

Major and minor salivary gland tumors

Marco Guzzo^a, Laura D. Locati^a, Franz J. Prott^b, Gemma Gatta^a, Mark McGurk^c,
Lisa Licitra^{a,*}

^a *Fondazione IRCCS “Istituto Nazionale dei Tumori”, Milan, Italy*

^b *Radiotherapy, Wiesbaden, Germany*

^c *Guy’s and St. Thomas’ Hospital Trust, London, UK*

Accepted 20 October 2009

Contents

1. General information	135
1.1. Epidemiological data	135
1.2. Etiological and risk factors	135
1.3. Screening and case finding	136
1.4. Referral	136
2. Pathology and biology	136
2.1. Histological types	136
2.2. Grading	136
2.3. Biological targets	137
3. Diagnosis	137
3.1. Signs and symptoms	137
3.1.1. Major salivary gland tumors	137
3.1.2. Minor salivary gland tumors	137
3.2. Diagnostic strategy	138
3.3. Pathological diagnosis	138
4. Staging	138
4.1. TNM classification [56]	138
4.1.1. Stage grouping	139
4.2. Staging procedures	139
5. Prognosis	139
5.1. Natural history	139
5.2. Prognostic factors	139
5.3. Predictive factors	140
6. Treatment	140
6.1. Treatment strategy	140
6.2. Major salivary gland tumors	140
6.2.1. Local and locoregional disease	140
6.3. Minor salivary gland tumors	141
6.3.1. Local disease and locoregional disease	141
6.4. Unresectable/inoperable locoregional disease	141
6.5. Local relapse	141
6.6. Regionally relapsing disease	141
6.7. Metastatic disease	142

* Corresponding author at: Head and Neck Medical Oncology Unit, Fondazione IRCCS “Istituto Nazionale dei Tumori”, Via Venezian 1, 20133 Milano, Italy. Tel.: +39 02 23903352; fax: +39 02 23903353.

E-mail address: lisa.licitra@istitutotumori.mi.it (L. Licitra).

7.	Late sequelae	142
7.1.	Treatment late effects and sequelae	142
7.2.	Related and secondary tumors	143
8.	Follow-up	143
8.1.	General principles and objectives	143
8.2.	Suggested protocols	143
	Reviewers	143
	Conflict of interest	143
	References	143
	Biographies	147

Abstract

Malignant salivary gland tumors are rare. The most common tumor site is the parotid. Aetiological factors are not clear. Nutrition may be a risk factor, as well as irradiation or a long-standing histologically benign tumor that occurs at youth. Painless swelling of a salivary gland should always be considered as suspicious, especially if no sign of inflammation is present. Signs and symptoms related to major salivary gland tumors differ from those concerning minor salivary gland tumors, as they depend on the different location of the salivary gland. Surgical excision represents the standard option in the treatment of resectable tumors of both major and minor salivary glands. Neutron, heavy ions or proton radiotherapy may be a treatment option for inoperable locoregional disease. Surgery, irradiation or re-irradiation are treatment options for local relapse, whereas radical neck dissection is indicated for regional relapses. Metastatic disease may be either treated with radiotherapy or palliative chemotherapy, depending on the site of metastases. For highly selected patients the employment of anti-androgen therapy is indicated. © 2009 Elsevier Ireland Ltd. All rights reserved.

Keywords: Evidence-based medicine; Review; Salivary gland tumors; Treatment

1. General information

1.1. Epidemiological data

Malignant neoplasms of the major salivary glands (ICD-O-2 C7.9, C8.0–C8.9) [1] are uncommon: the annual incidence rates in the world vary between slightly less than 2 and greater than 0.05 per 100,000 (Fig. 1) [2].

Tumors are mostly adenocarcinomas of the parotid, the largest salivary glands. These tumors are rare under the age of 40, and incidence at older ages is higher in men than in women (Fig. 2) [2].

Recently in the US, during 1974–1999, a significant increase in the incidence rate of salivary gland cancer was reported: these cancers accounted for 6.3% in 1974–1976, compared to 8.1% of all head and neck cancers in 1998–1999

($p = 0.002$) [3]. In Europe survival after salivary glands cancer was studied from population-based cancer registries by the EURO CARE project [4]. Relative survival for adults diagnosed with salivary gland cancer was 83% at one year, 69% at three years, and 65% at five years, with a significant difference between men and women, 58 and 72%, respectively. Five-year relative survival decreased markedly with age from 87% to 59% from the youngest (15–45 years) to the oldest age group of patients (75 years and over).

1.2. Etiological and risk factors

The causes of salivary gland cancer are largely unknown. Diet may be effective in preventing salivary gland cancer, by increasing consumption of fruits and vegetables, particularly those high in vitamin C, and limiting food high in cholesterol [5]. A case–control study conducted in the Chinese population revealed a significant protective effect of consumption of dark-yellow vegetables or liver, with about 70% reduced risk of salivary gland cancer among people in the highest intake group of these foods [6]. Irradiation may also be a cause of

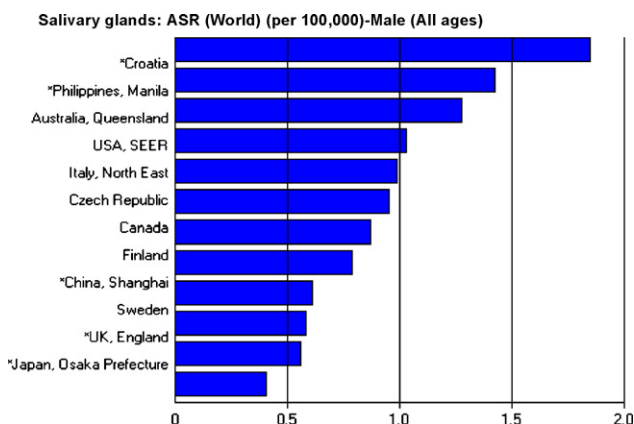


Fig. 1. Annual incidence rates in the world.

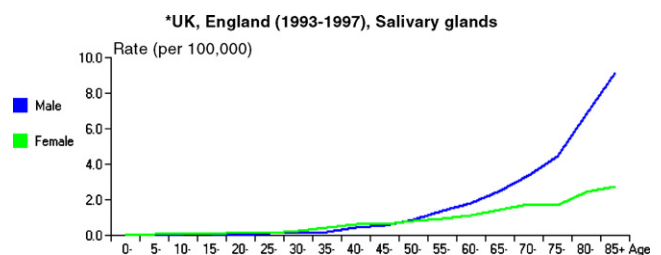


Fig. 2. Incidence per age.

malignant salivary gland tumors. This was found in Japanese survivors of the atomic bomb and in patients who received irradiation to the head and neck during childhood for benign conditions e.g. to reduce the size of the tonsils and adenoids [7]. The decline in incidence under age 70 in England and Wales is consistent with the reduction of repeated ionizing radiation exposure to medical or dental X-rays [8]. A history of prior cancers, especially those related with ultraviolet radiation, immunosuppression and Epstein-Barr virus, was found to be associated with salivary gland cancers in several studies. Among more than 5000 Swedish patients with Hodgkin's disease, there was a over 4-fold significant increase in cancer of the salivary glands [9]. A US and Swedish study revealed an increased risk of second cancer, including salivary gland tumors in more than 1000 children with a diagnosis of medulloblastoma [10]. On a total of about 70,000 Finnish patients with basal-cell carcinoma, the incidence rate to have a subsequent salivary gland carcinoma was 3.3-fold higher than in the general population [11].

Patients with a histologically benign tumor (e.g. pleomorphic adenoma) which occurs at a young age, have a higher risk of developing a malignant parotid carcinoma, since these tumors have the potential for malignant transformation (3–10%) [12].

In a large cohort of southern European men with, or at high risk of, HIV infection, a very high risk to have a cancer of salivary glands (SIR = 33.6) was found [13].

The workers in a variety of industries showed an increased incidence of salivary gland carcinoma including rubber manufacturing, exposure to nickel compound [14] and employment at hair dresser's and beauty shops [15].

Chronic inflammation of salivary glands is not clearly defined as a risk factor.

1.3. Screening and case finding

Malignant salivary gland tumors are rare; therefore, no screening programme has been developed. Screening is not recommended and clinical case finding has not been evaluated.

1.4. Referral

Malignant salivary gland tumors are uncommon and therefore it is recommended that treatment be given in experienced institutions, where a multidisciplinary team is available. Neutron radiotherapy, which is not available in every country, is recommended in some particular clinical situations.

2. Pathology and biology

2.1. Histological types

Salivary gland tumors are classified according to the new WHO histological classification published in 2005 [16]. This

includes the following histotypes. Histological classification of salivary gland tumors is evolving and the importance of tumor grading has become widely accepted, although this may be difficult even for an experienced pathologist.

