Three-dimensional conformal postoperative radiotherapy in patients with parotid tumors: 10 Years' experience at the European Institute of Oncology

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Three-dimensional conformal postoperative radiotherapy in patients with parotid tumors: 10 years’ experience at the European Institute of Oncology

Daniela Alterio, Barbara A Jereczek-Fossa, Mara Griseri, Alberto D’Onofrio, Gioacchino Giugliano, Maria R Fiore, Viviana Vitolo, Piero Fossati, Gaia Piperno, Luca S Calabrese, Elena Verri, Fausto G Chiesa, and Roberto Orecchia

1Division of Radiation Oncology, European Institute of Oncology, Milan; 2University of Milan, Milan; 3Division of Experimental Oncology, 4Division of Head and Neck Surgery, and 5Division of Medical Oncology, European Institute of Oncology, Milan, Italy

ABSTRACT

Aims and background. Salivary gland malignancies are rare. The aim of our study was to investigate radiotherapy-related toxicity and clinical outcome in patients treated at our division with postoperative radiotherapy (pRT) for parotid tumors.

Methods and study design. Forty-three consecutive patients (32 with primary parotid tumors, 9 with parotid metastases and 2 with recurrent benign diseases) were retrospectively analyzed.

Results. The median follow-up was 28 months. Twenty and 5 patients had a follow-up longer than 2 and 5 years, respectively. Thirty-seven patients were alive and most of them (78%) were free from disease. The local and distant control rates were higher in patients with primary parotid tumors (94% and 87.5%) than in patients with parotid metastases (87.5% and 75%). Grade 3 radiotherapy-related acute toxicity of skin and mucosa was recorded in 20.9% and 28% of patients, respectively. Two patients (4.7%) had grade 4 skin toxicity. Late toxicity data were available for 33 (77%) patients. None of the patients developed severe (grade 3 and 4) late toxicity of soft tissues, skin or temporomandibular joints.

Conclusions. Postoperative radiotherapy is a feasible treatment that was found to be effective mainly in patients with primary parotid tumors. Toxicity was acceptable but could probably be further reduced using more advanced radiotherapy techniques. Longer follow-up is required to achieve definitive results.

Introduction

Salivary gland malignant tumors account for about 3% of all head and neck cancers and 70% of them arise within the parotid gland. The histological characteristics and biological behavior can be very heterogeneous. Adenocarcinoma, mucoepidermoid carcinoma, squamous cell carcinoma and adenoid cystic carcinoma are the most frequent histological types.

Radical surgery is the main treatment option. Postoperative radiotherapy (pRT) is indicated for patients with adverse pathological risk factors such as high tumor grade, tumor size more than 4 cm, tumor localization within the deep lobe of the parotid, positive surgical margins, lymph node involvement, nerve infiltration, advanced pathological stage, perineural and perivascular invasion, soft tissue extension and recurrent tumor following resection. Adjuvant radiotherapy has been demonstrated to improve locoregional control but its impact on overall survival is still controversial. Because of the rarity and histological and clinical heterogeneity of these tu-
mors, prospective trials designed to evaluate the best treatment options are lacking and retrospective data are therefore required. The aim of this study was to review the data of all patients treated with pRT for parotid tumors at our division, reporting both radiotherapy-related acute and late toxicity and clinical outcome. The impact of surgical procedures and radiotherapy-related variables on normal tissue injury was also analyzed.

