 to 60 Gy, the most promising results were obtained with doses of 46 Gy [28,34,36]. In general, daily doses higher than 3 Gy cause an increase in the incidence of myelopathy: the effectiveness of radiotherapy must be balanced with its toxicity, and dosages must therefore be evaluated with great caution. Mitchell reported an incidence of 3rd or 4th grade side effects such as erythema, pharyngophagitis, tracheitis or myelopathy in 75% of patients treated with 60.8 Gy radiotherapy divided into 23 fractions twice a day. Such complications proved to be unacceptably high despite improvements in local control of the disease [37]. Tennvall reduced the total dose of 46 Gy (1.6 Gy twice daily) radiotherapy combined with the intravenous administration of doxorubicin (20 mg daily) used as radiosensitizer [34]. Thyroid anaplastic cell lines express numerous MRP (multi-resistant-associated protein), these are proteins that lead to the excretion of chemotherapeutic agents outside the cell [38]. For this reason chemotherapy is considered to be the weak ring in the multimodal treatment chain of these tumors. Doxorubicin is the most used chemotherapy drug in the treatment of thyroid anaplastic carcinoma. Doxorubicin monotherapy showed a response rate of 20%. Combination therapy with other chemotherapeutic drugs such as cisplatin, bleomycin or 5-fluorouracil showed a slight improvement in clinical response [39,40].

More recently, the introduction of paclitaxel has shown more promising results. Ain published a phase II trial on the use of paclitaxel in 19 patients with anaplastic thyroid cancer. Of these, a patient showed a complete response and 9 a partial response (tumor reduction> 50%) to therapy [41]. The combination of manumycin with paclitaxel has been shown to potentiate cytotoxic

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

effects and to increase apoptosis in *in vitro* and *in vivo* studies [42]. Similarly, the combination of gemcitabine and cisplatin has shown an interesting cytostatic activity *in vitro* [43]. The multimodal therapeutic regimen prevents death from asphyxia, but has no effect on distant disease sites, so in general it only has the effect of increasing the survival of a few months. Despite the widespread use of multimodal treatment there is no scientific evidence that demonstrates a significant increase in survival in these patients over the last 20 years, so new therapies for the treatment of anaplastic thyroid carcinoma are needed.

New Therapies

An adenovirus (ONYX-015) was developed targeting the anaplastic thyroid carcinoma cells, which carries the p53 oncosupressor gene. The wild-type p53 exogenous gene has been shown to increase the chemo-sensitivity of tumor cells causing cell death through the *in vitro* and *in vivo* induction of apoptosis by synergistically acting on paclitaxel and doxorubicin [44-46]. These results indicate the possibility of combining chemotherapy with gene therapy in the future. Some researchers are investigating the possibility to treat anaplastic thyroid tumors with radioiodine after gene therapy with the sodium-iodine symporter gene.

Combretastatin A4 is a direct agent to selectively block tumor neoangiogenesis. Phase I trial demonstrated drug efficacy without cytotoxic effects [47]. A patient treated with this drug after having exhausted all other therapeutic possibilities is alive at 36 months [48]. *In vivo* bovine semen ribonuclease injection and *in vitro* bone morphogenetic protein (**BMP-7**) administration have been shown to significantly reduce the proliferation of anaplastic thyroid carcinoma cells [49,50].

It has recently been shown that PPARγ (peroxisome proliferator-activated receptor) agonists inhibit cell proliferation by inducing apoptosis and induce re differentiation in thyroid cancer cell lines. Such agents may therefore be useful in the treatment of thyroid carcinomas that do not respond to traditional treatments [51]. The ability to overcome this highly aggressive, untreated tumor with conventional methods is now entrusted to the study of these new strategies and their future clinical application.

POORLY DIFFERENTIATED THYROID CANCER

There is growing evidence in the literature on the existence of a group of intermediate thyroid carcinomas both for morphological characteristics and for biological behavior and prognosis between differentiated carcinomas and anaplastic carcinoma [52,53]. There are controversies about the treatment of so-called poorly differentiated thyroid carcinomas that derive from the confusion on the criteria for its definition. These thyroid cancers were first described by Sakamoto in 1983 [54], since then many authors have included in this classification the most aggressive papillary carcinoma variants (columnar cells, high, solid, diffuse sclerosing cells) [55]. The fact that these variants of papillary carcinoma show a more aggressive behavior than the classical