• Benign epithelial tumors

Pleomorphic adenoma (8940/0)
Myoepithelioma (8982/0)
Basal cell adenoma (8147/0)
Warthin tumor (adenolymphoma) (8561/0)
Oncocytoma (oncocytic adenoma) (8290/0)
Canalicular adenoma (8149/0)
Sebaceous adenoma (8410/0)
Lymphadenoma (8410/0)
Sebaceous non-sebaceous ductal papilloma (8503/0)
Inverted ductal papilloma (8503/0)
Intraductal papilloma (8503/0)
Sialadenoma papilliferum (8406/0)
Cystadenoma (8440/0)

• Malignant epithelial tumors

Acinic cell carcinoma (8550/3)
Mucoepidermoid carcinoma (8430/3)
Adenoid cystic carcinoma (8200/3)
Polymorphous low-grade adenocarcinoma
Epithelial–myoepithelial carcinoma (8562/3)
Clear cell carcinoma, not otherwise specified (8310/3)
Basal cell adenocarcinoma (8147/3)
Sebaceous carcinoma (8410/3)
Sebaceous lymphadenocarcinoma (8410/3)
Cystadenocarcinoma (8440/3)
Low-grade cribriform cystadenocarcinoma
Mucinous adenocarcinoma (8480/3)
Oncocytic carcinoma (8290/3)
Salivary duct carcinoma (8500/3)
Adenocarcinoma NOS (8140/3)
Myoepithelial carcinoma (8982/3)
Carcinoma ex pleomorphic adenoma (8941/3)
Carcinosarcoma (8980/3)
Metastasizing pleomorphic adenoma (8940/1)
Squamous cell carcinoma (8070/3)
Small cell carcinoma (8041/3)
Large cell carcinoma (8012/3)
Lymphoepithelial carcinoma (8082/3)
Sialoblastoma (8974/1)
Soft tissue tumors
Haemangioma (9120/0)
Haematolymphoid tumors
Hodgkin lymphoma
Diffuse large B-cell lymphoma (9680/3)
Extranodal marginal zone B-cell lymphoma (9699/3)
Secondary tumors

2.2. Grading

The grade of a tumor (high, intermediate or low) is supposed to reflect the inherent biological nature of a tumor

Table 1
Frequency of expression of biological targets in SGCs.

Histotype	c-kit (%) [17,20,24,26,27,30,31]	EGFR (%) [17,20,32]	HER2 (%) [17,20,23,33]	AR (%) [17,34,35]
Adenoid cystic carcinoma	78–92	36–85	2–36	0
Mucoepidermoid	0–40	53–100	0–38	0
Adenocarcinoma	9	59	14–21	21
Salivary duct cancer	0–8	9–41	44–83	43–100

(aggressive, intermediate or indolent). Salivary carcinomas are classified into histological types or families. Most tumors in a family (adenocarcinoma, adenoid cystic carcinoma) have a similar biological nature (although not all of them do). Some families are known to be high grade or biologically aggressive (anaplastic, carcinoma in pleomorphic adenoma, squamous cell carcinoma (SCC), high-grade mucoepidermoid), some are low grade (acinic cell, low-grade adenocarcinoma, polymorphous low grade) or intermediate (adenoid-cystic carcinoma). Besides, in some tumor families histological features may identify a subgroup of tumors with an indolent or aggressive nature. This is the case for mucoepidermoid carcinoma, and to a lesser extend, for adenoid-cystic carcinoma and other groups. Prognosis of salivary gland tumors appears to correlate mainly with histological subtype. A group of neoplasms exists (e.g. salivary duct carcinoma, oncocytic carcinoma, squamous cell carcinoma, large cell carcinoma), which are considered as high-grade tumors with a poor prognosis. These show a high tendency to recur locally and frequently result into distant metastases. In 2005 WHO classification only mucoepidermoid carcinomas are graded by a point score system, as low-grade type (well differentiated), intermediate or high-grade type (poorly differentiated). Differences in tumor grade have been also suggested for adenocarcinoma NOS, salivary duct carcinoma and acinic cell carcinoma. In these cases, prognosis correlates with grading: high-grade tumors are associated with a poorer prognosis, whereas the prognosis of low-grade tumors is much more favourable. For most of the remaining malignant salivary gland tumors grading schemes do not seem to have any prognostic value.

2.3. Biological targets

Tyrosine kinase (TK) and hormonal receptors are currently the most investigated targets (Table 1). Epidermal growth factor receptor (EGFR) is the most expressed TK receptor in up to 71% of salivary gland cancers and its expression is detected in almost all malignant histotypes [17]. No correlation was found between EGFR expression and gene amplification analysis [17] and activating mutations within EGFR TK domain were very rare [18]. Controversial results were reported about the prognostic role of EGFR expression on disease-free survival and overall survival [19,20]. Human Epidermal growth factor receptor 2 (HER2) is present in particular histotypes derived from the excretory duct, such as salivary duct cancers. A correlation between HER2 3+ and gene amplification is found in at least 57–73% of cases [21,22]. Both HER2 overexpression and gene amplification

seems to correlate with a worse prognosis [23]. C-kit is expressed mostly in those histotypes originated from intercalated duct, such as adenoid cystic carcinoma, as well as in other malignant histotypes and benign tumors [24,25]. No genetic mutations at exons 11 and 17 were found and an autocrine/paracrine loop seems to be the most probable cause of c-kit activation mechanism [26–28]. Androgen receptor expression is rare and mainly restricted to salivary duct cancer and adenocarcinoma [17]. Estrogen and progesterone expression is very rare and it is found both in benign and malignant salivary gland tumors [29].

3. Diagnosis

3.1. Signs and symptoms

3.1.1. Major salivary gland tumors

Every painless swelling of a salivary gland must arouse suspicion, especially if there are no signs of inflammation. Malignant tumors comprise 15–32% of parotid tumors, 41–45% of submandibular tumors and 70–90% of sublingual tumors. As indicated above, malignant salivary tumors demonstrate a range of biological behaviors. About 40% of such tumors are indolent (especially in young people <40 years of age) and present as slow growing lumps and, if of long duration, they may be associated with pain or early nerve involvement. About 40% of tumors are also aggressive (especially in the elderly) and facial palsy may be a presenting feature but soon an evolving mass is evident. These tumors show frank evidence of malignancy [36,37]. Clinical indicators suggesting a malignant salivary gland tumor are: rapid growth rate, pain, facial nerve involvement, and cervical adenopathy. Every sign of facial nerve palsy, either complete or partial, is always a sign of a locally infiltrating parotid cancer [38,39]. Clinical presentation may also be characterised by parapharyngeal fullness, or palatal fullness. Trismus, skin ulceration and fistulas can be present in very advanced malignancies. On the other hand, a slow growth rate of an asymptomatic mass does not exclude a malignant nature [40].

3.1.2. Minor salivary gland tumors

There are between 450 and 750 minor salivary glands in the head and neck. About one half of the tumors that arise in these glands are malignant [40]. The incidence of malignancy depends on the site of occurrence. In the palate the rate is similar to that in the submandibular gland, i.e. 40–60%. But as one goes from the tongue to the floor of the mouth and

sublingual glands, the incidence increases up to 90% [41,42]. Signs and symptoms depend on tumor size and position and may vary according to tumor location. Minor salivary gland tumors are distributed in the upper aerodigestive tract, in the palate, paranasal sinuses and nasal cavity, tongue, floor of mouth, gingiva, pharynx, larynx and trachea. More than 50% of them are intraoral and usually cause a painless submucosal swelling. The mucosal layer is frequently adherent to the mass, with a small ulcer. Tumors arising in the oropharyngeal area can cause a painless lump. If the nasopharynx or the nasal cavity is infiltrated this may cause facial pain, nasal obstruction or bleeding. If the tumor [37] occurs in the larynx or trachea it can cause hoarseness, voice change, or dyspnoea.

3.2. Diagnostic strategy

Physical examination is the most important tool for diagnosis. Since approximately 80% of salivary gland tumors arise in the parotid and approximately 80% of them are benign, the initial diagnostic strategy should include differential diagnosis between tumor and other benign conditions, such as cysts, inflammatory processes and lymph node hyperplasia. When a malignant lesion is suspected, a pathological diagnosis is needed. Ultrasonography is a low cost modality with high sensitivity (approximately 100%—similar to CT scan) and it is always recommended as preoperative examination, since approximately 90% of tumors arise in the superficial lobe. Ultrasound proves excellent for differentiating intraglandular from extraglandular lesions, although it is not able to show part of the deeper parotid lobe [43–45]. CT or MRI may be useful [46]. MRI is particularly recommended in demonstrating the interface of tumor and surrounding tissues for a correct surgical planning, especially for larger tumors (more than 4 cm) and for those tumors arising in deep structures and/or involving them. The advantages of MRI include also the elimination of dental artifacts and the ability to distinguish between a tumor and obstructed secretions. MRI imaging is also recommended in minor salivary gland cancers that originate in oral and nasal cavity, as well as in paranasal sinuses where the full extent of the neoplasm usually can not be defined by means of clinical examination alone [47–49].

3.3. Pathological diagnosis

If there is frank evidence of malignancy and destructive surgery such as neck dissection and total parotidectomy is considered, tissue biopsy is then indicated. The penalty of using such radical surgery to treat a salivary gland tuberculosis (TB) or a lymphoma is obvious. The dilemma arises in the presence of an indolent cancer masquerading as a benign tumor. In this case, the clinician is principally reliant on clinical skills. An experienced clinician should be able to distinguish between the two in 90% of cases [50] and with the additional benefit of fine needle aspiration cytology (FNAC) the risk of treating a benign tumor inadvertently is even further reduced. FNAC has a high sensitivity and specificity

with an accuracy ranging from 87% to 96% [51] but the technique is operator sensitive. Sensitivity ranges between 73% and 86.6% both in malignant and in benign tumors while specificity was noted to be usually better in benign than in malignant tumors (97% vs. 85%) [52]. False negative diagnoses due to inadequate sampling appear to be the most frequent error. It enables to discriminate between a primary salivary tumor and a pathological lymph node in case of a periglandular nodule. Unnecessary surgery can be avoided in about one third of cases [53]. Repeated aspirations may be useful in order to diagnose a tumor with cystic degeneration, which is relatively frequent in mucoepidermoid carcinomas. The risk of seeding along the needle route has been demonstrated to be negligible. In spite of these observations, FNAC should be left to clinical discretion. It is inexpensive, simple to perform and, in appropriate hands, it is quite accurate and morbidity is very low.