**Materials and methods**

We retrospectively analyzed the data of all patients treated at the European Institute of Oncology (Milan, Italy) with pRT for parotid gland tumors from May 1997 to January 2007. Patients with macroscopic residual disease after surgery were excluded from the analysis. Locoregional clinical staging was performed using clinical and radiological examinations (ultrasonography and/or computed tomography and/or magnetic resonance). Distant metastases were detected using mainly total-body computed tomography. Surgical procedure characteristics were recorded in terms of superficial or total parotidectomy, lymph node dissection and facial nerve removal. The choice between different surgical approaches depended on tumor location, clinical stage and histological characteristics. Ipsilateral neck dissection was performed in case of high-grade tumors, clinical or radiological evidence of lymph node metastasis, or when the risk of lymph node involvement was estimated to be higher than 20%. Postoperative radiotherapy was proposed in case of advanced pathological stage (stage III and IV), positive surgical margins, high grade histology, recurrent tumor, facial nerve involvement and presence of lymph node metastasis. Tumor location in the deep parotid lobe and the presence of neural and/or vascular invasion were considered minor risk factors. The ipsilateral neck lymph node areas were irradiated in case of pathological lymph nodes or, as elective treatment, in high-risk patients. For patients with benign parotid tumors, pRT was indicated only in case of recurrent disease. The planned total pRT dose ranged from 60 Gy to 66 Gy for negative and positive microscopic surgical bed margins, respectively, and from 50 Gy to 60-66 Gy for negative and positive lymph nodes without or with extracapsular extension, respectively. Radiotherapy was performed using a linear accelerator of 6 MV-energy. A 3-dimensional conformal technique with unilateral wedge-pair fields was used to irradiate the surgical bed and upper neck lymph nodes. An anterior-posterior field was used to irradiate the ipsilateral middle and lower neck lymph node areas, when indicated. A conventional fractionation schedule (1 daily fraction of 2 Gy for 5 days/week) was used for all patients. The spinal cord was irradiated up to 40-42 Gy. When the tumor was located in the superficial parotid lobe or infiltrated the skin, a water-equivalent bolus was added for all or part of the treatment duration and/or a mixed photon-electron beam (6-16 MeV) technique (about 2/3 and 1/3 of the total dose in photon and electron beams, respectively) was used according to personalized treatment plans. Individualized mask head immobilization, simulation of all therapy phases and fields, orthogonal laser beams (to ensure position reproducibility), computed tomography-based treatment planning, customized shielding; in vivo dosimetry and electronic portal verification were employed. Target volume and organ at risk contouring and dose prescription were performed according to the International Commission on Radiation Units (ICRU) 62 guidelines. Radiotherapy-related acute and late skin, mucosa, soft tissue and temporomandibular joint toxicity was evaluated according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring system.

Follow-up was performed every 3 months for the first 2 years, every 4 months for the subsequent 3 years, and once a year thereafter. Both clinical and radiological examinations were carried out during follow-up.

Clinical outcome was evaluated in terms of disease-free and overall survival. Disease-free survival was considered the interval between the end of pRT and the appearance of local and/or distant recurrence. The association between clinical outcome (local relapse and distant metastasis) and pathological characteristics (tumor grade, pathological stage, lymph node metastasis, positive surgical margins and perineural invasion) was analyzed. The association between toxicity (skin, mucosa and soft tissue) and the total administered dose and surgical technique (total versus superficial parotidectomy) was also evaluated.

**Statistical methods**

Associations between clinical outcome and pathological characteristics were tested by Fisher’s exact test. Tumor grade was considered a binary variable (low and high). Similarly, pathological stage was binarized as follows: low for stage I and II, high for stage III and IV. The overall and disease-free actuarial survival curves were calculated and plotted using the Kaplan-Meier method. For skin, oral mucosa and soft tissues, the log-rank test was used to assess statistical differences in toxicity between subgroups determined by the binary variable related to surgery (total versus superficial parotidectomy) and total dose (dichotomized at its median value). For all statistical tests, the significance level was set at 0.05 (2-sided).

**Results**

Forty-three consecutive patients (23 men and 20 women) were eligible. Median age was 61 years (range, 24-93 years). Histological characteristics and pathologi-
cal stage are summarized in Table 1. Nine (20.9%) patients presented parotid gland or intraparotid lymph node metastasis from other primary tumors (squamous cell skin carcinoma, melanoma, kidney carcinoma and carcinoma of skin adnexa). Four patients were treated for local tumor recurrence (2 adenoid cystic carcinomas and 2 pleomorphic adenomas). The tumors were located in the deep, superficial and both parotid lobes in 15, 5 and 12 patients, respectively. In 11 patients tumor location was not specified.

Radical surgery was performed in all patients. Superficial and total parotidectomy was performed in 11 and 27 patients, respectively. A tumorectomy was performed in 5 patients. Facial nerve preservation was obtained in 31 (72%) patients. Among the 22 (51%) patients who underwent ipsilateral neck dissection, lymph node metastases were found in 16 (70%) patients (12 patients with primary parotid tumors and 4 patients with parotid metastases from other primaries). Microscopically positive surgical margins at the primary tumor site were found in 17 (39.5%) patients. Perineural invasion was present in 13 patients.

The median time between surgery and radiotherapy was 53 days. The mean total doses to the surgical bed, positive and negative lymph nodes were 62 Gy (range, 45-70 Gy), 60 Gy (range, 45-66 Gy) and 50 Gy (range, 45-60 Gy), respectively. Nineteen patients were treated with photon beams while for 24 patients a mixed photon/electron-beam technique was used (median dose of 50 Gy and 14 Gy for photon and electron fields, respectively). Forty-two patients completed the planned pRT course. One patient interrupted treatment at a total dose of 15 Gy because of early local recurrence.

