Update and perspectives on non-surgical treatment of salivary gland malignancies

Attualità e prospettive nel trattamento non chirurgico dei carcinomi delle ghiandole salivari

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Key words
Salivary gland carcinoma • Radiotherapy • Chemotherapy
• Biological therapy

Summary
Surgery is the treatment of choice for major and minor salivary gland malignancies. Herein, the role of radiation and medical treatment in the multidisciplinary management of salivary gland tumours is discussed. Neutron irradiation and hyperfractionated external beam mega voltage irradiation improve local control. Combination of three dimensional conformal radiotherapy and intensive-modulated radiation therapy provide better local tumour delineation, better field design to encompass the tumour allowing dose escalation to target while sparing the surrounding normal tissue. Cisplatin-based chemotherapy provides a response rate ≥ 45%, in a palliative setting. Concomitant chemo-radiotherapy could improve local control. Recent studies evaluated the expression of molecular targets in salivary gland carcinomas (c-kit = 53-90%, EGFR = 25-85%, c-erb-B2 = 11-57%, p53 = 11-67%, H ras = 18%); these targets are very important since new targeted drugs are now available. Anti-androgen therapy might have a role in the management of patients with ductal carcinoma. These new targeted drugs could be integrated with chemotherapy and radiotherapy in the treatment of locally advanced/metastatic salivary gland malignancies.

Riassunto
Nei carcinomi delle ghiandole salivari la chirurgia rimane l’opzione principale. In questo lavoro si analizzano le potenzialità e le prospettive delle terapie radianti e mediche nonché le loro possibili integrazioni. La radioterapia con neutroni e quella iperfrazionata sono in grado di migliorare il controllo locale. Le nuove tecniche di radioterapia (3D-CRT e IMRT) permettono di erogare alte dosi con risparmio di tossicità per i tessuti sani. La chemioterapia palliativa con combinazioni comprendenti cisplatino determina risposte oggettive nel 35-45% dei casi. Un uso concomitante alla radioterapia potrebbe aumentare il controllo locale. In questi carcinomi sono diffusamente presenti alcuni targets (c-kit = 53-90%, EGFR = 25-85%, c-erb-B2 = 11-57%, p53 = 11-67%, H ras = 18%) verso i quali disponiamo di nuovi farmaci. Nel carcinoma duttale si può ipotizzare l’utilizzo di una terapia anti-androgenica. Infine si prospettano le possibili integrazioni di questa terapia biologica con chemioterapia e radioterapia.

Introduction
Surgery is the treatment of choice for major and minor salivary gland malignancies; the ability of the well-trained head and neck surgeon to excise salivary gland malignancies, in any site, has probably not changed significantly over the last 20 years, although the availability of cutaneous, subcutaneous, osteocutaneous, and innervated muscle flaps has made reconstruction much easier, in those patients requiring very radical operations. Radiation therapy is indicated post-operatively for patients with high-grade neoplasms, involving surgical margins, local soft tissue, osseous, perineural, or lymphatic metastases. In unresectable cases, radiation therapy is the treatment of choice. Chemotherapy has a palliative role. The overall incidence of distant metastases is about 25%. The lungs are favoured sites for metastases, although bone, liver, central nervous system (CNS) and other organs may become involved. Locoregional recurrences, in selected cases, may be managed with further surgery or radiotherapy but long-term remissions are rare (<10%). However, most patients with recurrent or metastatic salivary gland cancer can be treated with chemotherapy with a palliative endpoint. Herein, the role of radiation and medical treatment is
discussed in the multidisciplinary management of salivary gland tumours. This integration is very important since, despite advances in loco-regional treatment, the 5-year survival of patients with high-grade histological pattern (adenoid cystic carcinoma, malignant mixed tumour, high grade adenocarcinoma, undifferentiated carcinoma, high grade mucoepidermoid carcinoma) or locally advanced disease is approximately 50%.