FNAC has a particular role in those cases where the suspected pathological diagnosis would change the therapeutic strategy.

It is strongly recommended when a salivary tumor is not suspected, such as TB, lymphoma, or an enlarged lymph node, in patients with autoimmune T-cell disease.

FNAC is also suggested in children where inflammatory tumors and benign cysts widely represent the major causes of salivary gland enlargement, particularly in the submandibular gland. The ratio of malignant to benign tumors is higher than in adults even though these cancers are normally indolent in nature. If mistaken for a benign tumor and inadequately excised then either further surgery may be required placing the facial nerve at risk or adjuvant RT may be considered [54].

Open biopsy is usually not recommended due to the risk of seeding. In the presence of small masses in minor salivary glands (palate, tongue), punch biopsy (dermatological punch) may be preferable to direct excision, unless the latter provides adequate margins, should the lesion prove to be malignant. The accuracy of frozen section diagnosis is quite controversial. False-positive rates account for 1.1%, false-negative rates are 2.6%. The accuracy rate is better for benign tumors than it is for malignant lesions (98.7% vs. 85.9%) [55]. The examination of frozen sections of the removed specimen, including periglandular lymph nodes, is performed by several surgeons to plan immediate neck dissection. This procedure has several limitations since it may be difficult to differentiate among various histotypes.

4. Staging

4.1. TNM classification [56]

• Primary tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Tumor 2 cm or less in greatest dimension without extraparenchymal extension*

T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*

T3 Tumor more than 4 cm and/or tumor with extraparenchymal extension*

T4a Tumor invades skin, mandible, ear canal, or facial nerve

T4b Tumor invades base of skull pterygoid plates or encases carotid artery

Note: (*) Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissue or nerve, except those listed under T4a and T4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

- **Regional lymph nodes (N)**

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2 Metastasis as specified in N2a, 2b, 2c below

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Note: Midline nodes are considered ipsilateral nodes.

- **Distant metastases (M)**

MX Distant metastases cannot be assessed

M0 No distant metastases

M1 Distant metastases

4.1.1. Stage grouping

- **Stage I**

T1, N0, M0

- **Stage II**

T2, N0, M0

- **Stage III**

T3, N0, M0 T1, T2, T3, N1, M0

- **Stage IVA**

T1, T2, T3, N2, M0 T4a, N0, N1, N2, M0

- **Stage IVB**

T4b, Any N, M0 Any T, N3, M0

- **Stage IVC**

Any T, Any N, M1

4.2. Staging procedures

Physical examination with consideration of facial nerve function and good clinical judgment represents the most important factor in clinical decision making. CT scan and/or MRI are recommended in the presence of malignant disease. Ultrasonography can complement these investigations and has the advantage of being a less expensive alternative

and can be used to aid in fine needle aspiration of the glands. FDG PET seems to be superior to CT and/or MRI for staging at the first diagnosis and in case of loco-regional recurrence and metastatic disease [57]. The technique is relatively new to salivary gland disease. FDG PET alone is not recommended as staging procedure but always in combination with CT scan and/or MRI. A chest CT scan is useful for excluding distant lung metastases [58], and it should be considered in high-grade histotypes and in locally-advanced disease.

5. Prognosis

5.1. Natural history

Malignant tumors of the salivary glands show widely different patterns of growth. The most common ones (adenoid cystic, mucoepidermoid low-grade, acinic cell carcinomas) frequently grow slowly, sometimes so slowly as to be mistaken for benign or non-neoplastic lesions, especially in the major salivary glands. Invasiveness usually extends parallel to the histopathological degree of malignancy, which accounts for both local recurrences and spreading. Lymphatic spread is generally less frequent than that of mucosal SCC but it can be very frequent in some particular histotypes, such as ductal carcinomas, high-grade mucoepidermoid carcinomas, carcinomas ex pleomorphic, adenoma squamous cell carcinomas. Lymphatic spread is not frequent in polymorphous low-grade adenocarcinoma, is rare in low-grade mucoepidermoid carcinoma and in adenoid cystic carcinoma.

Distant hematogenous metastases which localize most frequently in the lungs (80%) followed by bone (15%), liver and other sites (5%), are the main cause of death in malignant salivary gland tumors and depends on the degree of malignancy. Adenoid cystic carcinoma, adenocarcinoma NOS, carcinoma ex-mixed tumor, small cell carcinoma and ductal carcinoma show the highest distant metastases rate (up to 50%). Distant metastases from adenoid cystic carcinoma show a particularly slow evolution with survival reaching up to 20 years. Metastasizing pleomorphic adenoma is a rare histologically benign adenoma characterized by multiple local recurrences and a long interval between development of primary tumor and its distant metastases that usually occur to bone (50%) followed by lung and lymph nodes (30% both) [59].

All these remarks should be taken into consideration for treatment planning. Survival strongly correlates with clinical stage and grade. Histology is also a predictor of the tumor behavior and it contributes to optimize treatment. Survival of the most common major salivary gland malignancies is shown in Table 2.

5.2. Prognostic factors

Tumor stage, histology, grading, facial nerve paralysis, extra-parotid tumor extension and cervical node involvement are the most important tumor-related predictors of survival

Table 2
Survival rates of the most common major salivary gland malignancies.

Histology [16]	5-year survival	References
Polymorphous low-grade adenoca.	95–100%	[60,61]
Acinic cell carcinoma	75–96%	[62,63]
Mucoepidermoid ca. LG	75–89%	[62,64,65]
Myoepithelial ca.	67%	[66,67]
Mucoepidermoid ca. HG	23–50%	[62,64,65]
Adenoid cystic ca.	35–70% (10-ys DFS 10–20%)	[68,69]
Carcinoma ex pleomorphic adenoma	40% (30–96% correlated with histology)	[62,70,71]
Salivary duct ca. HG	4-ys DFS 20–35%	[72,73]

and they are all able to influence treatment outcome, although stage seems to be more important than grading [38,74–76]. Patient's age and positive surgical margins, along with the prognostic factors reported above, have to be considered as the main issues for loco-regional control in parotid gland cancer [77,78]. Other prognostic factors in adenoid cystic carcinoma are perineural invasion, and solid histological features [79]. Ki-67 tumor value could provide a further prognostic factor, since it is significantly higher in cases of treatment failure and large tumors [80]. In case of epithelial–myoepithelial carcinoma, margin status, angiolymphatic invasion, tumor necrosis and myoepithelial anaplasia seem to be the most important predictors of recurrence [81]. Among the small subset of minor salivary glands cancers, the site of occurrence also seems effective in predicting prognosis [82]. High FDG uptake (SUVs > 4.0) of primary tumor correlates with a lower disease free survival, although high SUV is not a prognostic factor for survival [83].

5.3. Predictive factors

The factors which predict the response to treatment are probably growth rate (short interval between primary treatment and occurrence of distant metastases) and high malignancy grade, although this has not been substantiated in the literature.

6. Treatment

6.1. Treatment strategy

According to the National Comprehensive Cancer Network (NCCN) guidelines, the standard treatment of resectable carcinomas of the major and minor salivary glands is surgical excision, on a type C basis. A routine prophylactic neck dissection is not recommended. However, it is standard in selected cases. Postoperative radiotherapy is recommended on a type R basis in selected patients. Primary radiotherapy is recommended, on a type R basis, for patients who refuse surgery or suffer from an inoperable/unresectable

tumor. For both major and minor salivary gland tumors the role of chemotherapy is only suitable for individual clinical use, on a type 3 level of evidence, in a palliative fashion for unresectable relapsing disease, for patients not amenable to radiotherapy, and for patients with metastatic disease.

6.2. Major salivary gland tumors

6.2.1. Local and locoregional disease

The treatment of salivary gland tumors has to be individualized to each patient, more than in other neoplasms. For this reason, experience is very important.

The standard treatment on a type C basis of resectable carcinomas of the major salivary glands is a well planned and carefully executed surgical excision. Superficial parotidectomy with facial nerve dissection is considered the primary diagnostic procedure of choice for all parotid neoplasms, as well as the therapeutic procedure for malignant tumors that occur in the superficial lobe of the gland. Conversely, enucleation will result in higher rates of recurrence and facial nerve dysfunction. Partial superficial parotidectomy, as described by Leverstein, seems to be safe and effective in treating benign tumors [84]. In the case of large extension into the parapharyngeal space, the surgical exposure of the deep lobe may be achieved also by cervical approach and/or may require mandibulotomy. A balance between eradicating the tumor and preserving the facial nerve is warranted. Radical parotidectomy including the facial nerve, is the standard option, on a type C basis, if the tumor is adherent or infiltrative to other structures (preoperative facial palsy, skin and bone involvement). Immediate nerve grafting is recommended in patients under 65 years while for older patients only rehabilitative local procedures are recommended. Retromandibular parotid gland tumors need a trans-cervical approach, only a few may need a mandibulectomy for access. For submandibular tumors excision of the whole gland alone is occasionally adequate treatment when the lesion is small and well confined to the parenchyma and of low-grade histology. In every other case an adequate resection is recommended, i.e. including the bed of the gland and any adjacent structure in contact with it, up to a real supra-omohyoid dissection (removal of levels I, II and III lymph nodes). This procedure provides tissue for diagnosis and it also removes the primary echelon lymph nodes at risk for metastasis [85].

