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CURRENT CONCEPTS IN ENDOCRINE SURGERY

New trends in the treatment of undifferentiated carcinomas of the thyroid

Paolo Miccoli · Gabriele Materazzi · Alessandro Antonelli · Erica Panicucci · Gianluca Frustaci · Piero Berti

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Abstract
Introduction Malignant tumours of the thyroid are generally classified as either well-differentiated thyroid carcinoma, which is composed of papillary and follicular carcinoma, or undifferentiated/anaplastic thyroid carcinoma (ATC). ATC is not only the most lethal disease in the field of endocrine surgery but also one of the most aggressive tumours characterized by an almost invariable fatal outcome, which only very rarely exceeds a 1-year course.
Discussion The impact of surgical resection in association with external beam radiation on ATC outcome has been extensively investigated also in studies based on multicentric database, and there is a general agreement on the significance of a complete resection of the tumour. It has been difficult up to now to collect data regarding chemotherapy adjuvant treatment. In spite of the lack of an extensive review about the results of this kind of treatment by itself or as part of a multimodal approach, it seems that among the several chemotherapy agents experienced, none proved to influence significantly ATC prognosis. Neither doxorubicin (the most commonly used) nor other drugs, such as cisplatin, bleomycin, fluorouracil or cyclophosphamide, showed any real efficacy in controlling the disease.
Conclusion The most recent development in this field seems to be represented by the possibility offered by PPARg agonists; even more promising might be the use of adenovirus-mediated *p53* tumour suppressor gene therapy or BMP-7. All these new therapies need further confirmation coming from ongoing clinical trials such as those involving the use of vascular and growth factor-targeted agents.

Keywords Anaplastic carcinoma · Undifferentiated · Thyroidectomy · Chemotherapy · Radiotherapy

P. Miccoli · G. Materazzi (✉) · E. Panicucci · G. Frustaci · P. Berti
Department of Surgery, University of Pisa,
Pisa, Italy
e-mail: gmaterazzi@yahoo.com

A. Antonelli
Department of Internal Medicine, University of Pisa,
Pisa, Italy

Introduction

Epidemiology

Malignant tumours of the thyroid are generally classified as either well-differentiated thyroid carcinoma (WDTC), which is composed of papillary and follicular carcinoma, or undifferentiated/anaplastic thyroid carcinoma (ATC). ATC is not only the most lethal disease in the field of endocrine surgery but also one of the most aggressive tumours characterized by an almost invariable fatal outcome, which only very rarely exceeds a 1-year course [1]. Moreover, recently, there has been a growing evidence for the existence of an intermediate class of malignant tumours between WDTC and ATC, the so-called poorly differentiated thyroid carcinoma. This class of malignancies may represent an intermediate entity in the progression of WDTC to ATC [2–5], and it sometimes shows clinical behaviour intermediate between WDTC and ATC [6, 7].

ATC characteristically manifests suddenly as a rapidly growing thyroid mass and mostly arising from a benign thyroid disease or a pre-existing differentiated thyroid carcinoma [8]. Fortunately, it accounts for only 1 to 2% of all thyroid tumours but 14–39% of thyroid carcinoma deaths [9, 10]. It usually follows a rapidly fatal course with

most patients dying a few months after their diagnosis by uncontrolled neck disease. Median survival is 4 to 12 months from time of diagnosis [11, 12]. Long-term survivors are very rare, and when long survival rates are reported, histopathological diagnosis may be questionable. However, in a recent review by the Surveillance Epidemiology and End Results registry database, it has been assumed that since the 1970s, ATC misdiagnoses became very rare [3, 13].

Most of the patients (>50%) present at diagnosis with metastatic disease in the regional lymph nodes or systemically. Although ATC accounts for a small part of thyroid cancers, it is responsible for more than 50% of the 1,200 deaths per year attributed to thyroid cancer [14]. The incidence of this rare tumour has been decreasing over the past years, whereas that of WDTC is increasing. The main reason may be that many tumours previously classified as ATC have now been recognized as lymphomas or poorly differentiated medullary carcinomas by means of immunochemistry [15].