Radiotherapy

Photon or electron beam post-operative radiation therapy can lead to 34-74% improvement in local control 7. A review of the literature on inoperable tumours showed loco-regional control rates of 4-54% with low-LET (Linear Energy Transfer) (photons, electrons) 3-4. The most effective non-surgical treatment for inoperable salivary gland neoplasms, especially adenoid cystic carcinoma, is neutron irradiation 5-6. A prospective clinical trial showed that neutron irradiation is superior to high-energy X-rays in the treatment of macroscopic salivary gland lesions (local control 64% vs 31%; 2-year overall survival 68% vs 25%) 5. However, it is well known that such treatment is available at only a few centres. Bulky salivary tumours can also be successfully palliated by the combined use of localized hyperthermia and external beam radiotherapy or brachytherapy 7-8. The permanent implantation of iodine-125 sources or the use of after-loading low- or high-dose rate removable iridium-192 implants may produce effective palliation 8. The use of hyperfractionated external beam mega voltage irradiation consisting of multiple daily 160 cGy fractions for a total tumour dose of 65 to 70 Gy in 5-6 weeks has also recently been proposed, with excellent local control rates 9.

Three-dimensional (3D) conformal radiation therapy allows radiation therapy fields to conform to the shape of the target area; it achieves isodose distributions that maximally cover the target while minimally irradiating normal tissue, and uses beams-eye treatment planning to avoid underdosage of any area of the target volume. Therefore, we have a combination of better local tumour delineation, better field design to encompass the tumour, and a technique that allows dose escalation to target while sparing the surrounding normal tissue.

Palliative chemotherapy

In combined chemotherapy for head and neck cancer, salivary carcinoma shows a poor clinical outcome, and it has been suggested that the sensitivity and/or mechanism of resistance to anti-cancer drugs are different between these two conditions. P-glycoprotein expression is associated with multidrug resistance and in salivary gland malignancies is an inherent phenotype caused both by high levels of P-glycoprotein induction and activated production during treatment, while that in squamous cell carcinoma is an acquired phenotype chiefly caused by induction of P-glycoprotein 11. With regard to advanced loco-regional or metastatic salivary gland carcinomas, only small series of patients, treated uniformly with single agent chemotherapy, have been reported. Cisplatin is considered the most active drug and is the “backbone” of polychemotherapeutic regimens; in 1981-1982 cisplatin has been reported to provide a response rate up to 70% in case series with fewer than 15 cases each 12-13.

In 1991, Licitra et al. showed that cisplatin provided an overall response rate of 16% in 25 consecutive patients; in 19 patients, not previously treated with chemotherapy, the response rate was 21%. Response duration was between 5 and 9 months and median overall survival time was 14 months 14. As single agents, epirubicin and mitoxantrone are reported to provide a 10% response rate (Table I) 15-17. Tannock and Sutherland reported objective responses in 4 out of 12 patients following fluorouracil administration but the estimates of tumour response are not clearly described 18. Cyclophosphamide + vincristine + 5-fluorouracil combination has not been proven more effective than single agent chemotherapy 19; the addition of cyclophosphamide appears to enhance the efficacy of adriamycin alone 20 (Table I).

We have recently shown a moderate activity of vinorelbine 21-22. A series of 20 patients (13 male, 7 female, median age 61 years, range 27-64) with recurrent adenocarcinoma-like tumours of major (10 patients) and minor (10 patients) salivary gland origin (13 adenoid cystic carcinoma, 5 adenocarcinoma, 1 malignant mixed tumour, 1 undifferentiated carcinoma) were treated with vinorelbine at the dose of 30 mg/m² iv weekly. Of these patients, 16 had previously been treated with surgery plus radiation, 3 with surgery plus radiotherapy plus novantrone and 1 with radiotherapy alone. Nine patients had local recurrence, 2 local relapse plus metastases and 9 metastases alone. The site of metastases were: lung (7 cases), bone (1 case), lung+bone (2 cases) and lung+bone+lymph node+skin (1 case). Overall, 174 courses were given (median 9, range 6-19). Responses were: partial response (PR) in 4 patients (20%) with a median duration of 6 months (3-9), 9 no change (NC) (45%) with a median duration of 3.5 months and 7 progressive disease (PD) (35%). The median survival duration was 10 months for PR/NC.
patients, 4 months for non-responders. Median overall survival was 7 months. The treatment was well tolerated and toxicity was manageable.