For 7 patients temporary interruption of pRT treatment due to acute toxicity (4 patients) or machine breakdown (3 patients) was recorded. The maximum length of the interruption was 10 consecutive days. Eight patients were also given chemotherapy. All these patients had high-grade tumors: 3 adenocarcinomas, 1 carcinosarcoma, 1 squamous cell carcinoma, 1 undifferentiated tumor, 1 mucoepidermoid carcinoma, and 1 parotid gland metastasis from another primary tumor. Of the 7 patients with primary parotid tumors, 2 patients (1 with a poorly differentiated tumor and 1 with a high-grade mucoepidermoid tumor) received chemotherapy both before (vinorelbine, cisplatin and 5-fluorouracil for the patient with the poorly differentiated tumor and epirubicin, cisplatin and 5-fluorouracil for the patient with the mucoepidermoid tumor) and after surgery (carboplatin for both patients) concomitantly with pRT; 1 patient (undifferentiated tumor) was treated with concomitant chemotherapy (carboplatin) and pRT; 1 patient (adenocarcinoma) was treated with chemotherapy (cisplatin and vinorelbine) after surgery and before pRT. In the last 3 patients (1 patient with a carcinosarcoma and 2 patients with adenocarcinomas) chemotherapy (adriamycin and cisplatin for the patient with carcinosarcoma, epidoxorubicin and methotrexate for 1 patient with adenocarcinoma, and unknown agents for 1 patient with adenocarcinoma) was administered because of local or distant recurrence after pRT.

### Acute and late toxicity

In all patients acute toxicity occurring during the radiotherapy course was recorded and is summarized in Table 2. Grade 3 skin and mucosa toxicity was present in 9 (20.9%) and 12 (28%) patients, respectively. Three (4.7%) patients suffered from grade 4 acute skin toxicity which required temporary interruption of the pRT. No patient had grade 4 mucosa toxicity.

Late toxicity (evaluated at least 3 months from the end of pRT) was recorded for 33 (77%) patients with a mean follow-up of 30 months (range, 3-79 months). Seventeen patients (51%) had a follow-up longer than 2 years. None of the patients experienced grade 3 or 4 late toxicity of mucosa, skin, soft tissues or temporomandibular joints. One patient had grade 2 toxicity of the oral mucosa 5 months after the end of radiotherapy and 3 patients had grade 2 skin toxicity at a mean time of 8 months from the end of radiotherapy (range, 3-16 months).

### Table 1 - Tumor characteristics

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant primary tumor</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>9</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>6</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>6</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Mixed malignant tumor</td>
<td>2</td>
</tr>
<tr>
<td>Epithelial-myoepithelial tumor</td>
<td>1</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Undifferentiated tumor</td>
<td>1</td>
</tr>
<tr>
<td>Parotid gland metastasis from other primary tumors</td>
<td>9</td>
</tr>
</tbody>
</table>

### Table 2 - Acute toxicity evaluated according to RTOG-EORTC scoring system

<table>
<thead>
<tr>
<th></th>
<th>Grade 0 (%)</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>4 (9.3%)</td>
<td>8 (18.6%)</td>
<td>20 (46.5%)</td>
<td>9 (20.9%)</td>
<td>2 (4.65%)</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>6 (13.9%)</td>
<td>13 (30.2%)</td>
<td>12 (27.9%)</td>
<td>12 (28%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

D ALTERIO, BA JERECEK-FOSSA, M GRISER ET AL
months). No major complications of bone and central and/or peripheral nervous system were observed. No association was found between radiotherapy-related acute and late toxicity (skin, mucosa and soft tissue) and total dose to the surgical tumor bed and surgical procedure.

**Clinical outcome**

The mean follow-up was 28 months (range, 0-84 months). Twenty (48%) and 5 (12%) patients had a follow-up longer than 2 and 5 years, respectively. Thirty-seven (86%) patients were alive at last follow-up and most of them (78%) were free from disease. Among 32 patients with a diagnosis of a primary parotid gland tumor, 2 (6%) experienced local recurrence and 4 (12.5%) developed distant metastases. Five patients died of disease progression. The median time to progression after pRT was 13 months. The overall and disease-free survival curves are illustrated in Figures 1 and 2, respectively.