Clinical presentation

The mean age of the patients at presentation is 55 to 65 years with the prevalence of women [16, 17]. The commonest presentation is a rapidly enlarging mass in the neck, with a mean size of 8 cm ranging from 3 to 20 cm, and symptoms of compression such as dyspnea, dysphagia, hoarseness, stridor and neck pain [16, 17]. Patients present with laryngeal nerve palsy in 30% of cases, whereas surrounding structures (muscle, larynx, esophagus, trachea) may be involved in up to 70% of cases [11, 18]. About 50% of patients are metastatic at presentation, whereas another 25% develop new metastasis during the rapid course of the disease. Common sites of metastasis are lung (80%), bone (10%) and brain (10%) [16, 17].

Surgical treatment

Small ATC tumours that are incidentally discovered have been reported to have a more favourable prognosis, and those that are confined to the neck also show a better prognosis compared to tumours with distant metastases [19, 20]. Surgical approach may be generally inappropriate because ATC presents as a huge cancerous mass invading adjacent structures with distant metastases at time of diagnosis. Some experts advocate aggressive multimodal treatment for selected patients with malignancies at an early stage, but it is unclear whether such approach significantly improves survival [21, 26].

The role of surgery in ATC remains controversial. Most studies report that neither extent of resection nor completeness in the operative field has a significant effect on survival [27], but some studies suggest that in a small number of patients with localized disease, complete resection of the tumour can improve survival [13, 24, 25, 28, 29]. The recently published consensus on the surgical treatment of ATC recommends complete surgical resection whenever possible in selected patients [30]. Nevertheless, attempt to complete resection may be justified only if postoperative morbidity rate remains low. Bilateral vocal cords palsy, major bleeding and esophageal fistula are dramatic and life-threatening complications. They can compromise survival by themselves or, more frequently, delay further adjuvant therapy. For the same reasons, resection of vital structures like larynx or esophagus should be avoided [30].

The second role played by surgery is palliation. Partial resection of the tumour followed by radiotherapy and chemotherapy may delay or avoid airway obstruction and prevent death from asphyxiation, but it is clear that this may improve survival only for a few months. In some cases, tracheostomy can be performed at surgery if airway obstruction is present due to bilateral laryngeal nerve palsy or compression by the unresectable neoplastic mass. Nevertheless, some authors noted that patients undergoing prophylactic tracheostomy had lower survival rates compared with patients who did not receive tracheostomy [26, 31].

Multimodality treatment

The medical treatment of patients diagnosed with ATC is not standardized. Medical treatment is almost always used in combination with surgery to achieve the best control of ATC.

The aim of surgery is to obtain macroscopic complete resection before chemotherapy because this has been shown to improve the course of the disease [23]. In this recent study, 26 out of 33 patients were operated, but only 8 out of 26 had a complete resection, whereas the rest underwent palliative resections. Patients were treated with total thyroidectomy (TT) followed by adjuvant radiotherapy (RT; 45–75 Gy) and doxorubicin chemotherapy (CT) too. Median survival for these two groups was 43 vs 3 months, respectively [23].

Similarly, in another study [32], patients treated with TT followed by RT and CT survived longer than those who had a residual disease postoperatively (median survival 8 vs 2 months).

In most of the studies, surgery is the first-line treatment in resectable cases [23, 33, 34], followed by other treatments; however, other studies propose RT/CT before surgery, which may enhance operability [35, 36]. This method might convert inoperable patients to operable; furthermore, the early treatment with CT could also prevent

or delay the development of distant disease. Potential disadvantages of this approach include a delay in securing an airway and in TT because of the side effects of RT/CT. This method results in more patients achieving local control after TT, with death from local disease in only 24% of cases and some patients surviving beyond 2 years [35].

However, the lack of controlled evidence does not permit us to clarify whether this method confers a significant clinical benefit.

Radiotherapy

Simpson [37] first reported treatment of ATC with a small number of large radiation fractions (350–800 cGy). This protocol failed to eradicate local disease and prolong survival.

Hyperfractionated local radiotherapy seems to be more effective in local control than conventional treatment even if severe side effects may be present. In 14 patients treated with hyperfractionation RT (100 cGy, four times daily), a complete tumour regression was obtained in 43% and partial regression in 50% [38]. However, three treatment-related deaths were observed.

Among 51 patients who received external beam radiotherapy and surgery [39], patients with distant metastases but locally free of disease had a median survival of 7.5 months compared with 1.6 months for those with residual local disease.