In general lymph node metastasis rates are low (14–20%) [86] and occur more frequently in high-grade and advanced T-stage tumors and (or) in presence of extracapsular extension or facial paralysis irrespective of histology [74,87–89]. In such patients a selective prophylactic neck dissection may be appropriate on a type R basis. The old adage that has stood the test of time is that “if one enters the neck for any reason one should proceed to some form of neck dissection”. Consequently a prophylactic neck dissection should be reserved for selected patients whose primary resection may be facilitated by lymphadenectomy. The incidence of nodal metastases in parotid adenoid cystic carcinoma is generally low and conse-

quently the indication for any kind of neck dissection remains questionable [90]. Conventional neck dissection is standard treatment in patients with nodal involvement. Selective neck dissection should include levels I, II, and III for cancer of the submandibular–sublingual glands, and levels IB, II, III, IV, and VA for parotid cancer. Modified radical neck dissection is an acceptable treatment for N1 neck, if the node is mobile and for selected N2b necks (<3 nodes, <3 cm, mobile) on a type 3 level of evidence [91–94].

In all locations, postoperative radiotherapy with photons is recommended, on a type R basis, for patients with residual disease after surgery (e.g. R1- or R2-resection), or in the presence of extensive nodal involvement (e.g. more than 3 metastatic nodes) or capsular rupture. Postoperative radiotherapy is suitable for individual clinical use, on a type-3 evidence case, under the following circumstances:

- for undifferentiated and high-grade tumors;
- in the presence of perineural invasion;
- in the presence of advanced disease (facial nerve involvement, deep lobe involvement [95–100]);
- in cases of close or positive margins and/or lymphatic/vascular invasion.

In the NCCN guidelines concomitant chemo-radiotherapy could also be indicated in the same clinical and pathological situations on a type-2b recommendation (lower level of evidence, non-uniform consensus, no major disagreement).

These recommendations refer to all histological types of malignant major and minor salivary gland tumors, with the exception of adenoid cystic carcinomas. For patients with minimal residual disease after surgery (R1-resection) a dose of 60–66 Gy photons in daily fractions of 2 Gy over 6 weeks is advisable. Patients with postsurgical macroscopic disease (R2-resection), with unresectable primary tumors or with inoperable recurrent tumors should receive doses of 60 Gy photons. An additional dose of 10 Gy is usually given through reduced portals to the volume of known residual disease. In these selected patients an optional mixed-beam therapy, consisting of photons and a neutron boost, can be applied. Irradiation of the adjacent neck lymph nodes should be administered with 50–60 Gy photons if there is tumor involvement. After a neck dissection, irradiation of the neck is optional. Elective neck irradiation in case of clinically negative necks reduced the 10-year nodal failure rate from 26% to 0% [78]. Postoperative neutron, heavy ions or proton radiotherapy is recommended, on a type 2 level of evidence [101–110] in adenoid cystic carcinoma, since it is associated with a better tumor control than the one achieved by radiotherapy with photons. This radiotherapy is suitable for individual clinical use, on a type R basis, even after complete resection (R0). Doses ranging from 15 to 20 Gy are given depending on the energy and type of fractionation because of the higher relative biologic effectiveness (RBE) of neutrons, heavy ions and protons.

6.3. Minor salivary gland tumors

6.3.1. Local disease and locoregional disease

Minor salivary gland tumors may arise anywhere in the head and neck. Local and loco-regional surgical excision is the recommended treatment. In general, the treatment of these tumors follows the pattern adopted for squamous cell carcinomas arising in the upper aerodigestive tract. A low rate of cervical lymph node metastases has been reported [82,111]. Therefore, there is probably little benefit from elective neck dissection for patients with small and low-grade tumors of the minor salivary glands. Postoperative radiotherapy is recommended, on a type R basis, in patients with advanced disease.

6.4. Unresectable/inoperable locoregional disease

In cases of unresectable/inoperable locoregional disease neutron, heavy ions or proton radiotherapy is recommended, on a type 2 level of evidence [112].

Patients are usually treated either with neutron alone or a mixed beam irradiation. Long term locoregional control may reach 67% compared to average long term locoregional tumor control rates of approximately 25% for standard fractionated radiations. Normal tissue toxicities do not seem to be different from those observed in patients treated with photons. The 6 year actuarial rate of development of grade 3 or 4 long term toxicity (RTOG criteria) was 10% in 279 salivary gland tumor patients treated with neutron therapy [113]. This is absolutely comparable to the toxicities known by photons radiotherapy, concerning xerostomia, facial nerve damage and skin fibrosis.

In 20 patients treated with neutrons with advanced adenoid cystic carcinoma there were only 2 patients with late grade 3 toxicity, no grade 4 toxicity was described [114].

But these data may change during the next years, because all photon patients in this collectives were irradiated without the modern techniques of intensity modulated radiotherapy (IMRT) or image guided radiotherapy (IGRT).

With these new techniques late toxicities were described below 5% [115].

6.5. Local relapse

Surgery, irradiation, or re-irradiation are suitable for individual clinical use, on a type R basis for local relapse. Endpoints of treatment are frequently palliative. If irradiation is possible, neutron, heavy ions or proton radiotherapy is recommended. If surgery and irradiation are not feasible, palliative chemotherapy (see Section 6.6) may be considered. Hyperthermia associated with radiation therapy is investigational only [116,117].

6.6. Regionally relapsing disease

The standard treatment for late regional lymph node metastases is modified radical or classic radical neck dis-

Table 3
Phase II study with biological drugs.

Author, year	Histotypes	Drug	Target	Response rate (%)	SD \geq 6 months (%)
Hotte SJ, 2005 [135]	ACC = 16	Imatinib	c-kit	0	12
Haddad R, 2003 [139]	ACC = 2; non-ACC = 12	Trastuzumab	HER2	7	n.r.
Glisson BS, 2005 [136]	ACC = 19; non-ACC = 10	Gefitinib	EGFR	0	n.r.
Agulnik M, 2007 [138]	ACC = 20; non-ACC = 20	Lapatinib	HER2/EGFR	0	47
Locati LD, 2008 [19]	ACC = 23; non-ACC = 7	Cetuximab	EGFR	0	50

section according to the extension of disease. Postoperative radiotherapy is recommended for patients with a massive involvement of the neck nodes (more than 3 nodes) or in the presence of capsular rupture. Recurrence within the field of a previous neck dissection can be treated with radiotherapy or surgical excision, if possible, but the prognosis is dismal.

6.7. Metastatic disease

Carcinomas of the salivary glands may metastasize to lymph nodes, lung, liver and bone. Distant metastases develop with wide variability according to the histology. Metastases are rare in low-grade tumor (i.e. low-grade mucoepidermoid carcinoma, polymorphous low-grade adenocarcinoma or clear cell carcinoma). High-grade salivary duct carcinomas and squamous cell carcinomas show distant metastases in 46% and 30% of cases, respectively. High-grade mucoepidermoid and acinic cell carcinomas develop metastases in 5–16% of cases. Metastases from adenoid cystic carcinoma range from 25 to 55% and usually show indolent asymptomatic courses. Solitary metastases of lung and liver can be resected. Lung metastasectomy in a highly selected subset of patients provides a prolonged freedom from progression but whether this could be translated into a survival benefit, is still a matter of debate [118]. Bone metastases are rare, but if there is a risk of fracture or drug-resistant pain, radiotherapy or surgery is recommended. Palliative chemotherapy is suitable for individual clinical use, on a type 3 level of evidence. The most studied regimen, consisting of cyclophosphamide plus doxorubicin and cisplatin (CAP), produced a response rates ranging from 22% to 100% and complete responses in up to 70% of cases. However, these outstanding data should be interpreted with caution since derived from old series with few patients. Data derived from the combination of carboplatin with paclitaxel did not gain better results [119]. The best single-agent activity has been reported for cisplatin, 5-fluorouracil (5-FU) or doxorubicin, albeit in small series of patients. Is still not clear whether combination chemotherapy has any advantage over single agent chemotherapy [102,120–131]. Chemotherapy activity seems to be histotype driven. It has been suggested that patients with adenocarcinoma, adenoid cystic carcinoma, acinar cell carcinoma, and malignant mixed tumors are similarly sensitive to the CAP regimen. Patients with mucoepidermoid and undifferentiated tumors, however, appear to respond better to those drugs active against squamous cell carcinomas (e.g. cisplatin, 5-FU, methotrexate) [132]. Paclitaxel seems to be

active in histotypes other than ACC [133], gemcitabine also resulted in no activity in ACC [134]. Patients responding to chemotherapy have not been documented to have a survival benefit over non-responding patients. Despite the absence of a survival benefit, the palliative effect of chemotherapy was often pronounced.

Some phase II trials on tailored therapies have been conducted (Table 3). Among these studies, no activity was verified for imatinib, gefitinib, cetuximab and lapatinib [135–138]. One long-lasting partial response was reported with trastuzumab in a case of HER2 3+ mucoepidermoid cancer [139]. Rare objective responses to imatinib were published [140,141], favoured in case of strong c-kit immunostaining [141].