Cisplatin and vinorelbine have been shown to have a synergistic activity both in vitro and in vivo. Between April 1993 and April 1997, 36 patients in a phase II randomized trial received either cisplatin 80 mg/m², on day 1, plus vinorelbine 25 mg/m², on days 1 and 8 (every 3 weeks) for a minimum of 3 cycles (16 patients; arm A), or vinorelbine, 30 mg/m²/week, for a minimum of 9 weeks (20 patients; arm B). This study population comprised 23 males and 13 females, median age 59 years (range 20-74) and a median Eastern Cooperative Oncology Group (ECOG) performance status of 1 (range 0-2). Of these patients, 4 had been previously treated with surgery or radiotherapy, 27 had been treated with surgery plus radiotherapy, and 5 had been treated with surgery plus radiotherapy plus mitoxantrone. As far as concerns tumour type, 18 patients had major salivary gland tumours, and 18 had a minor salivary gland tumour; 9 patients had adenocarcinoma, 22 had adenoid cystic carcinoma, 1 had a malignant mixed carcinoma, 3 had undifferentiated carcinoma and 1 had a mucoepidermoid carcinoma. The site of recurrence was local (16 patients), local plus metastases in 5 patients and metastases only in 15 patients. These characteristics were well balanced between the two arms. In arms A and B, a complete response (CR) was observed in 3 patients (19%) and no patient, respectively; a PR was observed in 4 (25%) and 4 patients (20%), respectively; no change was observed in 6 (37.5%) and 9 patients (45%), respectively; and progressive disease was observed in 3 (19%) and 7 patients (35%), respectively. The median duration of the CR was 15+ months (range 6-27+) and for PR the median duration was 7.5 months (range, 3-11+) and 6 months (range 3-9) in arms A and B, respectively. The median overall survival durations for arms A and B were 11 months (range 3-29+) and 8.5 months (range 2.5-16), respectively; a significant difference in >12 months survival was noted in arm A (p<0.05).

At 2 years, 19% of patients treated with the combination were alive whereas in the vinorelbine alone arm, no patient was still alive at 2 years. The survival curve analysis showed a trend (p=0.058) toward better survival in the cisplatin plus vinorelbine arm. The median survival for patients achieving CR was 19+ months; the median survival of patients achieving a PR was 12.5 months for arm A and 9 months for arm B. Patients with an ECOG performance status of 0-1 had a median survival of 10.5 months, which was statistically better (p<0.05) than patients with an ECOG performance status of 2 (median survival time, 4.5 months).

Grade 2-3 nausea and emesis was statistically higher (p<0.001) in arm A; there was no significant difference with regard to other side-effects between the two treatment arms.

Chemotherapy regimens including cisplatin, adriamycin, and cyclophosphamide have shown significant efficacy with overall response rates of 27-50%. Chemotherapy regimens combining cisplatin, adriamycin or epirubicin+ 5-fluorouracil achieved over-

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Table I. Results of chemotherapy in salivary gland tumours.