Among 17 patients treated with high-dose accelerated radiotherapy (60.8 Gy in 1.9 Gy twice daily fractions), a 59% response rate was reported including 3 complete responders; at the time of death, 76% maintained local control [40].

In 19 patients with locally advanced ATC [41, 42], an 84% complete response was reported to hyperfractionated RT (57.6 Gy in 1.6 Gy, twice daily fractions, 3 days/week) combined with weekly concomitant doxorubicin (10 mg/m^2); the median survival was 12 months; 68% maintained local control at the time of death.

Doses reported in the literature for ATC (conventional RT and altered fractionation RT) vary considerably. There is, however, some evidence that doses above 45–50 Gy [22, 40] should be considered a minimum if the intent is radical.

Chemotherapy

The most used agent in ATC is doxorubicin, either alone or in combination with bleomycin, cyclophosphamide, 5-fluorouracil, cisplatin, mitoxantrone or paclitaxel. Myelosuppresion and enhanced cutaneous and mucosal reactions are all associated with the administration of doxorubicin.

In vitro chemosensitivity testing has been proposed to avoid ineffective chemotherapy [43]. Doxorubicin has been used in monotherapy, but the results have been disappointing [44, 45]. However, the results of combination chemotherapy with doxorubicin (60 mg/m^2) and cisplatin (40 mg/m^2) were encouraging, and 6 out of 18 patients had a response [45]. This study showed that the response achieved with a combination of drugs is superior to that of single-agent chemotherapy.

In a Japanese study [46], 15 patients with ATC received cisplatin (40 mg/m^2), doxorubicin (60 mg/m^2), etoposide (100 mg/m^2, 3/4, 3 days) and peplomycin (5 mg); 11 died of disease within 7 months after treatment, and 4 survived from 3 to 11 months.

Eighty-nine patients [47] with ATC received vinblastine, cisplatin, doxorubicin and mitoxantrone as primary treatment preoperatively, and 15% died before surgery. Of the patients who completed the treatment, only 9% survived longer than 1 year.

High-dose CT and bone marrow transplant have also been reported [32]. Nine patients were treated with bleomycin, cyclophosphamide and 5-fluorouracil concomitantly with RT (30–40 Gy). Results were disappointing, with most benefiting from only transient remission and a median survival of 3 months. Twenty patients with ATC were treated with combined doxorubicin/cisplatin, or mitoxantrone alone, with RT (17.5 Gy in seven fractions); only three patients survived for >20 months [48]. Nineteen patients with persistent local or metastatic ATC received infusional paclitaxel (120–225 mg/m^2); a response rate of 57% including one complete response were reported [49].

Our single-institution experience with ATC dates since the 1990s, but it is important to stress the fact that during the recent years, our policy of ATC treatment somewhat changed. ATC was obviously present in our series since the 1990s, but data reported in this review are regarding patients treated since 2001 and not before; in fact, from that point on, all the patients affected by ATC were approached with the same operative strategy, aiming to remove all or at least the most possible neoplastic tissue in the thyroid bed, to give patients the possibility to receive radiotherapy and chemotherapy postoperatively.

Between July 2001 and May 2006, we treated 2,254 patients with primary thyroid carcinoma at the Department of General Surgery, University of Pisa. Of these patients, 17 (0.7%) had ATC diagnosed by means of fine needle aspiration biopsy, open biopsy or surgery and then confirmed at final histology. Malignancies occurring in the same period and defined at final histology as poorly differentiated, less well differentiated, follicular carcinomas with insular components, primordial cell tumours and all comprised in trabecular, solid and insular variants were excluded from this series, aiming to analyse exclusively the outcome of patients affected by "true" ATC.

There was no standardized protocol in selecting patients for postoperative chemotherapy (various combinations of doxorubicin, cisplatin and vinblastine) or radiotherapy (a

dose of ≥45 Gy in 70% and a dose of <0.45 Gy in 30% of the patients receiving the treatment).

Complete resection was defined as leaving no gross or microscopic disease behind after surgery. Incomplete resection was defined as leaving unresectable neoplastic tissue macroscopically evident in the thyroid bed.

Survival was calculated from the start of treatment until the date of death. Survival curves were estimated by the method of Kaplan and Meier and compared for statistical significance by the log-rank test. A P value of less than 0.05 was considered statistically significant.