Even the employment of bortezomib, a proteasome inhibitor, in 25 ACC cases within a phase II study did not result in any objective response [142]. A partial response in one ACC case has been reported within a phase I trial with AG-013736, a TK-inhibitor of all vascular endothelial growth factor receptors, PDGF-beta and wild type c-kit, suggesting a potential activity of antivascular drug in ACC [143].

The employment of target therapies is only currently recommended within clinical trials.

7. Late sequelae

7.1. Treatment late effects and sequelae

Facial nerve morbidity is more likely to occur as a complication of treatment of malignant tumors. Temporary postoperative paresis is quite common (range 8–38%). Conversely, definitive facial nerve paralysis is rare and it strictly depends on whether surgical intervention is performed on a primary tumor or on a local recurrence. In fact, in the former case it occurs in about 1% of patients, while in the latter case it occurs in 15–40% of patients [144–146]. It has been shown that nerve sacrifice is rarely necessary, unless the nerve is directly involved by the tumor. Furthermore, radical resection is often not necessary if postoperative radiotherapy is given [62]. Additional postoperative sequelae are salivary fistulae and neuromas of the greater auricular nerve. Minor complications are more common after parotidectomy: Frey's syndrome (local facial sweating and flushing during meals) occurs in varying degrees in 20–40% of cases; anesthesia in the periauricular skin is almost constant [147]. Sequelae due to radiotherapy should be divided into acute and late

side-effects. Mild acute side-effects consist of skin erythema, mucositis and dysphagia. Severe acute side-effects manifest as desquamation and mucosal ulcers. Late side-effects consist of telangiectasia, permanent taste impairment, subcutaneous fibrosis, xerostomia and otitis externa or media associated with partial hearing loss and pain [148,149]. Bone necrosis rarely occurs.

7.2. Related and secondary tumors

Second tumors may occasionally arise in the irradiated areas. The latent period for development of the irradiation-induced cancers varies from 10 to 25 years.

8. Follow-up

8.1. General principles and objectives

The aims of follow-up in disease-free patients are early recognition of locoregional relapse, to allow for effective salvage treatment and early recognition of treatment complications (i.e. xerostomia and trismus) and their treatment. Follow-up appointments are scheduled on an individual basis determined by risk of occurrence. Periodical examinations should be carried out by head and neck surgeons along with radiation or medical oncologists and dentists, when the patient received combined radiotherapy and chemotherapy.

8.2. Suggested protocols

Local recurrence represents the main cause of treatment failure, followed by cervical neck metastasis and distant metastasis. The relative risk depends on tumor grade and stage, positive nodal disease, facial nerve involvement and extraparenchymal extension. Seventy per cent of local recurrences are observed within three years, except in cases of low grade and adenoid cystic histology. Consequently, patients should be strictly followed up during this period. According to the individual patient's characteristics a proper schedule could be as follows: first year posttreatment: every 1–3 months. Second year: every 2–4 months. Third year: every 3–6 months. Fourth and fifth years: every 4–6 months. After 5 years: every 12 months. All salivary gland malignancies require a follow-up period of 20 years for true measures of clinical outcome in particular in the case of low-grade tumors and adenoid cystic carcinomas. Yearly chest X-rays can be considered in high-grade tumors and in submandibular and minor salivary gland cancers on a type R basis, as these tumors are associated with frequent occurrence of pulmonary metastases. Chest CT scan should be performed in cases of local relapse, when salvage treatment is planned. TSH analysis could be indicated every 6–12 months, in case of neck irradiation.

Reviewers

David Pfister, MD, Memorial Sloan-Kettering Cancer Center, Division of Solid Tumor Oncology, 1275 York Avenue, NY 10021-6007, United States.

Robert L. Witt, MD, FACS, Ear, Nose and Throat Specialist, Head and Neck Surgery, Christiana Hospital, Medical Arts Pavilion 1, Suite #112, 4745 Stanton-Ogletown Road, Newark, DE 19713-2070, United States.

Conflict of interest

Lisa Licitra, MD has served as Advisory Board Member for Amgen, Glaxo Smith Kline, Merck Serono. The remaining authors have no conflict of interest to be disclosed.

References

- [1] WHO, World Health Organization. International statistical classification of diseases and related health problems, tenth revision, vol. 1. Geneva; 1992.
- [2] Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents, vol. VIII. IARC Scientific Publications No. 155. Lyon: IARC Press; 2002.
- [3] Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer* 2005;114:806–16.
- [4] Berrino F, De AR, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–1999: results of the EURO CARE-4 study. *Lancet Oncol* 2007;8:773–83.
- [5] Horn-Ross PL, Morrow M, Ljung BM. Diet and the risk of salivary gland cancer. *Am J Epidemiol* 1997;146:171–6.
- [6] Zheng W, Shu XO, Ji BT, Gao YT. Diet and other risk factors for cancer of the salivary glands: a population-based case–control study. *Int J Cancer* 1996;67:194–8.
- [7] Schneider AB, Lubin J, Ron E, et al. Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose–response relationships. *Radiat Res* 1998;149:625–30.
- [8] Coleman MP, Babb P, Daniecki P, et al. Cancer survival trends in England and Wales, 1971–1995: deprivation and NHS region. *Studies in medical and population subjects no. 61*. London: The Stationary Office. 1999.
- [9] Dong C, Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958–1996: a search for common mechanisms. *Br J Cancer* 2001;85:997–1005.
- [10] Goldstein AM, Yuen J, Tucker MA. Second cancers after medulloblastoma: population-based results from the United States and Sweden. *Cancer Causes Control* 1997;8:865–71.
- [11] Milan T, Pukkala E, Verkasalo PK, et al. Subsequent primary cancers after basal-cell carcinoma: a nationwide study in Finland from 1953 to 1995. *Int J Cancer* 2000;87:283–8.
- [12] Spitz MR, Tilley BC, Batsakis JG, Gibeau JM, Newell GR. Risk factors for major salivary gland carcinoma. A case–comparison study. *Cancer* 1984;54:1854–9.
- [13] Serraino D, Boschini A, Carrieri P, et al. Cancer risk among men with, or at risk of HIV infection in southern Europe. *AIDS* 2000;14:553–9.
- [14] Horn-Ross PL, Ljung BM, Morrow M. Environmental factors and the risk of salivary gland cancer. *Epidemiology* 1997;8:414–9.