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Complete + Partial remissions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>16%</td>
<td>14</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>10%</td>
<td>15</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>5-12%</td>
<td>16,17</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>20%</td>
<td>22</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>18%</td>
<td>33</td>
</tr>
<tr>
<td>CYC+S-FU+VCR</td>
<td>25%</td>
<td>19</td>
</tr>
<tr>
<td>Adriamycin+CYC</td>
<td>38%</td>
<td>20</td>
</tr>
<tr>
<td>Cisplatin+S-FU</td>
<td>0%</td>
<td>32</td>
</tr>
<tr>
<td>Cisplatin+Adriamycin+CYC</td>
<td>27-46-50%</td>
<td>24-26</td>
</tr>
<tr>
<td>Cisplatin+Adriamycin+S-FU</td>
<td>37%</td>
<td>27</td>
</tr>
<tr>
<td>Cisplatin+Epirubicin+S-FU</td>
<td>44%</td>
<td>28</td>
</tr>
<tr>
<td>Cisplatin+Adriamycin+CYC+S-FU</td>
<td>50%</td>
<td>31</td>
</tr>
<tr>
<td>Cisplatin+Adriamycin+Bleomycin</td>
<td>33%</td>
<td>30</td>
</tr>
<tr>
<td>Cisplatin+Vinorelbine</td>
<td>44%</td>
<td>23</td>
</tr>
<tr>
<td>Cisplatin+VP-16+Bleomycin</td>
<td>45%</td>
<td>29</td>
</tr>
<tr>
<td>Carboplatin+Paclitaxel</td>
<td>14%*</td>
<td>33</td>
</tr>
</tbody>
</table>

* >50% Cisplatin pre-treated; CYC: cyclophosphamide; VCR: vincristine
all response rates between 37 and 47%; comparable results were obtained with the combinations of cisplatin, bleomycin and Adriamycin or VP-16 (Overall Response Rate – ORR = 33-45%) 29 30. The 16 evaluable patients with recurrent or non-resectable salivary gland malignancies were treated with a combination of fluorouracil, Adriamycin, cyclophosphamide, and cisplatin. A total of 111 courses of chemotherapy were given, yielding one complete (6%) and seven partial responses (44%) 31. The median duration of the objective response was 32 weeks and the median overall survival was 72 weeks. Haematologic toxicity was significant and 7 patients (44%) developed neutropenic fever; 3 patients (18%) developed an increase in serum creatinine >1.5 mg/dl during the course of treatment. Response duration, or overall patient survival, of this intensive regimen was comparable to that in other published therapeutic trials concerning this disease. The combination of cisplatin and fluorouracil, the most commonly used regimen in squamous cell head and neck cancer, yielded disappointing results in terms of objective response rates 32. Taxol is an efficacious drug, in salivary gland carcinomas, especially in mucoepidermoid carcinoma and adenocarcinoma 33, given the promising response rates obtained in other diseases, paclitaxel and carboplatin seem to be a logical combination to be used in advanced salivary gland tumours. A total of 14 patients (10 male, 4 female; median age 55 years, range 20-70) with recurrent carcinomas of major (9 patients) and minor (5 patients) salivary gland origin (histology: 1 adenocarcinoma, 10 adenoid cystic carcinoma, 2 undifferentiated carcinoma, 1 mucoepidermoid carcinoma) were treated by us with carboplatin area under curve (AUC) 5.5 and paclitaxel 175 mg/m² (3-hour infusion) on day 1 (interval=3 weeks) 34. All patients had previously been submitted to surgery and radiotherapy and 8 treated with a cisplatinum combination. One had a local lesion, 7 loco-regional recurrence and metastases and 6 had only metastases. Overall, 65 courses were given (median 5; range 2-6). The responses were: PR in 2 patients (14%) lasting 5 and 12 months, 7 NC (50%) with a median duration of 8.5 months (range 5-12), and 5 PD (36%). The median survival time was 13.5 months for PR/NC patients, 6 months for non responders; median overall survival was 12.5 months (3-17+). The treatment was well tolerated and toxicity was manageable. Our study suggests that this combination has a moderate efficacy; the poor results were probably due to the high percentage of adenoid cystic carcinoma with distant metastases and to the large number of patients previously treated with chemotherapy for recurrence. Second-line chemotherapy was ineffective. In murine salivary gland carcinoma, docetaxel has proven to be effective; no data have been reported in humans 35. In metastatic/recurrent disease, the following conclusions can be drawn 36:

- cisplatin, anthracyclines, paclitaxel and vinorelbine are the most effective agents;
- chemotherapy regimens combining cisplatin, anthracycline or vinorelbine are well tolerated with objective responses that appear to be superior to those observed after mono-chemotherapy; our randomized trial has confirmed this hypothesis. Triple therapy is probably not more effective than double combined therapy. Combination regimens are more toxic than single-agent chemotherapy;
- responses are more frequent in chemotherapy-naive patients and in cases with loco-regional disease; adenoid cystic carcinoma seems less chemosensitive than adenocarcinoma; mucoepidermoid carcinoma responds to the drugs effective in squamous cell head and neck carcinoma even if the response rate is lower;
- median CR duration is 7-18 months;
- patients achieving stable disease can achieve a transient subjective improvement;
- despite the absence of an apparent survival benefit, palliation of pain and local disease is frequently pronounced;
- the optimal drug combination remains to be defined;
- patients with bulky disease, impaired performance status, or marginal nutritional status might be best treated by supportive care.

**Neo-adjuvant chemotherapy**

Response to neo-adjuvant chemotherapy in squamous cell carcinoma of the head and neck predicts a better prognosis and permits a conservative treatment, but it has been shown to have no impact on survival 37. Nine patients were treated with cisplatin, doxorubicin, and 5-fluorouracil combination chemotherapy; one complete remission (11%) and 2 partial remissions (22%) were observed 27. In recurrent/metastatic disease, this regimen led to the same response rate. There may also be a role for neo-adjuvant chemotherapy in selected patients who have inoperable primary tumours, although more effective chemotherapy regimens must be used. The responsiveness to a neo-adjuvant scheme could be important to plan the subsequent chemotherapy concomitant with radiotherapy of in an adjuvant setting.
Six patients with T3-4 N0-1 inoperable lesions were treated with radiotherapy alone are very disappointing. Undifferentiated carcinomas of the parotid gland 39. Concomitant radio-chemotherapy in locally advanced head and neck cancer, a recent meta-analysis has shown a significant benefit of chemotherapy concomitant with conventional radiotherapy versus radiotherapy alone 37. Two recent and well-conducted randomised trials 40,41 have investigated concurrent cisplatin and conventional radiotherapy, in an adjuvant setting, versus conventional post-operative radiotherapy in patients with high risk of recurrence. Clinical outcomes were better in the combination arm. We have recently reported the feasibility of adjuvant cisplatin+ VP-16 after chemo-radiation of undifferentiated carcinoma of the parotid gland 39.

Concomitant chemo-radiation therapy

In locally advanced head and neck cancer, a recent meta-analysis has shown a significant benefit of chemotherapy concomitant with conventional radiotherapy versus radiotherapy alone 37. Two recent and well-conducted randomised trials 40,41 have investigated concurrent cisplatin and conventional radiotherapy, in an adjuvant setting, versus conventional post-operative radiotherapy in patients with high risk of recurrence. Clinical outcomes were better in the combination arm. We have recently reported personal data following concomitant radio-chemotherapy in locally advanced undifferentiated carcinomas of the parotid gland 39. Undifferentiated carcinoma is a poor-prognosis lesion. In patients treated with radical surgery and adjuvant post-operative radiotherapy, the 5-year survival is 33%. Results in inoperable T3-4N0-1 lesions, treated with radiotherapy alone are very disappointing. Six patients with T3-4 N0-1 inoperable lesions were treated with conventional radiotherapy (64-70 Gy, 2 Gy per fraction 5 times a week) and concomitant cisplatin (100 mg/m², days 1, 22 and 43). Four weeks after radiotherapy, adjuvant chemotherapy (cisplatin 80 mg/m², day 1 + VP-16 100 mg/m², days 1, 3, 5 at 3-week intervals, for 3 cycles) was given. A median dose of 66 Gy was delivered, and all patients received 3 courses of cisplatin during radiotherapy. Five out of 6 patients received all three chemotherapeutic adjuvant courses. Two months after the end of treatment, 3 CR (50%), 2 PR (33%) and 1 NC (16%) were observed. Median CR and PR duration was 26 and 10 months, respectively. Median overall survival was 18 months. No severe acute or late toxicity was observed. We had only one refusal before the third adjuvant planned course, probably due to the low mucosal toxicity of cisplatin and VP-16 at the adopted dose level. The impact of the whole treatment on survival is difficult to define. Due to the histologic type and the bulky lesions, we could expect a very poor prognosis. It was encouraging to have observed three long-term complete responses, without severe late side-effects. These results indicate that chemotherapy may be another effective way to enhance radiotherapy.