The clinical characteristics of the 17 patients with ATC are shown in Table 1. There were 4 men and 13 women with a mean age at presentation of 71.4 years (range 42–85). Two patients had a history of WDTC, and they had been previously submitted to partial thyroidectomy. The mean tumour size was 6.7 cm (range 3–10). Synchronous distant metastases at diagnosis were found in 11 (64.7%) patients.

Surgery was performed in all patients. Complete resection of the neoplastic mass was achieved in ten (58.8%) patients, whereas in seven (42.2%), an incomplete resection was performed due to the local tumour extension to vascular or vital structures. Only two patients received preoperative chemotherapy and radiotherapy.

Multimodality treatment (complete resection of the tumour followed by radiotherapy and chemotherapy) was achieved in six patients. Radiotherapy alone after surgery was performed in four patients.

Three patients were lost at follow-up. Thirteen died, and one is alive with a survival of 3 months and is undergoing only radiation therapy because chemotherapy was refused. The median overall survival of the 17 patients was 5.7 (2–24) months and is shown in Fig. 1. The longest survival registered in our series was 24 months, and this is probably due to the fact that the neoplasia was small (3 cm in diameter) and completely included in the thyroid gland, so

Table 1 Clinical characteristics of 17 patients with ATC at the time of diagnosis

Clinical characteristics	Number (Percent)
Age	
40–59	2 (11.7%)
60–79	10 (58.8%)
80–90	5 (29.5%)
Sex	
Male	4 (23.5%)
Female	13 (76.5%)
Tumour size (cm)	
<5	14 (82.3%)
≥5	3 (17.7%)
Distant metastasis	
Absent	5 (29.5%)
Present	12 (70.5%)

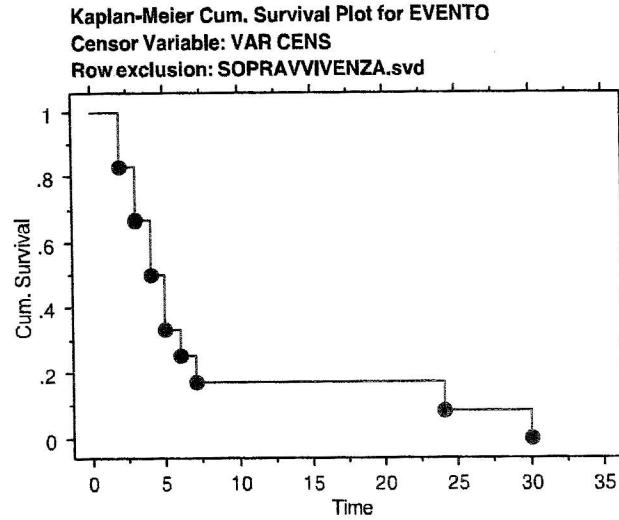

Fig. 1 Overall survival curve in the 17 patients with ATC. Median survival is 5.7 months

to achieve, at the time of operation, complete resection of the tumour.

No association was found between longer survival and maximum diameter of neoplasia, chemotherapy–radiation therapy, distant metastasis and age (Figs. 2 and 3).

Univariate analysis showed that extent of surgery was the most important and independent factor influencing time of survival in ATC, but a statistically significant difference between the two groups (complete resection and incomplete resection) was not found (Fig. 4).

Future directions

ATC remains one of the deadliest of human malignancies. Novel treatment strategies are necessary if we are to make any progress in treating ATC.

Peroxisome proliferator-activated receptor-gamma (PPARg) is a member of a superfamily of nuclear hormone receptors [50]. Activation of PPARg isoforms elicits both antineoplastic [50] and anti-inflammatory effects [51] in several types of mammalian cells. Recently, it has been shown that ligands for PPARg induce apoptosis and exert antiproliferative effects on human papillary carcinoma cells [52], prevent distant metastasis of BHP18-21 tumours in nude mice in vivo [52] and induce redifferentiation in thyroid cancer cell lines [53–56]. The authors concluded that PPARg agonists may therefore be effective therapeutic agents for the treatment of patients with thyroid cancer that fails to respond to traditional treatments [53–56]. Moreover, the expressions of the PPARg gene and protein were examined in five human anaplastic cancer cell lines [57]. The five cell lines showed a higher level of the PPARg gene and protein expression than papillary thyroid cancer. PPARg ligands inhibited cell proliferation by inducing apoptosis.

