Radiation therapy for parotid gland tumors: long term data from a large single Institution experience.

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Abstract

Background

parotid gland tumors (PGT) are rare entities. Surgery plays a key role in the treatment of PGT, post-operative radiation therapy (PORT) is necessary in order to reduce the recurrence rates. Histological subtypes (HS) and differentiation grade (DG) are extremely various and so is their clinical behavior. This large retrospective paper aims to identify factors associated with treatment toxicity, loco-regional recurrence and survival in patients with PGT.

Methods

152 patients with PGT were treated with surgery and PORT at our Department between 1992 and 2019. Medical records reported patients, disease and treatment characteristics, acute and late toxicities. Loco-regional control (LC), overall survival (OS), cancer specific survival (CSS) and metastases free survival (MFS) were analyzed as outcome endpoints.

Results

severe (> G2) acute mucositis and dermatitis were 20% and 10% respectively. Severe acute mucositis was reported more frequently in patients treated with > 60 Gy on tumor bed (p = .001) and in patients treated also on the neck (p = .006). The most frequent reported late toxicities were skin fibrosis (any grade) and xerostomia (≤ G2), 67% and 50% respectively. LC, OS, CSS and MFS rates at 10 year were respectively 67, 64, 76, 80 (%). Better Karnofsky Performance Status at diagnosis, more favorable HS, well differentiated PGT, less advanced pathological stage and the absence of nodal disease are related with better survival outcomes.

Conclusion

our data are in line with current literature: high grade and locally advanced PGT have the worst prognosis. Clinical trials are needed to define better treatment strategies for PGT.

Background

Parotid gland tumors (PGT) are rare entities. The incidence ranges between 0.5 and 2% of all malignancies; they represent about 6% of all head and neck cancers [1, 2]. PGT, as other salivary gland cancers (SGC), can occur in people of any age but the incidence increases in older people. The average age at diagnosis is about 60 years [3]; yet, these malignancies are not exceptional in younger ages. PGT are the most frequent salivary gland lesions, they are benign in about 70% of the cases and often arise from the superficial lobe of the gland [4, 5]. PGT histological subtypes (HS) and cytological differentiation grade (DG) are extremely variable, as their clinical behavior.

Mucoepidermoid carcinoma (MEC) is one of the most common HS (about 30% of the cases). MEC is usually well differentiated, slow growing and with a good prognosis. Yet, some cases are poorly differentiated, aggressive, with tendency to loco-regional recurrence and distant metastases (particularly in males and in older ages). The risk of nodal metastases increases with increasing grade (3.3% in low grade and 34% in high grade MEC [6, 7]). Adenoid cystic carcinoma (AdCC) consists of 10% of all PGT and is more common in the submandibular gland. AdCC is locally aggressive with relapses even many years after primary treatment. Perineural invasion is the hallmark of AdCC: the disease can reach the skull base along the cranial nerves. Due to its neurotropism, facial nerve palsy is one of the most frequent clinical presentation of AdCC [6]. Nodal dissemination is unlikely whereas distant metastases (lung) are not

rare. Acinic cell carcinoma (ACC) is another common HS of PGT. ACC is usually well differentiated and has an excellent long-term prognosis. Salivary duct carcinoma (SDC) and squamous cell carcinoma (SCC) are rare and aggressive malignancies [6]. Lastly, pleomorphic adenoma (PA) is the most frequent lesion of the parotid gland. It is a benign entity, yet often multinodular and it can recur many years after the primary treatment and can cause facial nerve palsy. Furthermore, the risk of malignant transformation of PA is about 3% and carcinoma ex-pleomorphic adenoma (CA ex PA) are typically poorly differentiated and locally aggressive [6].

Metastases from PGT are rare and they are typically found in liver, lung and bone. Patients more at risk of developing secondary lesions are those with poorly differentiated carcinomas. Moreover, PGT can develop metastases many years after the primary diagnosis [8]. Hence, life-long follow up (FU) is mandatory, at least for high risk patients [9].

To our knowledge, to date there are no clear recognized risk factors for PGT. A Canadian case-control study suggested that some lifestyle factors (smoking, obesity, alcohol consumption, processed meat and occupational exposure to radiation as well as previous radiation therapy for another head and neck cancer) may contribute to the develop of PGT [10]. Since the rarity of the disease a multidisciplinary treatment approach is mandatory, especially for locally advanced cancer. When feasible, surgery is recommended in almost any case [11]. Post operative radiation therapy (PORT) is performed in order to reduce the risk of loco regional relapse [11].