- [15] Swanson GM, Burns PB. Cancers of the salivary gland: workplace risks among women and men. *Ann Epidemiol* 1997;7:369–74.
- [16] Barnes L, Eveson JW, Reichart P, Sidransky D. World Health Organization classification of tumours. In: Pathology and genetics of head and neck tumours. Lyon: IARC Press; 2005. p. 254–8.
- [17] Locati LD, Losa M, Perrone F, et al. C252 treatment relevant immunophenotyping of 139 Salivary Gland Carcinoma (SGCs). In: AACR-NCI-EORTC international conference on molecular targets and cancer therapeutics. 2005.
- [18] Dahse R, Driemel O, Schwarz S, et al. Epidermal growth factor receptor kinase domain mutations are rare in salivary gland carcinomas. *Br J Cancer* 2009;100:623–5.
- [19] Locati LD, Bossi P, Lo Vullo S, et al. Prognostic role of epidermal growth factor receptors 1 & 2, androgen receptor and kit in 111 salivary gland cancer. In: 7th international conference on head & neck cancer. 2008. p. S067.
- [20] Ettl T, Schwarz S, Kleinsasser N, et al. Overexpression of EGFR and absence of C-KIT expression correlate with poor prognosis in salivary gland carcinomas. *Histopathology* 2008;53:567–77.
- [21] Skalova A, Starek I, Vanecek T, et al. Expression of HER-2/neu gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence in-situ hybridization and immunohistochemistry. *Histopathology* 2003;42:348–56.
- [22] Dagrada GP, Negri T, Tamborini E, Pierotti MA, Pilotti S. Expression of HER-2/neu gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence in-situ hybridization and immunohistochemistry. *Histopathology* 2004;44:301–2.
- [23] Press MF, Pike MC, Hung G, et al. Amplification and overexpression of HER-2/neu in carcinomas of the salivary gland: correlation with poor prognosis. *Cancer Res* 1994;54:5675–82.
- [24] Andreadis D, Epivatianos A, Pouloupoulos A, et al. Detection of C-KIT (CD117) molecule in benign and malignant salivary gland tumours. *Oral Oncol* 2006;42:57–65.
- [25] Chandan VS, Wilbur D, Faquin WC, Khurana KK. Is c-kit (CD117) immunolocalization in cell block preparations useful in the differentiation of adenoid cystic carcinoma from pleomorphic adenoma? *Cancer* 2004;102:207–9.
- [26] Holst VA, Marshall CE, Moskaluk CA, Frierson Jr HF. KIT protein expression and analysis of c-kit gene mutation in adenoid cystic carcinoma. *Mod Pathol* 1999;12:956–60.
- [27] Jeng YM, Lin CY, Hsu HC. Expression of the c-kit protein is associated with certain subtypes of salivary gland carcinoma. *Cancer Lett* 2000;154:107–11.
- [28] Sorensen KB, Godballe C, de SK, Kroghdal A. Parotid carcinoma: expression of kit protein and epidermal growth factor receptor. *J Oral Pathol Med* 2006;35:286–91.
- [29] Glas AS, Hollema H, Nap RE, Plukker JT. Expression of estrogen receptor, progesterone receptor, and insulin-like growth factor receptor-1 and of MIB-1 in patients with recurrent pleomorphic adenoma of the parotid gland. *Cancer* 2002;94:2211–6.
- [30] Penner CR, Folpe AL, Budnick SD. C-kit expression distinguishes salivary gland adenoid cystic carcinoma from polymorphous low-grade adenocarcinoma. *Mod Pathol* 2002;15:687–91.
- [31] Edwards PC, Bhuiya T, Kelsch RD. C-kit expression in the salivary gland neoplasms adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and monomorphic adenoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;95:586–93.
- [32] Vered M, Braunstein E, Buchner A. Immunohistochemical study of epidermal growth factor receptor in adenoid cystic carcinoma of salivary gland origin. *Head Neck* 2002;24:632–6.
- [33] Glisson B, Colevas AD, Haddad R, et al. HER2 expression in salivary gland carcinomas: dependence on histological subtype. *Clin Cancer Res* 2004;10:944–6.
- [34] Nasser SM, Faquin WC, Dayal Y. Expression of androgen, estrogen, and progesterone receptors in salivary gland tumors. Frequent expression of androgen receptor in a subset of malignant salivary gland tumors. *Am J Clin Pathol* 2003;119:801–6.
- [35] Moriki T, Ueta S, Takahashi T, Mitani M, Ichien M. Salivary duct carcinoma: cytologic characteristics and application of androgen receptor immunostaining for diagnosis. *Cancer* 2001;93:344–50.
- [36] Andersen LJ, Therkildsen MH, Ockelmann HH, et al. Malignant epithelial tumors in the minor salivary glands, the submandibular gland, and the sublingual gland. Prognostic factors and treatment results. *Cancer* 1991;68:2431–7.
- [37] Ellis GL, Auclair PL, editors. Tumors of the salivary glands. AFIP atlas of tumor pathology, 4th series, fascicle 9. Silver Spring, MD: ARP Press; 2008.
- [38] Hocwald E, Yoo GH, Adsay V, et al. Prognostic factors in major salivary gland cancer. *Laryngoscope* 2001;111:1434–9.
- [39] Lima RA, Tavares MR, Dias FL, et al. Clinical prognostic factors in malignant parotid gland tumors. *Otolaryngol Head Neck Surg* 2005;133:702–8.
- [40] Batsakis JG, editor. Tumours of the head and neck. Clinical and pathological considerations. 2nd ed. Baltimore/London: Williams & Wilkins; 1982.
- [41] Waldron CA, el-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases. *Oral Surg Oral Med Oral Pathol* 1988;66:323–33.
- [42] Lopes MA, Kowalski LP, da Cunha SG, Paes de AO. A clinicopathologic study of 196 intraoral minor salivary gland tumours. *J Oral Pathol Med* 1999;28:264–7.
- [43] Kress E, Schulz HG, Neumann T. Diagnosis of diseases of the large salivary glands of the head by ultrasound, sialography and CT-sialography: a comparison of methods. *HNO* 1993;345–51 [German].
- [44] Kurabayashi T, Ida M, Ohbayashi N, Ishii J, Sasaki T. Criteria for differentiating superficial from deep lobe tumours of the parotid gland by computed tomography. *Dentomaxillofac Radiol* 1993;22:81–5.
- [45] Traxler M, Schurawitzki H, Ulm C, et al. Sonography of nonneoplastic disorders of the salivary glands. *Int J Oral Maxillofac Surg* 1992;21:360–3.
- [46] Spiro RH. Changing trends in the management of salivary tumors. *Semin Surg Oncol* 1995;11:240–5.
- [47] Casselman JW, Mancuso AA. Major salivary gland masses: comparison of MR imaging and CT. *Radiology* 1987;165:183–9.
- [48] Byrne MN, Spector JG, Garvin CF, Gado MH. Preoperative assessment of parotid masses: a comparative evaluation of radiologic techniques to histopathologic diagnosis. *Laryngoscope* 1989;99:284–92.
- [49] Weber AL. Imaging of the salivary glands. *Curr Opin Radiol* 1992;4:117–22.
- [50] Renehan A, Gleave EN, Hancock BD, Smith P, McGurk M. Long-term follow-up of over 1000 patients with salivary gland tumours treated in a single centre. *Br J Surg* 1996;83:1750–4.
- [51] Gal R. Fine needle aspiration of the salivary glands: a review. *Oper Tech Otolaryngol Head Neck Surg* 1996;7:323–6.
- [52] Riley N, Allison R, Stevenson S. Fine-needle aspiration cytology in parotid masses: our experience in Canterbury, New Zealand. *ANZ J Surg* 2005;75:144–6.
- [53] Ellis GL, Auclair PL. Tumors of the salivary glands, atlas of tumor pathology, 3rd series, fascicle 17. Washington, DC: Armed Forces Institute of Pathology; 1996. p. 135–6.
- [54] Guzzo M, Ferrari A, Marcon I, et al. Salivary gland neoplasms in children: the experience of the Istituto Nazionale Tumori di Milan. *Pediatr Blood Cancer* 2006;47:806–10.
- [55] Gnepp DR, Brandwein MS, Henley JD. Salivary and lacrimal glands. In: Gnepp DR, editor. Diagnostic surgical pathology of head and neck. Philadelphia: Saunders; 2001. p. 408.
- [56] UICC. UICC (International Union Against Cancer). In: Sobin LH, Wittekind Ch, editors. TNM classification of malignant tumours. 6th ed. New York, Chichester, Weinheim, Brisbane, Singapore, Toronto: Wiley-Liss; 2002.
- [57] Cermik TF, Mavi A, Acikgoz G, et al. FDG PET in detecting primary and recurrent malignant salivary gland tumors. *Clin Nucl Med* 2007;32:286–91.