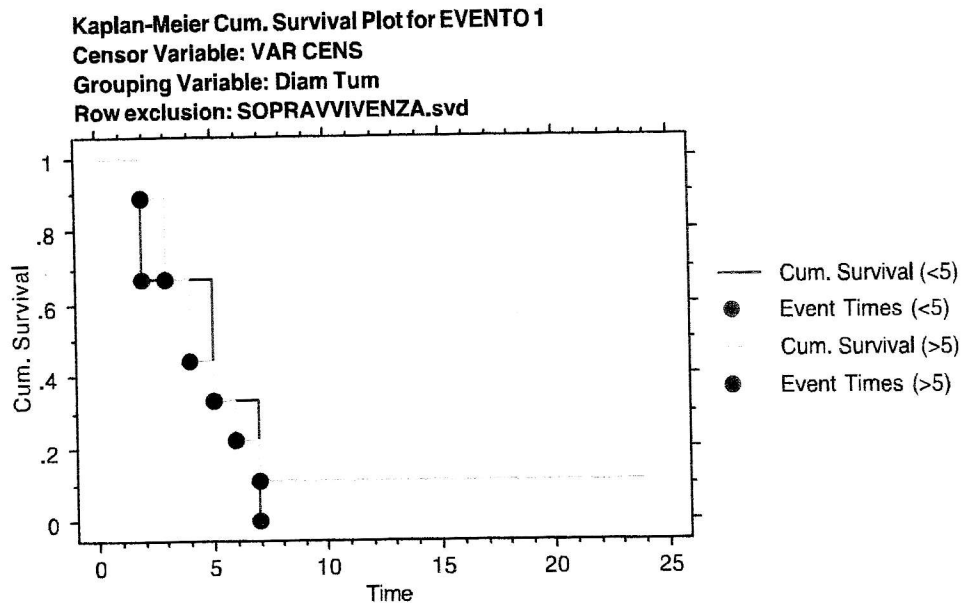

Fig. 2 Survival curves of patients affected by ATC with a tumour smaller than 5 cm in diameter and those with a tumor of 5 cm in diameter or larger (P=NS)

PPARg ligands also downregulated the invasive potential of five cell lines [57]. These results have been confirmed by other studies [55, 58]. More recently, it has been shown that troglitazone treatment overcomes the resistance to doxorubicin in the doxorubicin-resistant K562 human leukemia cells by downregulating glyoxalase 1 expression [59]. Moreover, it has been demonstrated that PPARg ligands may enhance the etoposide-induced apoptosis by modulating the topoisomerase-II alpha expression through binding to direct-repeat-1-like element in several leukemia cell lines [60]. However, until now, to our knowledge, no study has evaluated the possible antiproliferative effect of PPARg agonists in "primary cultured cells from human ATC" (ANA) nor compared it to the effects of antiblastics.

Promising future directives include tumour suppressor gene therapy, induction of cell cycle arrest and selective inhibition of certain proteins. It was shown that adenovirus-mediated *p53* tumour suppressor gene therapy increased the chemosensitivity of ATC to doxorubicin both in vitro [61] and in vivo [62]. Studies using bone morphogenetic protein (BMP-7) and bovine seminal ribonuclease have shown efficacy in treating ATC in vitro and in vivo [63, 64].

Furthermore, several ongoing clinical trials are using vascular and growth factor-targeted therapies or combretastatin A4 phosphate.

These novel treatment strategies for ATC hold promise to make progress in understanding the pathogenesis and treating ATC.