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

type does not in itself justify the inclusion of these variants between poorly differentiated tumors, the definition of which is given by the tumor architecture and whose prognosis is still worse [56]. Some poorly differentiated thyroid tumors have been mistakenly classified in the past as anaplastic carcinomas. In 1984, Carcangiu based the classification only on histopathological criteria used the term insular carcinoma to describe a class of thyroid cancer with aggressive clinical behavior in a series of 25 patients [57]. In 2006 an international consensus conference was held in Turin in order to establish diagnostic criteria for poorly differentiated thyroid tumors [58]: they are follicular origin lesions (medullary carcinomas are not included in this group), unlike anaplastic carcinomas they produce thyroglobulin, however, the immunohistochemical analysis is typically focal and weak, they are histologically composed of nests, islands or trabeculae of tumor cells having poor cytoplasm and a high core/cytoplasm ratio, mitotic activity including the identification of abnormal mitotic figures is evident, there are constant areas of tumor necrosis and occasionally pleomorphic cells. Two subgroups of poorly differentiated carcinomas are associated with the same prognosis: insular carcinomas, thus named for their resemblance to insular carcinoid tumors, and the other subtypes, characterized by a smaller insular component and the presence of larger cells. Capsular and vascular invasion are very common for both subtypes. The concomitant presence of well-differentiated carcinoma or anaplastic carcinoma has been widely documented [59,60]. The study published by Volante included 183 patients with poorly differentiated thyroid carcinoma, whether focal or predominant. In both cases, the clinical behavior of the lesion was more aggressive than well differentiated carcinoma [61].

Fine-needle aspiration may provide a suspect but does not allow a preoperative diagnosis of poorly differentiated carcinoma [62]. In insular carcinoma, the mutation of the p53 gene is found in more than 25% of cases, suggesting that it is an intermediate form in the dedifferentiation process from well-differentiated carcinoma to anaplastic carcinoma [53]. Poorly differentiated carcinomas have a mean size of 4 cm and may appear as a single or multi nodular lesions. The ratio of men to women is 1: 2. In more than 50% of cases regional metastases are present in the lymph nodes. Poorly differentiated carcinomas generally account for 2-3% of malignant thyroid lesions, though in the northern areas of northern Italy they constitute 15% of thyroid malignancies [52,53]. Genetic and environmental factors play a key role in the genesis of these cancers (probably related to diet, including poor iodine intake). Survival at 5 and 10 years for insular carcinoma was 72.2% and 52% respectively [53]. The rarity of these tumors and the scarcity of the studies available in the literature do not allow to draw definitive conclusions on the best therapeutic management to be adopted. Surgical treatment is the main therapeutic approach, while the use of radiometabolic therapy, external radiotherapy or chemotherapy is still controversial. The proportion of patients with poorly differentiated carcinomas able to concentrate sufficient radioiodine to allow appropriate treatment is unknown, although some studies seem to report data close to 85%. Given the possible radioiodine uptake and the absence of morbidity, some authors recommend radioiodine treatment in all patients with poorly differentiated thyroid

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

cancer after surgical treatment [52,53]. External radiation therapy is administered to reduce the risk of local recurrence, although no increase in survival has been reported [56]. External radiation therapy is recommended for T3 tumors in the absence of distant metastasis, in all T4 tumors, and in the case of regional lymph node involvement.

If surgery has been able to completely resect the tumor, radio metabolic therapy must precede external radiotherapy. If surgical therapy has been incomplete it may be advantageous to start radiotherapy immediately [53]. The *in vitro* chemo-sensitivity of poorly differentiated thyroid carcinoma has been low. However, a study of thirty patients with not operable poorly differentiated thyroid carcinoma reports over 50% of the response (some totals) to an intense chemotherapy regimen based on the administration of methotrexate, vinblastine, adriamycin and bleomycin, associated with external radiotherapy. In half the cases, the tumors were re-staged and underwent surgery [63].

Given the tendency for these tumors to recur and metastasize, patients should be closely monitored. Follow-up of serum thyroglobulin (which is the key to the distinction between poorly differentiated carcinomas and anaplastic) may be useful for the diagnosis of recurrences. Recently, the use of FDG-PET has proved to be very useful in the diagnosis of recurrent or neo plastic disease, and is particularly well suited for those patients with high levels of thyroglobulin and negative scintigraphy [64].