New targets

Recent studies have evaluated the expression of molecular targets in salivary gland carcinomas; these targets are very important since new targeted drugs are now available. In squamous cell head and neck cancer, these drugs have obtained a response rate between 6% and 20% and a disease stabilization of 25% to 40% (Table II). Proteins encoded by tyrosine-kinase receptors, such as c-kit, are widely expressed in salivary gland malignancies (Table III). The c-kit protein, a receptor tyrosine kinase that plays an important role in the development of haematopoietic cells, melanocytes and germ cells, is expressed in mastocytes, gastrointestinal stromal cell tumours, and several other tumours. Gain-of-function mutations in exon 11 and exon 17 have been shown as a mechanism of c-kit activation in some tumours. Although varying in intensity of staining, c-kit expression was identified very often in adenoid cystic carcinoma, lymphoepithelioma-like carcinomas and myoepithelial carcinomas 42-44. By DNA sequencing, genetic alterations of the c-kit juxtamembrane domain (exon 11) and the tyrosine kinase domain (exon 17) were not found in all three types of salivary carcinoma that had c-kit expression. c-kit expression was noted in 90% of adenoid cystic carcinomas; an association between the presence of at least 50% c-Kit positive neoplastic cells and grade 3 or a solid growth pattern was observed; c-kit immunostaining may be a valuable adjunctive tool for differentiating salivary gland adenoid cystic carcinoma from polymorphous low-grade adenocarcinoma which does not express c-kit 45. Imatinib mesylate (Glivec™ is the commercial name) was identified as a potent protein kinase inhibitor of c-kit, the platelet-derived growth factor, and v-Abl; phase I and II trials in chronic myeloid leukemia proved the validity of this concept. In gastrointestinal stromal tumours, which have a high c-kit expression, this drug has proven highly effective. The role of this drug in ade-
noid cystic carcinoma has not been investigated but it
is extremely important to explore the activity espe-
cially in the more aggressive types.

The Epidermal Growth Factor (EGF) is an important
mediator of cell growth, differentiation, and survival.
Among the peptide growth factors, EGF and tumour
growth factor-alpha (TGF-α) are believed to be the
main endogenous ligands that result in EGFR recep-
tor EGFR-mediated stimulation for tumour growth
and progression, angiogenesis, cell survival, and
metastasis. The frequency of positive EGFR staining
in salivary gland tumours is different (Table III),
probably due to the different methods of evaluation;
as far as concerns salivary carcinomas, EGFR was
reported in 85% of adenoid cystic carcinomas even if
a positivity of 20-30% was more frequently de-
scribed 46-48. A variety of agents have been developed
over the last few years that inhibit the EGFR signal,
such as monoclonal antibody (Cetuximab) directed
against its external ligand-binding domains and syn-
thetic tyrosine-kinase inhibitors that act directly on
the cytoplasmatic domain of EGFR (Iressa, OSI
774). These agents, in vitro and in vivo, are able to
reduce tumour cell growth by inducing apoptosis and
to modulate inhibition of production of angiogenetic
factors. Anti-EGFR agents are currently under inves-
tigation in phase II/III trials combined with standard
chemotherapy and radiotherapy, as radiosensitizers,
in patients with head and neck (Table II), lung, renal,
gastric and prostate cancer.