- [58] Jackel MC, Reischl A, Huppert P. Efficacy of radiologic screening for distant metastases and second primaries in newly diagnosed patients with head and neck cancer. *Laryngoscope* 2007;117:242–7.
- [59] Chen I, Tu H. Pleomorphic adenoma of the parotid gland metastasizing to the cervical lymph node. *Otolaryngol Head Neck Surg* 2000;122:455–7.
- [60] Castle JT, Thompson LD, Frommelt RA, Wenig BM, Kessler HP. Polymorphous low grade adenocarcinoma: a clinicopathologic study of 164 cases. *Cancer* 1999;86:207–19.
- [61] Evans HL, Luna MA. Polymorphous low-grade adenocarcinoma: a study of 40 cases with long-term follow up and an evaluation of the importance of papillary areas. *Am J Surg Pathol* 2000;24:1319–28.
- [62] Witt RL. Major salivary gland cancer. *Surg Oncol Clin N Am* 2004;13:113–27.
- [63] Hickman RE, Cawson RA, Duffy SW. The prognosis of specific types of salivary gland tumors. *Cancer* 1984;54:1620–4.
- [64] Guzzo M, Andreola S, Sirizzotti G, Cantu G. Mucoepidermoid carcinoma of the salivary glands: clinicopathologic review of 108 patients treated at the National Cancer Institute of Milan. *Ann Surg Oncol* 2002;9:688–95.
- [65] Clode AL, Fonseca I, Santos JR, Soares J. Mucoepidermoid carcinoma of the salivary glands: a reappraisal of the influence of tumor differentiation on prognosis. *J Surg Oncol* 1991;46:100–6.
- [66] Nagao T, Sugano I, Ishida Y, et al. Salivary gland malignant myoepithelioma: a clinicopathologic and immunohistochemical study of ten cases. *Cancer* 1998;83:1292–9.
- [67] Di Palma S, Guzzo M. Malignant myoepithelioma of salivary glands: clinicopathological features of ten cases. *Virchows Arch A Pathol Anat Histopathol* 1993;423:389–96.
- [68] Hamper K, Lazar F, Dietel M, et al. Prognostic factors for adenoid cystic carcinoma of the head and neck: a retrospective evaluation of 96 cases. *J Oral Pathol Med* 1990;19:101–7.
- [69] Perzin KH, Gullane P, Clairmont AC. Adenoid cystic carcinomas arising in salivary glands: a correlation of histologic features and clinical course. *Cancer* 1978;42:265–82.
- [70] Tortoledo ME, Luna MA, Batsakis JG. Carcinomas ex pleomorphic adenoma and malignant mixed tumors. *Histomorphologic indexes. Arch Otolaryngol* 1984;110:172–6.
- [71] Lewis JE, Olsen KD, Sebo TJ. Carcinoma ex pleomorphic adenoma: pathologic analysis of 73 cases. *Hum Pathol* 2001;32:596–604.
- [72] Guzzo M, Di Palma S, Grandi C, Molinari R. Salivary duct carcinoma: clinical characteristics and treatment strategies. *Head Neck* 1997;19:126–33.
- [73] Barnes L, Rao U, Krause J, et al. Salivary duct carcinoma. Part I. A clinicopathologic evaluation and DNA image analysis of 13 cases with review of the literature. *Oral Surg Oral Med Oral Pathol* 1994;78:64–73.
- [74] Bhattacharyya N, Fried MP. Nodal metastasis in major salivary gland cancer: predictive factors and effects on survival. *Arch Otolaryngol Head Neck Surg* 2002;128:904–8.
- [75] Frankenthaler RA, Luna MA, Lee SS, et al. Prognostic variables in parotid gland cancer. *Arch Otolaryngol-Head Neck Surg* 1991;117:1251–6.
- [76] Spiro RH, Huvos AG. Stage means more than grade in adenoid cystic carcinoma. *Am J Surg* 1992;164:623–8.
- [77] Carrillo JF, Vazquez R, Ramirez-Ortega MC, et al. Multivariate prediction of the probability of recurrence in patients with carcinoma of the parotid gland. *Cancer* 2007;109:2043–51.
- [78] Chen AM, Garcia J, Lee NY, Bucci MK, Eisele DW. Patterns of nodal relapse after surgery and postoperative radiation therapy for carcinomas of the major and minor salivary glands: what is the role of elective neck irradiation? *Int J Radiat Oncol Biol Phys* 2007;67:988–94.
- [79] Fordice J, Kershaw C, El-Naggar A, Goepfert H. Adenoid cystic carcinoma of the head and neck: predictors of morbidity and mortality. *Arch Otolaryngol Head Neck Surg* 1999;125:149–52.
- [80] Triantafyllidou K, Dimitrakopoulos J, Iordanidis F, Koufogiannis D. Management of adenoid cystic carcinoma of minor salivary glands. *J Oral Maxillofac Surg* 2006;64:1114–20.
- [81] Seethala RR, Barnes EL, Hunt JL. Epithelial–myoepithelial carcinoma: a review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. *Am J Surg Pathol* 2007;31:44–57.
- [82] Strick MJ, Kelly C, Soames JV, McLean NR. Malignant tumours of the minor salivary glands—a 20 year review. *Br J Plast Surg* 2004;57:624–31.
- [83] Roh JL, Kim HS, Park CI. Randomized clinical trial comparing partial parotidectomy versus superficial or total parotidectomy. *Br J Surg* 2007;94:1081–7.
- [84] Leverstein H, van der Wal JE, Tiwari RM, van dW I, Snow GB. Surgical management of 246 previously untreated pleomorphic adenomas of the parotid gland. *Br J Surg* 1997;84:399–403.
- [85] Weber RS, Byers RM, Petit B, et al. Submandibular gland tumors. Adverse histologic factors and therapeutic implications. *Arch Otolaryngol Head Neck Surg* 1990;116:1055–60.
- [86] Stennert E, Kisner D, Jungehuelsing M, et al. High incidence of lymph node metastasis in major salivary gland cancer. *Arch Otolaryngol Head Neck Surg* 2003;129:720–3.
- [87] Scianna JM, Petruzzelli GJ. Contemporary management of tumors of the salivary glands. *Curr Oncol Rep* 2007;9:134–8.
- [88] Bell RB, Dierks EJ, Homer L, Potter BE. Management and outcome of patients with malignant salivary gland tumors. *J Oral Maxillofac Surg* 2005;63:917–28.
- [89] Armstrong JG, Harrison LB, Thaler HT, et al. The indications for elective treatment of the neck in cancer of the major salivary glands. *Cancer* 1992;69:615–9.
- [90] Ferlito A, Shaha AR, Rinaldo A, Mondin V. Management of clinically negative cervical lymph nodes in patients with malignant neoplasms of the parotid gland. *ORL J Otorhinolaryngol Relat Spec* 2001;63:123–6.
- [91] Ferlito A, Shaha AR, Rinaldo A. Surgical management of head and neck cancer: the next decade. *Acta Otolaryngol* 2001;121:772–6.
- [92] Gavilan C, Gavilan J. Five-year results of functional neck dissection for cancer of the larynx. *Arch Otolaryngol Head Neck Surg* 1989;115:1193–6.
- [93] Lingeman RE, Helmus C, Stephens R, Ulm J. Neck dissection: radical or conservative. *Ann Otol Rhinol Laryngol* 1977;86:737–44.
- [94] Molinari R, Cantu G, Chiesa F, Grandi C. Retrospective comparison of conservative and radical neck dissection in laryngeal cancer. *Ann Otol Rhinol Laryngol* 1980;89:578–81.
- [95] Borthne A, Kjelleveid K, Kaalhus O, Vermund H. Salivary gland malignant neoplasms: treatment and prognosis. *Int J Radiat Oncol Biol Phys* 1986;12:747–54.
- [96] Elkon D, Colman M, Hendrickson FR. Radiation therapy in the treatment of malignant salivary gland tumors. *Cancer* 1978;41:502–6.
- [97] Fitzpatrick PJ, Theriault C. Malignant salivary gland tumors. *Int J Radiat Oncol Biol Phys* 1986;12:1743–7.
- [98] Harrison LB, Armstrong JG, Spiro RH, Fass DE, Strong EW. Postoperative radiation therapy for major salivary gland malignancies. *J Surg Oncol* 1990;45:52–5.
- [99] McNaney D, McNeese MD, Guillaumondegui OM, Fletcher GH, Oswald MJ. Postoperative irradiation in malignant epithelial tumors of the parotid. *Int J Radiat Oncol Biol Phys* 1983;9:1289–95.
- [100] North CA, Lee DJ, Piantadosi S, Zahurak M, Johns ME. Carcinoma of the major salivary glands treated by surgery or surgery plus postoperative radiotherapy. *Int J Radiat Oncol Biol Phys* 1990;18:1319–26.
- [101] Catterall M, Errington RD. The implications of improved treatment of malignant salivary gland tumors by fast neutron radiotherapy. *Int J Radiat Oncol Biol Phys* 1987;13:1313–8.
- [102] Douglas JG, Laramore GE, Austin-Seymour M, et al. Neutron radiotherapy for adenoid cystic carcinoma of minor salivary glands. *Int J Radiat Oncol Biol Phys* 1996;36:87–93.