References

1. Pasieka JL. Anaplastc thyroid cancer. Curr Opin Oncol. 2003; 15: 78-83.
2. Bakiri F, Djemli FK, Mokrane LA, Djidel FK. The relative roles of endemic goiter and socioeconomic development status in the prognosis of thyroid carcinoma. Cancer. 1998; 82: 1146-1153.
3. Pettersson B, Coleman MP, Ron E, Adami HO. Iodine supplementation in Sweden and regional trends in thyroid cancer incidence by histopathologic type. Int J Cancer. 1996; 65: 13-19.
4. Demeter JG, De Jong SA, Lawrence AM, Paloyan E. Anaplastic thyroid carcinoma: risk factors and outcome. Surgery. 1991; 110: 956-963.
5. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. Cancer. 2005; 103: 1330-1335.
6. Chandrakanth A, Ashok RS. Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors and treatment approaches. Ann Surg Oncol. 2006; 13: 453-464.
7. Venkatesh S, Ordonez N, Schultz P. Anaplastic carcinoma of the thyroid. Cancer. 1990; 66: 321-330.
8. McIver B, Hay ID, Giuffrida D, Dvorak CE, Grant CS, et al. Anaplastic thyroid carcinoma: a 50 year experience at a single institution. Surgery. 2001; 130: 1028-1034.
9. Besic N, Hocevar M, Zgajne J, Pogacnik A, Grazio-Frkovic S, et al. Prognostic factors in anaplastic carcinoma of the thyroid-a multivariate survival analysis of 188 patients. Langenbeck's Arch Surg. 2005; 390: 203-208.
10. Sugitani I, Kasia N, Fujimoto Y, Yanagisawa A. Prognostic factors and therapeutic strategy for anaplastic carcinoma of the thyroid. World J Surg. 2001; 25: 617-622.
11. Sugino K, Ito K, Mimura T, Nagahama M, Fukunari N, et al. The important role of operations in the management of anaplastic thyroid carcinoma. Surgery. 2002; 131: 245-248.
12. Rosai J, Saxen EA, Woolner L. Undifferentiated and poorly differentiated carcinoma. Seminar Diagn Pathol. 1985; 2: 123-136.
13. Nel CJ, van Heerden JA, Goellner JR, Gharib H, McConahey WM, et al. Anaplastic carcinoma of the thyroid: a clinicopathologic study of 82 cases. Mayo Clin Proc. 1985; 60: 51-58.

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

14. Ibanez ML, Russell WO, Albores-Saavedra J, Lampertico P, White EC, et al. Thyroid carcinoma-biologic behaviour and mortality: post mortem findings in 42 cases including 27 in which the disease was fatal. Cancer. 1966; 19: 1039-1052.

15. Miura D, Wada N, Chin K, Magrane GG, Wong M, et al. Anaplastic thyroid cancer: cytogenetic patterns by comparative genomic hybridization. Thyroid. 2003; 13: 283-290.

16. Ain KB. Anaplastic thyroid carcinoma: behaviour, biology and therapeutic approaches. Thyroid. 1998; 8: 715-726.

17. Quiros RM, Ding HG, Gattuso P, Prinz RA, Xu X. Evidence that the subset of anaplastic thyroid carcinomas are derived from papillary carcinomas due to BRAF and p53 mutations. Cancer. 2005; 103: 2261-2268.

18. Moretti F, Farsetti A, Soddu S, Misiti S, Crescenzi M, et al. p53 re expression inhibits proliferation and restores differentiation of human thyroid anaplastic carcinoma cells. Oncogene. 1997; 14: 729-740.

19. Weisman SM, Loree TR, Rigual NR, Hicks WL Jr, Douglas WG, et al. Anaplastic transformation of thyroid cancer; review of clinical, pathologic and molecular evidence provides new insights into disease biology and future therapy. Head Neck. 2003; 25: 662-670.

20. Us-Krasovec M, Golouh R, Auersperg M, Besic N, Ruparcic-Oblak L. Anaplastic carcinoma in fine needle aspirates. Acta Cytol. 1996; 40: 953-958.

21. Ain KB. Anaplastic thyroid carcinoma: a therapeutic challenge. Semin Surg Oncol. 1999; 16: 64-69.

22. Khan N, Oriuchi N, Higuchi T, Endo K. Review of FDG-PET in the follow-up of medullary and anaplastic thyroid carcinomas. Cancer control. 2005; 12: 254-260.

23. Hotling T, Meybier H, Buhr H. Status of tracheotomy in treatment of the respiratory emergency in anaplastic thyroid cancer. Wien Klin Wochenschr. 1990; 102: 264-266.

24. Hopkins C, Stearns M, Watkinson AF. Palliative tracheal stenting in invasive papillary thyroid carcinoma. J Laryngol Otol. 2001; 115: 935-937.