These agents can improve the efficacy of platinoids,
taxanes and anthracyclines cytotoxic; these groups of
cytostatics are the most effective in salivary gland
malignancy 49 50. Cetuximab (IMC-225), a chimeric
monoclonal antibody that specifically binds to the
EGFR with high affinity, overcomes resistance to
cisplatin in cisplatin-refractory advanced head and
neck squamous cell carcinoma 51.

Protein kinase A inhibitors and VEGFR inhibitors
have a synergistic effect in combination with EGFR
inhibitors 52 53; multitarget therapy seems very inter-
esting.

COX-2 inhibitors enhance antitumoural activity of
EGFR and HER-2/neu inhibitors 54 55. COX-2 in-
hibitors, show promise in combination with radiation
therapy and inhibit angiogenesis 56 57.

The HER2 oncogene is differently expressed in sali-
vary gland malignancies 56 60 (Table III); its overex-
pression correlates with poor prognosis. We have
monoclonal antibodies and tyrosine kinase inhibitors
for the erbB-2 receptor which could be used alone or
in combination for salivary gland malignancies.
The p53 tumour suppressor gene may be involved in salivary gland carcinogenesis, and its oncoprotein expression is an independent indicator of clinical aggressiveness in patients with carcinoma of the parotid gland. The p53 expression is associated with certain histological types (adenocarcinoma, pleomorphic adenoma, salivary duct carcinoma), advanced tumour stage and high-cell proliferative activity. p53 gene replacement therapy (adenovirus-p53) and strategies aimed specifically at enhancing viral replication in cells with defective p53 protein (ONIX-015) have been explored in clinical trials.

H-ras mutations, predominantly at codon 12, were detected in 18% of mucoepidermoid carcinomas; mutations were observed more often in high grade lesions. Ras overexpression correlates with radioresistance; farnesyl transferase inhibitors, are able to enhance tumour radiosensitivity. These drugs can also acquire resistance to either paclitaxel and epothilones.

Vascular Endothelial Growth Factor inhibitors (mono-clonal antibodies and tyrosine kinase inhibitors) combined with radiation show a very favourable interaction in the tumour model system. Salivary duct carcinoma is a high grade aggressive malignancy of the major salivary glands. The microscopic features are remarkably similar to those of mammary ductal carcinoma, suggesting that these tumours may share antigenic or hormonal features. This tumour frequently expresses androgen receptor (90%), EGFR (90%) and TGF-α (67%) suggesting the presence of an androgen receptor-mediated TGF-α/EGFR autocrine pathway in these neoplasms.

The same tumour expresses Prostatic Acid Phosphatase (PAP)(38%) and Prostatic-Specific Antigen (PSA) (18%), indicative of a close immunophenotypic homology between this cancer and prostatic carcinoma. These observations raise the possibility that anti-androgen therapy, possibly with anti-EGFR therapy, might have a role in the management of patients with disseminated disease.

**Perspectives of combined treatments**

Cisplatin-based chemotherapy can enhance radiation therapy, and some new target therapies can obtain the same result. In inoperable lesions, we could integrate radiation therapy with medical treatments; a comparable strategy could be evaluated in the post-operative adjuvant setting. New target drugs, if proven effective in salivary gland malignancies, could be used in the adjuvant setting of high risk patients. Neo-adjuvant medical regimens could be used in locally advanced lesions to obtain a down-staging. Palliative treatments could integrate new target drugs. Phase I and II studies, with these new agents, will be very important.

**References**

NON-SURGICAL TREATMENT OF SALIVARY GLAND MALIGNANCIES