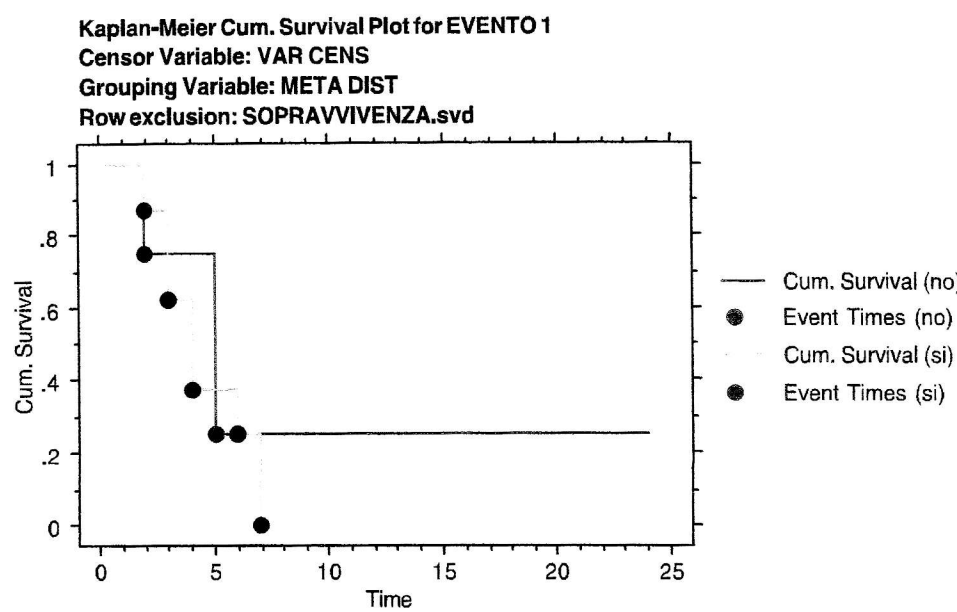

Fig. 3 Outcome of 17 patients with ATC presenting with distant metastases or without distant metastases (P=NS)

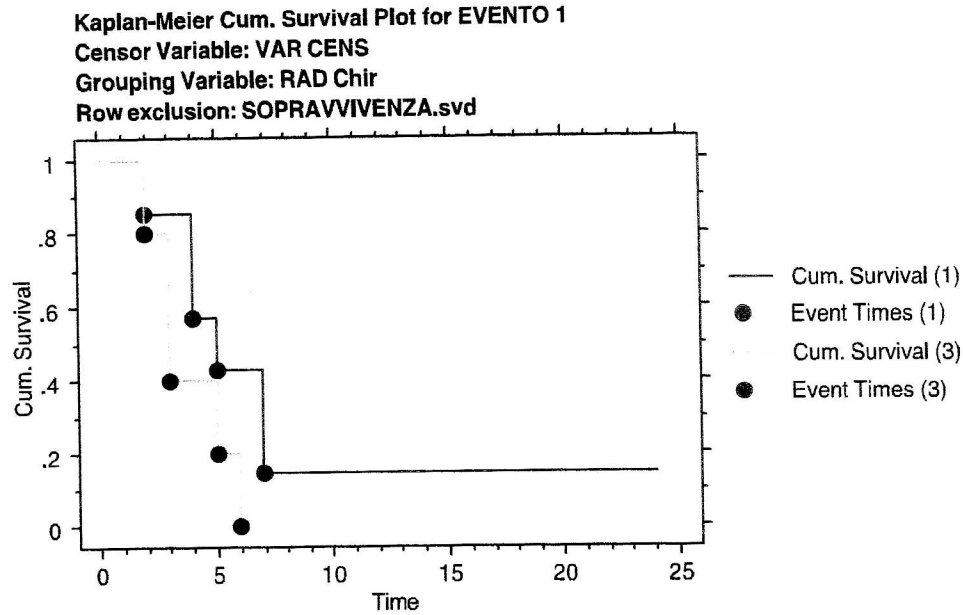

Fig. 4 Survival curves of the 17 patients with ATC treated by complete resection or incomplete resection (P=NS)

Conclusions

The impact of surgical resection in association with external beam radiation on ATC outcome has been extensively investigated also in studies based on multicentric database [22], and there is a general agreement on the significance of a complete resection of the tumour.

It has been difficult up to now to collect data regarding chemotherapy adjuvant treatment. In spite of the lack of an extensive review about the results of this kind of treatment by itself or as part of a multimodal approach, it seems that among the several chemotherapy agents experienced, none proved to influence significantly ATC prognosis. Neither doxorubicin (the most commonly used) nor other drugs, such as cisplatin, bleomycin, fluorouracil or cyclophosphamide, showed any real efficacy in controlling the disease.

The most recent development in this field seems to be represented by the possibility offered by PPARg agonists; even more promising might be the use of adenovirus-mediated *p53* tumour suppressor gene therapy or BMP-7. All these new therapies need further confirmation coming from ongoing clinical trials such as those involving the use of vascular and growth factor-targeted agents.

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