25. Haigh PI, Ituarte P, Wu H-S, Treseler PA, Posner MD, et al. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. Cancer. 2001; 91: 2335-2342.

26. Nilsson O, Lindberg J, Zedenius J. Anaplastic giant cell carcinoma of the thyroid gland: treatment and survival over a 25 year period. World J Surg. 1998; 22: 725-730.

27. Tan RK, Finley RK III, Driscoll D, Bakamjian V, Hicks WL Jr, et al. Anaplastic carcinoma of the thyroid: a 24 year experience. Head Neck. 1995; 17: 41-48.

28. Junor EJ, Paul J, Reed NS. Anaplastic thyroid carcinoma: 91 patients treated by surgery and radiotherapy. Eur J Surg Oncol. 1992; 18: 83-88.

29. Cobin RH, Gharib H, Bergman DAL. AACE/AAES medical/surgical guidelines for clinical practice: management of throid cancer. Endocr Pract. 2001; 7: 202-220.

30. Lang BH, Lo CY. Surgical options in undifferentiated thyroid carcinoma. World J Surg. 2007; 31: 969-977.

31. Passler C, Sheuba C, Prager G, Kaserer K, Flores JA, et al. Anaplastic thyroid carcinoma: a retrospective analysis. Langenbeck's Arch Surg. 1999; 384: 284-293.

32. Wallin G, Lundell G, Tenvall J. Anaplastic giant cell thyroid carcinoma. Scand J Surg. 2004; 93: 272-277.

33. Pudney D, Lau H, Reuther D, Falck V. Clinical experience of the multimodality management of anaplastic thyroid cancer and literature review. Thyroid. 2007; 17: 1243-1250.

34. Tennvall J, Lundell G, Wahleberg P, Bergenfelz A, Grimelius L, et al. Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery. Br J Cancer. 2002; 86: 1848-1853.

35. De Crevoisier R, Baudin E, Bachelot A, Leboulleux S, Travagli JP, et al. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy and hyperfractionated accelerated external radiotherapy. Int J Radiat Oncol Biol Phys. 2004; 60: 1137-1143.

36. Kobayashi T, Asakawa H, Umeshita K, Takeda T, Maruyama H, et al. Treatment of 37 patients with anaplastic carcinoma of the thyroid. Head Neck. 1996; 18: 36-41.

37. Mitchell G, Huddart R, Harmer C. Phase II evaluation of high dose accelerated radiotherapy for anaplastic thyroid carcinoma. Radiother Oncol. 1999; 50: 33-38.

38. Lenhert M. Clinical multi drug resistance in cancer: a multifactorial problem. Eur J Cancer. 1996; 32: 912-920.

39. De Besi P, Busnardo B, Toso S, Girelli ME, Nacamulli D, et al. Combined chemotherapy with bleomycin, adriamycin, and platinum in advanced thyroid cancer. J Endocrinol Invest. 1991; 14: 475-480.

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.

40. Williams SD, Birch R, Einhorn LH: Phase II evaluation of doxorubicin plus cisplatin in advanced thyroid cancer: A Southeastern Cancer Study Group Trial. Cancer Treat Rep. 1986; 70: 405-407.

41. Ain KB, Egorin MJ, DeSimone PA. Treatment of anaplastic thyroid carcinoma with paclitaxel: Phase 2 trial using ninety-sixhour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (**CATCHIT**) Group. Thyroid. 2000; 10: 587-594.

42. 42.Yeung S, Xu G, Pan J, Christgen M, Bamiagis A. Manumycin enhances the cytotoxic effect of paclitaxel on anaplastic thyroid carcinoma cells. Cancer Res. 2000; 60: 650-656.

43. Voigt W, Bulankin A, Muller T, Schoeber C, Grothey A, et al. Schedule dependent antagonism of gemcitabine and cisplatin in human anaplastic thyroid cancer cell lines. Clin Cancer Res. 2000; 6: 2087-2093.

44. Portella G, Scala S, Vitagliano D, Vecchio G, Fusco A. ONYX-015, an E1B gene-defective adenovirus, induces cell death in human anaplastic thyroid carcinoma cell lines. J Clin Endocrinol Metab. 2002; 87: 2525-2531.

45. Blagosklonny MV, Giannakakou P, Wojtowicz M, Romanova LY, Ain KB, et al. Effects of p53-expressing adenovius on the chemosensivity and differentiation of anaplastic thyroid cancer cells. J Clin Endocrinol Metab. 1998; 83: 2516-2522.