**Discussion**

We performed a retrospective analysis on 43 patients treated with surgery and 3-dimensional conformal pRT in order to evaluate the outcome and the incidence of acute and late toxicity in a group of patients treated with a homogeneous and adequate radiotherapy technique.

**Table 3 - Clinical outcome according to histological characteristics of primary parotid gland tumors**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Free from disease less than 5 years</th>
<th>Free from disease more than 5 years</th>
<th>Local recurrence</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>3/9</td>
<td>1/9</td>
<td>2/9</td>
<td>3/9</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>5/6</td>
<td>-</td>
<td>-</td>
<td>1/6</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>6/6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>1/3</td>
<td>2/3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Salivary gland duct carcinoma</td>
<td>3/3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mixed malignant tumor</td>
<td>1/2</td>
<td>1/2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pleomorphic adenoma</td>
<td>2/2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>1/1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>1/1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>1/1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

**Table 4 - Mortality according to histological characteristics**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Patients died/Total number of patients with the same histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>2/9</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>1/6</td>
</tr>
<tr>
<td>Mixed malignant tumor</td>
<td>1/3</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>1/1</td>
</tr>
</tbody>
</table>
Our study confirmed the rarity and the histological heterogeneity of parotid tumors. Between 1997 and 2007 at the head and neck surgery division of our institute 636 patients underwent surgical procedures on the parotid gland (from simple tumorectomy to total parotidectomy) for parotid gland tumors and 162 (25%) of them were found to have malignant neoplasms. The most frequently recorded histological types in our series were adenocarcinoma followed by adenoid cystic carcinoma and mucoepidermoid carcinoma, reflecting the higher incidence of these types compared to others. In line with the literature data, we found that the incidence of lymph node metastasis depended on the grade of lymph node tropism of the primary tumor: no patient with adenoid cystic carcinoma had lymph node metastases while in other histological types (adenocarcinoma, squamous cell carcinoma), a higher rate of lymph node metastasis was detected.

Radical surgery remains the primary treatment option for parotid malignancies. The higher local control rate obtained in high-risk patients treated with pRT than in those treated with surgery only was confirmed in retrospective analyses. Our preliminary results are comparable with the literature data and confirmed the excellent local control rate in high-risk patients treated with surgery and pRT but a larger number of patients and a longer follow-up are necessary to obtain definitive data. However, the impact of pRT on overall survival remains controversial. Armstrong et al. in a matched-pair analysis found that pRT significantly improved overall survival in patients with advanced stage disease (stage III and IV) and lymph node metastases. A recent review by Jeannon et al. showed the same results with improved overall survival for patients with adverse risk factors treated with pRT. These results were, however, not confirmed by other authors. Significantly, about 80% of distant metastases appeared in spite of locoregional control and most patients died because of distant progressive cancer. In our series, 12% of patients with a diagnosis of primary parotid gland tumors developed distant metastases. The heterogeneity of the histological specimens, the limited number of patients and the short follow-up did not permit us to obtain conclusive results in terms of the association between pathological risk factors and clinical outcome. Nevertheless, some considerations can be made: in our study about 20% of patients with high-grade tumors developed local or distant recurrence and, foremost, all patients who developed distant metastases had no locoregional relapse. These data support the need to give systemic therapy to patients with poor histological prognostic factors. Adjuvant chemotherapy has not yet been demonstrated to have a role in the management of patients with parotid tumors and its use is limited to palliative treatment. It is the standard approach only in case of locoregional recurrence, when curative surgery is not feasible, and/or in case of metastatic disease. The results of different phase II clinical trials with small sample sizes showed objective response rates ranging from 15% to 50% with a response duration ranging from 6 to 9 months.

Molecular profiling is an emerging field of interest to identify patients with poor prognosis. Prospective clinical trials using novel therapeutic agents, for example new molecular target drugs, are therefore needed.