The aim of the present retrospective analysis on a large single institution series is to describe the pattern of failure of all PGT HS treated with PORT and to identify factors associated with treatment toxicity, loco-regional recurrence and survival.

Methods

Between July 1992 and May 2019, a total of 152 patients with PGT were treated with PORT at the Brescia University Radiation Oncology Department. Data regarding patients' characteristics, clinical and histo-pathological features and treatment modalities were obtained from the retrospective review of medical records. PGT were retrospectively restaged according to the current TNM classification [12].

Main treatment related toxicities were recorded and subsequently analyzed: dysphagia, xerostomia, mucositis, dermatitis and tissue sclerosis, trismus. All the toxicities were defined as acute if diagnosed up to 3 months from the end of radiation therapy and were considered late if detected later. All the toxicities were retrospectively re-evaluated using current NCI-CTCAE scale (v. 5.0–2017)[13].

We analyzed loco-regional control (LC), overall survival (OS), cancer specific survival (CSS) and metastases free survival (MFS) as outcome endpoints. Time of occurrence of all the events was measured from the date of primary surgery. Local failures included local or nodal relapses. Two-year, five-year and ten-year estimates of the probability of LC, OS, CSS and MFS were calculated using the Kaplan-Meier method, with comparisons among groups performed with two-sided log-rank tests [14]. A Cox proportional hazards model was planned to find independent predictors of loco-regional recurrence and survival. Univariate analysis led the selection of variables to consider as predictors. All tests were two tailed and the probability value of less than .05 was considered statistically significant. Gathered data were analyzed using SPSS ® software [15].

Results

Patients and disease characteristics

Complete description of patients and disease characteristics is available in Table 1. Briefly, patients characteristics were well balanced in terms of gender and smoke habit; patients were usually not alcohol abusers and they were in good clinical conditions at the time of diagnosis: Karnofsky Performance Status (KPS) was 100 – 90 in more than 60% of cases. Age at presentation was variable, ranging from 12 to 87 years (mean 57). Several HS were reported: the most frequent ones were MEC (18%), ACC (13%) and not otherwise specified adenocarcinoma (NOS AC) (11%); in our series 11% of the patients were treated with PORT for recurrent or persistent PA. DG was available in only 121 patients: 67 cases were classifiable as low grade (LG) tumors, 54 cases as high grade (HG). PA was arbitrarily considered as LG tumor due to its benign behavior.

Table 1
Patients and PGT characteristics at baseline.

Characteristics	
Age	Mean 57 y (range 12–87)
Age (classes)	113 (74)
< 70 y	39 (26)
≥ 70 y	
Sex	81 (53)
M	71 (47)
F	
Smoke	91 (60)
No	61 (40)
Yes	
KPS	96 (63)
100 – 90	52 (34)
80 – 70	4 (3)
60 or less	
Histological subtypes	20 (13)
ACC	28 (18)
MEC	15 (10)
AdCC	14 (9)
SDC	17 (11)
NOS AC	10 (7)
CA ex PA	7 (5)
SCC	16 (11)
PA	25 (16)
Others	

Note: all data are presented as No (%) unless otherwise indicated. KPS = Karnofsky Performance Status, ACC = acinic cell carcinoma, MEC = mucoepidermoid carcinoma, AdCC = adenoid cystic carcinoma, SDC = salivary duct carcinoma, NOS AC = not otherwise specified adenocarcinoma, CA ex PA = carcinoma ex pleomorphic adenoma, SCC = squamous cell carcinoma, PA = pleomorphic adenoma, LG = low grade, HG = high grade.

* Cytological grade was available in 121 patients.

^ Pathological stage includes 136 patients with the exclusion of pleomorphic adenomas.

° Correct definition of margin status was available in 126 patients.

Characteristics	
Differentiation grade*	67 (55)
LG	54 (45)
HG	
Pathological stage^	92 (68)
I-III	44 (32)
IVa-IVb	
Margins°	56 (44)
R0/R close	62 (49)
R1	8 (7)
R2	

Note: all data are presented as No (%) unless otherwise indicated. KPS = Karnofsky Performance Status, ACC = acinic cell carcinoma, MEC = mucoepidermoid carcinoma, AdCC = adenoid cystic carcinoma, SDC = salivary duct carcinoma, NOS AC = not otherwise specified adenocarcinoma, CA ex PA = carcinoma ex pleomorphic adenoma, SCC = squamous cell carcinoma, PA = pleomorphic adenoma, LG = low grade, HG = high grade.