46. Nagayama Y, Yokoi H, Takeda K, Hasegawa M, Nishihara E, et al. Adenovirus-mediated tumor suppressor p53 gene therapy for anaplastic thyroid carcinoma *in vitro* and *in vivo*. JClin Endocrinol Metab. 2000; 85: 4081-4086.

47. Dowlati A, Robertson C, Cooney M, Petros WP, Stratford M, et al. A phase I pharmacokinetic and translational study of the novel vascular targeting agent combretastatin a-4 phosphate on a single dose intravenous schedule in patients with advanced cancer. Cancer Res. 2002; 15: 3408-3416.

48. Randal J. Antiangiogenesis drugs target specific cancers, mechanisms. J Natl Cancer Inst. 2000; 92: 520-522.

49. Franzen A, Heldin NE. BMP-7-induced cell cycle arrest of anaplastic thyroid carcinoma cells via p21 and p27. Biochem Biophys Res Commun. 2001; 285: 773-781.

50. Kotchetkov R, Cinatl J, Krivtchik AA, Vogel JU, Matousek J, et al. Selective activity of BS-RNase against anaplastic thyroid cancer. Anticancer Res. 2001; 21: 1035-1042.

51. Park JW, Zarnegar R, Kanauchi H, , Wong MG, Hyun WC, et al. Troglitazone, the peroxisome proliferator-activated receptor-gamma agonist, induces antiporliferation and redifferentiatio in human thyroid cancer cell lines. Thyroid. 2005; 15: 222-231.

52. Patel KN, Shaha AR. Poorly differentiated and anaplastic thyroid cancer. Cancer control. 2006; 13: 119-128.

53. Sanders EM, LiVolsi VA, Brierley J, Shin J, Randolph GW. An evidence-based review of poorly differentiated thyroid cancer. World J Surg. 2007; 31: 934-945.

54. Sakamoto A, Kasai n, Sugano H. Poorly differentiated carcinoma of the thyroid. A clinicopathologic entity for a high-risk group of papillary and follicular carcinomas. Cancer. 1983; 52: 1849-1855.

55. Pilotti S, Collini P, Manzari A, Marubini E, Rilke F. Poorly differentiated forms of papillary thyroid carcinoma: distinctive entities or morphological patterns? Semin Diagn Pathol. 1995; 12: 249-255.

56. Akslen LA, LiVolsi VA. Poorly differentiated thyroid carcinoma: it is important. Am J Surg Pathol. 2000; 24: 310-313.

57. Carcangiu ML, Zampi G, Rosai J. Poorly differentiated ("insular") thyroid carcinoma. Am J Surg Pathol 1984; 8: 655-668.

58. Volante M, Collini P, Nikiforov YE, Sakamoto A, Kakudo K, et al. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. Am J Surg Pathol. 2007; 31: 1256-1264.

59. Lam KY, Lo CY, Chan KW, Wan KY. Insular and anaplastic carcinoma of the thyroid: a 45-year comparative study at a single institution and a review of the significance of p53 and p21. Ann Surg. 2000; 231: 329-338.

60. Pilotti S, Collini P, Del Bo R, Cattoretti G, Pierotti MA, et al. A novel panel of antibodies that segregates immunocytochemically poorly differentiated carcinoma from undifferentiated carcinoma of the thyroid gland. Am J Surg Pathol. 1994; 18: 1054-1064.

61. Volante M, Landolfi S, Chiusa L, Palestini N, Motta M, et al. Poorly differentiated carcinomas of the thyroid with trabecular, insular and solid patterns. A clinico-pathological study of 183 cases. Cancer. 2004; 100: 950-957.

62. Pietribiasi F, Sapino A, Papotti M, Bussolati G. Cytologic features of poorlydifferentiated "insular" carcinoma of the thyroid, as revealed by fine-needleaspiration biopsy. Am J Clin Pathol. 1990; 94: 687-692.

63. Auersperg M, Us-Krasovec M, Petric G, Pogacnik A, Besic N. Results of combined modality treatment in poorly differentiated and anaplastic thyroid carcinoma. Wien Klin Wochenschr. 1990; 27: 267-270.

64. Wang W, Larson SM, Fazzari M, Tickoo SK, Kolbert K, et al. Prognostic value of [18F] fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J Clin Endocrinol Metab. 2000; 85: 1107-1113.

Copyright © Ricci G.This book chapter is open access distributed under the Creative Commons Attribution 4.0 International License, which allows users to download, copy and build upon published articles even for commercial purposes, as long as the author and publisher are properly credited.