- [103] Garden AS, Weber RS, Ang KK, et al. Postoperative radiation therapy for malignant tumors of minor salivary glands, outcome and patterns of failure. *Cancer* 1994;73:2563–9.
- [104] Garden AS, El-Naggar AK, Morrison WH, et al. Postoperative radiotherapy for malignant tumors of the parotid gland. *Int J Radiat Oncol Biol Phys* 1997;37:79–85.
- [105] Griffin BR, Laramore GE, Russell KJ, Griffin TW, Eenmaa J. Fast neutron radiotherapy for advanced malignant salivary gland tumors. *Radiother Oncol* 1988;12:105–11.
- [106] Griffin TW, Pajak TF, Laramore GE, et al. Neutron vs photon irradiation of inoperable salivary gland tumors: results of an RTOG-MRC cooperative randomized study. *Int J Radiat Oncol Biol Phys* 1988;15:1085–90.
- [107] Krull A, Schwarz R, Heyer D, Timm H, Schmidt R. Results of neutron therapy in recurrent malignant salivary gland tumors in the head and neck area. *Strahlenther Onkol* 1995;171:265–71.
- [108] Saroja KR, Mansell J, Hendrickson FR, Cohen L, Lennox A. An update on malignant salivary gland tumors treated with neutrons at Fermilab. *Int J Radiat Oncol Biol Phys* 1987;13:1319–25.
- [109] Sessions RB, Lehane DE, Smith RJ, Bryan RN, Suen JY. Intra-arterial cisplatin treatment of adenoid cystic carcinoma. *Arch Otolaryngol* 1982;108:221–4.
- [110] Stelzer KJ, Laramore GE, Griffin TW, et al. Fast neutron radiotherapy. The University of Washington experience. *Acta Oncol* 1994;33:275–80.
- [111] Terhaard CH, Lubsen H, Van dT I, et al. Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. *Head Neck* 2004;26:681–92.
- [112] Radiation Therapy Oncology Group. Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. Medical Research Council. *Int J Radiat Oncol Biol Phys* 1993;27:235–40.
- [113] Douglas JG, Koh WJ, Austin-Seymour M, Laramore GE. Treatment of salivary gland neoplasms with fast neutron radiotherapy. *Arch Otolaryngol Head Neck Surg* 2003;129:944–8.
- [114] Bittner N, Koh WJ, Laramore GE, et al. Treatment of locally advanced adenoid cystic carcinoma of the trachea with neutron radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;72:410–4.
- [115] Schulz-Ertner D, Nikoghosyan A, Dindinger B, et al. Therapy strategies for locally advanced adenoid cystic carcinomas using modern radiation therapy techniques. *Cancer* 2005;104:338–44.
- [116] Barnett TA, Kapp DS, Goffinet DR. Adenoid cystic carcinoma of the salivary glands. Management of recurrent, advanced, or persistent disease with hyperthermia and radiation therapy. *Cancer* 1990;65:2648–56.
- [117] Gabriele P, Amichetti M, Orecchia R, Valdagni R. Hyperthermia and radiation therapy for inoperable or recurrent parotid carcinoma. A phase I/II study. *Cancer* 1995;75:908–13.
- [118] Locati LD, Guzzo M, Bossi P, et al. Lung metastasectomy in adenoid cystic carcinoma (ACC) of salivary gland. *Oral Oncol* 2005;41:890–4.
- [119] Laurie SA, Licitra L. Systemic therapy in the palliative management of advanced salivary gland cancers. *J Clin Oncol* 2006;24:2673–8.
- [120] Airoidi M, Brando V, Giordano C, et al. Chemotherapy for recurrent salivary gland malignancies: experience of the ENT Department of Turin University. *ORL J Oto-Rhino-Laryngol Relat Spec* 1994;56:105–11.
- [121] Alberts DS, Manning MR, Coulthard SW, Koopmann CFJ, Herman TS. Adriamycin/cis-platinum/cyclophosphamide combination chemotherapy for advanced carcinoma of the parotid gland. *Cancer* 1981;47:645–8.
- [122] Belani CP, Eisenberger MA, Gray WC. Preliminary experience with chemotherapy in advanced salivary gland neoplasms. *Med Pediatr Oncol* 1988;16:197–202.
- [123] Creagan ET, Woods JE, Rubin J, Schaid DJ. Cisplatin-based chemotherapy for neoplasms arising from salivary glands and contiguous structures in the head and neck. *Cancer* 1988;62:2313–9.
- [124] Dimery IW, Legha SS, Shirinian M, Hong WK. Fluorouracil, doxorubicin, cyclophosphamide, and cisplatin combination chemotherapy in advanced or recurrent salivary gland carcinoma. *J Clin Oncol* 1990;8:1056–62.
- [125] Jones AS, Phillips DE, Cook JA, Helliwell TR. A randomised phase II trial of epirubicin and 5-fluorouracil versus cisplatin in the palliation of advanced and recurrent malignant tumour of the salivary glands. *Br J Cancer* 1993;67:112–4.
- [126] Licitra L, Marchini S, Spinazze S, et al. Cisplatin in advanced salivary gland carcinoma. A phase II study of 25 patients. *Cancer* 1991;68:1874–7.
- [127] Licitra L, Cavina R, Grandi C, et al. Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma. A phase II trial of 22 patients. *Ann Oncol* 1996;7:640–2.
- [128] Posner MR, Ervin TJ, Weichselbaum RR, Fabian RL, Miller D. Chemotherapy of advanced salivary gland neoplasms. *Cancer* 1982;50:2261–4.
- [129] Schramm VLJ, Srodes C, Myers EN. Cisplatin therapy for adenoid cystic carcinoma. *Arch Otolaryngol* 1981;107:739–41.
- [130] Triozzi PL, Brantley A, Fisher S, et al. 5-Fluorouracil, cyclophosphamide, and vincristine for adenoid cystic carcinoma of the head and neck. *Cancer* 1987;59:887–90.
- [131] Venook AP, Tseng AJ, Meyers FJ, et al. Cisplatin, doxorubicin, and 5-fluorouracil chemotherapy for salivary gland malignancies: a pilot study of the Northern California Oncology Group. *J Clin Oncol* 1987;5:951–5.
- [132] Kaplan MJ, Johns ME, Cantrell RW. Chemotherapy for salivary gland cancer. *Otolaryngol Head Neck Surg* 1986;95:165–70.
- [133] Gilbert J, Li Y, Pinto HA, et al. Phase II trial of taxol in salivary gland malignancies (E1394): a trial of the Eastern Cooperative Oncology Group. *Head Neck* 2006;28:197–204.
- [134] van Herpen CM, Locati LD, Buter J, et al. Phase II study on gemcitabine in recurrent and/or metastatic adenoid cystic carcinoma of the head and neck (EORTC 24982). *Eur J Cancer* 2008;44:2542–5.
- [135] Hotte SJ, Winquist EW, Lamont E, et al. Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: a Princess Margaret Hospital phase II consortium study. *J Clin Oncol* 2005;23:585–90.
- [136] Glisson BS, Blumenschein G, Francisco M, et al. Phase II trial of gefitinib in patients with incurable salivary gland cancer. In: ASCO Annual Meeting Proceedings, vol. 23. 2005. p. 508s.
- [137] Locati LD, Bossi P, Perrone F, et al. Cetuximab in recurrent and/or metastatic salivary gland carcinomas: a phase II study. *Oral Oncol* 2009;45:574–8.
- [138] Agulnik M, Cohen EW, Cohen RB, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. *J Clin Oncol* 2007;25:3978–84.
- [139] Haddad R, Colevas AD, Krane JF, et al. Herceptin in patients with advanced or metastatic salivary gland carcinomas. A phase II study. *Oral Oncol* 2003;39:724–7.
- [140] Alcedo JC, Fabrega JM, Arosemena JR, Urrutia A. Imatinib mesylate as treatment for adenoid cystic carcinoma of the salivary glands: report of two successfully treated cases. *Head Neck* 2004;26:829–31.
- [141] Faivre S, Raymond E, Casiraghi O, Temam S, Berthaud P. Imatinib mesylate can induce objective response in progressing, highly expressing KIT adenoid cystic carcinoma of the salivary glands. *J Clin Oncol* 2005;23:6271–3.
- [142] Argiris A, Goldwasser MA, Burtneis B, et al. A phase II trial of PS-341 (bortezomib) followed by the addition of doxorubicin at progression in incurable adenoid cystic carcinoma of the head and neck: An Eastern Cooperative Oncology Group study. ASCO Annual Meeting Proceedings Part I, vol. 24, no. 18S (June 20 Supplement). *J Clin Oncol* 2006;5573.

- [143] Rugo HS, Herbst RS, Liu G, et al. Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: pharmacokinetic and clinical results. *J Clin Oncol* 2005;23: 5474–83.
- [144] Helmus C. Subtotal parotidectomy: a 10-year review (1985–1994). *Laryngoscope* 1997;107:1024–7.
- [145] Stevens KL, Hobsley M. The treatment of pleomorphic adenomas by formal parotidectomy. *Br J Surg* 1982;69:1–3.
- [146] Myssiorek D, Ruah CB, Hybels RL. Recurrent pleomorphic adenomas of the parotid gland. *Head Neck* 1990;12:332–6.
- [147] Simpson JR. Cancer of the salivary glands. In: Perez CA, Brady LW, editors. *Radiation oncology*. Philadelphia: Lippincott; 1987. p. 513–28.
- [148] McNeese MD, Fletcher GH. Tumors of the major and minor salivary glands. *Radiation therapy of head and neck cancer*. Berlin, Heidelberg, New York, London, Paris, Tokyo: Springer-Verlag; 1989. p. 181–96.
- [149] Moss WT. The salivary glands. In: Moss' radiation oncology: rationale, technique, results. 7th ed. Mosby; 1994. p. 121–31.

Biographies

Marco Guzzo is assistant surgeon at Otolaryngology Unit at Fondazione IRCCS “Istituto Nazionale dei Tumori” in Milan, Italy.

Laura D. Locati is assistant physician at Head and Neck Medical Oncology Unit at Fondazione IRCCS “Istituto Nazionale dei Tumori” in Milan, Italy.

Franz J. Prott is head of the Radiotherapy Department in a radiologic private institution in Wiesbaden. Furthermore he is professor for radiology at the University of Münster/Germany.

Gemma Gatta is head of the Evaluative Epidemiology Unit at Fondazione IRCCS “Istituto Nazionale dei Tumori” in Milan, Italy. She is also the principal investigator of the European Commission funded project ‘Rare cancer surveillance in Europe’.

Mark McGurk is head of Oral & Maxillofacial Surgery Department at Guy's and St. Thomas' Hospital Trust London.

Lisa Licitra is head of the Head and Neck Medical Oncology Unit at Fondazione IRCCS “Istituto Nazionale dei Tumori” in Milan, Italy. She is also ESTRO (European Society for Therapeutic Radiology and Oncology) honorary member.

START METHODOLOGY

START is an evidence-based instrument. This means that statements on main clinical "options" are codified and accompanied by a codified "type of basis", as follows, according to a classification originally devised for the **START** project. The **START** Editorial team is glad to receive comments on this (please, address them to the [START Secretariat](#)). The background has been detailed in [Ann Oncol 1999; 10: 769-774](#).

TYPE of OPTION

START provides the following diagnostic and treatment options. The "standard" and the "individualised" options are coupled with ranked types of basis,

● **STANDARD ("standard", "recommended" [or "not recommended"])**

This can be considered a conventional choice for the average patient.

● **INDIVIDUALIZED ("suitable for individual clinical use")**

This is not a standard option, but it can be a reasonable choice for the individual patient. The patient should be informed that the option is not standard and the decision must be shared with the patient.

● **INVESTIGATIONAL ONLY ("investigational")**

This is something which, in principle, can be offered to the patient only within a clinical study.

TYPE of BASIS for available options

START provides an appropriate basis for each clinical option. Types of basis are ranked in five levels.

● **"TYPE C basis" (General consensus)**

There is a widespread consolidated consensus. Randomised trials have not been carried out or have been inadequate, but the issue is settled without major controversy: currently, no (further) experimental evidence is felt to be needed

● **"TYPE 1 evidence" (Randomised trial(s) available, strong evidence)**

Consistent results have been provided by more than one randomised trials, and/or a reliable meta-analysis was performed. In some instances, one randomised trial can be considered sufficient to support this type of evidence. Further confirmatory trials do not seem necessary.

● **"TYPE 2 evidence" (Randomised trial(s) available, weak evidence)**

One or more randomised trials have been completed, but the evidence they provide is not considered definitive (their results are not consistent, and/or they are methodologically unsatisfactory, etc.). Some controlled evidence has therefore been provided, but confirmatory trials would be desirable.

● **"TYPE 3 evidence" (External controlled comparisons available)**

Evidence is available from non-randomised studies, with external controls allowing comparisons. Some uncontrolled evidence has therefore been provided, but trials would be desirable.

● **"TYPE R basis" (Rational inference)**

Little or no direct evidence from clinical studies is available. Yet clinical conclusions can be rationally inferred from available data and knowledge (e.g. by rationally combining pieces of information from published studies and observations; for a rare neoplasm, or presentation, through analogy with a related, more common tumour, or presentation; etc.). The inference can be more or less strong, and trials may, or may not, be desirable (although sometimes unfeasible).