Radiotherapy technique-related factors could be also analyzed to evaluate their impact on patient outcome and toxicity. Yaparpalvi et al. performed a dosimetric analysis focused on different pRT techniques used for parotid gland tumors. They concluded that ipsilateral wedge-pair fields, 3-field and mixed electron-photon beam techniques were the optimal conventional techniques, taking in account both the dose distribution to the surgical bed and the irradiation of non-target tissues. Garden et al. performed a retrospective analysis of patients treated with pRT for parotid gland tumors using both wedge-pair and ipsilateral field techniques. No difference was detected in terms of locoregional control between the 2 techniques but a higher complication rate was found in patients treated with the wedge-pair field modality. Because of the rarity of parotid tumors mostly retrospective studies were performed with patients treated using uni-dimensional or 2-dimensional radiotherapy techniques or with altered fractionation schedule. In some retrospective analyses no other information than total dose was mentioned and no radiotherapy technique-related details were provided by the authors. The time interval between surgery and radiotherapy seems to play a minor role in pRT of parotid gland tumors compared with other squamous cell carcinomas of the head and neck region, probably due to the slow growth of salivary gland cancers. By contrast, a dose-response relationship was found for salivary malignancies: total doses of at least 60 Gy, >65 Gy and 70 Gy were thus recommended for microscopically negative and positive margins and gross residual disease, respectively. Elective irradiation of neck lymph nodes is a matter of controversy and the decision could be based on scheduled risk factor estimates as proposed by Terhaard et al. A minimum dose of 46 Gy for elective lymph node irradiation was recommended. The heterogeneity and adequacy of radiotherapy techniques and doses should therefore be considered when large retrospective analyses covering several decades are performed.

Different acute and late radiotherapy-related toxicities have been described when pRT was delivered to the parotid surgical bed. Ipsilateral hearing loss, soft tissue or bone necrosis, temporal lobe necrosis, hypopituitarism, brachial plexopathy, myelopathy, ear canal stenosis, recurrent facial cellulitis and frozen temporomandibular joint were reported by Garden et al. in a retrospective analysis of 166 patients with a median follow-up of 155 months and a minimum follow-up of survivor patients of 5 years. These toxicities could be relat-
ed to different factors: radiotherapy technique, size of treatment field, total dose and dose/fraction. Acute and late radiotherapy-related toxicity was not often evaluated in retrospective analyses and was focused on auditory structure damage in most cases.24

In order to reduce the radiotherapy-related toxicity, different modern radiotherapy techniques have been evaluated. Nutting et al.25 found that 3-dimensional conformal radiotherapy plans produced equivalent coverage of the target volume and reduced the absorbed dose to the cochlea, oral cavity, brain and other normal tissues compared to conventional radiotherapy. Further reduction of non-target tissue irradiation has been obtained using intensity-modulated radiation therapy (IMRT).25-27. The best IMRT field arrangement for pRT of the parotid gland is under investigation; 3 or 4 optimized fields seem to maintain the advantage of more complex IMRT plans, reducing the dose to the contralateral parotid gland compared to a 7- or 9-field arrangement.25,28

Although major limitations of our study are the relatively small number of patients and the short follow-up, using a homogeneous and adequate (in terms of treatment plan and total dose) 3-dimensional conformal technique (which is the standard treatment in our division), our results confirmed that pRT to the parotid surgical bed was a feasible treatment with an acceptable acute and late toxicity rate of skin, mucosa, soft tissue and temporomandibular joint structures. Most patients, in fact, did not develop severe acute and late toxicity. These results could be of some usefulness for comparison with other retrospective series or with prospective studies focused on more complex radiation treatments like IMRT. No association was found between toxicity and either surgical procedure or total dose of radiotherapy in our analysis, probably due to the homogeneity of treatments. A correlation between hearing loss and absorbed dose by the auditory apparatus was also performed in this set of patients. The results are currently under investigation and will be the subject of a separate report.

In cases of unresectable, residual or recurrent parotid gland tumor, hadron therapy could also be an option.29 In a phase III randomized clinical trial, patients with adenoid cystic carcinoma were randomized to be treated with neutron or photon therapy.30 Hadron therapy with neutrons yielded a higher local control rate than photons but no differences in overall survival were observed. These encouraging preliminary results are limited by the small number of equipped centers, the high cost of the treatments, and the non-negligible reported neutron beam toxicity.31-33 More promising results have been reported for heavy-ion-beam radiotherapy.29

In conclusion, our retrospective analysis confirms that postoperative 3-dimensional conformal radiotherapy is a feasible and effective treatment mainly in patients with primary parotid gland tumors. A lower local and distant control rate was recorded in patients with parotid metastases from other primaries compared to those treated for primary parotid cancers. The radiotherapy-related toxicity proved acceptable but more advanced radiotherapy techniques like IMRT could probably further reduce the incidence and severity of both acute and late toxicity. Distant metastases continue to represent the main cause of therapy failure. Further studies using novel systemic agents are therefore required for poor-prognosis patients.

References