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All patients underwent upfront surgery with total or partial parotidectomy at surgeon's discretion. The review of the pathological report showed very advanced disease (stage IVA or IVB) in about 30% of the cases (PA was excluded from the pathological staging system). Loco-regional lymph-nodes were involved in 37 patients: all of them underwent neck dissection (classical or modified at otolaryngologist's discretion). Correct definition of residual margin took a large part of the pathological report reviewing: unfortunately data about possible microscopic residual disease were unreliable or not available in 26 patients even after the revision by our Pathology Department. Due to this unreliability those cases were excluded from further statistical analysis involving margin status. Margin was defined as close when tumor was identified at more than 1 mm but less than 5 mm from it and was defined as involved when the distance was 1 mm or less.

Characteristics of RT

All patients underwent PORT. In all the cases radiation therapy (RT) target included the parotid bed with a median dose of 60 Gy (range 46–70 Gy): in 9 cases the dose required was 70 Gy (or bioequivalent) due to the presence of macroscopical

residual disease after surgery. Irradiation of the ipsilateral neck levels was omitted in more than half of the patients with malignant tumors. When performed, RT on the neck lymph-nodes was categorized as PORT (after neck dissection), radical (when macroscopical disease was still present in the neck lymph-nodes) or precautional (on a not violated neck). RT median dose on the neck was 51.2 Gy (range 48–70 Gy); neck levels submitted to RT were selected at radiation oncologist discretion. All the details of radiation treatment are shown in Table 2.

Table 2
Radiation therapy features.

Characteristic	
RT on parotid bed	9 (6)
Radical (70 Gy or bioequivalent)	141 (94)
Post operative	
RT on ipsilateral neck levels	77 (51)
No	7 (5)
Radical (70 Gy or bioequivalent)	34 (22)
Post operative	34 (22)
Precautional	
RT dose prescribed on parotid bed	89 (59)
≤ 60 Gy (2 Gy/fraction)	63 (41)
> 60 Gy (2 Gy/fraction)	
RT technique	11 (7)
2D RT	112 (74)
3DCRT	12 (8)
IMRT	4 (3)
VMAT	13 (8)
Tomotherapy	

Note: all data are presented as No (%) unless otherwise indicated. RT = radiation therapy, 2D RT = two dimensional radiation therapy, 3DCRT = three dimensional conformal radiation therapy, IMRT = intensity modulated radiation therapy, VMAT = volumetric modulated arc therapy.

Acute and late toxicities

Acute toxicities are described in Table 3. Mucositis and dermatitis were the most frequent reported acute toxicities. Mucositis of any grade was reported in 92% and dermatitis in 97% of the patients. Severe skin or mucosal toxicities were the following: >G2 mucositis was reported in almost 20% of the cases while > G2 dermatitis was seen in about 10%. Furthermore, 49% of the patients reported ≤ G2 dysphagia and hospitalization or feeding tube was necessary in 2 patients. Sixty-four patients (42%) reported ≤ G2 xerostomia. RT dose was related to the grade of acute toxicity. G3 mucositis was reported in only 10% of the patients treated on tumor bed with 60 Gy or less while this percentage grew up to 33% in patients treated with more than 60 Gy ($p = .001$). Similarly, G1-G2 xerostomia rates increased from 34 to 54% ($p = .013$) and G1-G2 dysphagia reached 56% (versus 44%, p = ns) when RT dose to the target was in excess of 60 Gy. RT

volumes were also related to the onset of acute toxicities: >G2 mucositis increased from 12–28% in patients treated also on the neck (p = .006).

Table 3
Acute toxicities.

Characteristic	
Mucositis	12 (8)
None	60 (39)
G1	50 (33)
G2	30 (20)
G3	
Neck swelling	129 (85)
None	23 (15)
G1	
Dermatitis	4 (3)
None	71 (47)
G1	63 (41)
G2	14 (9)
G3	
Dysphagia	76 (50)
None	42 (28)
G1	32 (21)
G2	2 (1)
G3	
Xerostomia	88 (58)
None	56 (37)
G1	8 (5)
G2	
Note: all data are presented as No (%).	

Late toxicities are reported in Table 4: adequately prolonged FU (median 52 months) was available in 129 patients. The most frequent late toxicity reported was skin fibrosis (any grade) diagnosed in 67% of the patients. Almost 90% of the patients did not report any kind of late dysphagia while late G1-G2 xerostomia was reported in slightly more than half of the patients. As well as for acute toxicities, RT dose was linked to the grade of late toxicity but the correlation between RT dose and late toxicity reached statistical significance only for xerostomia: G1-G2 cases increased from 43–69% when RT dose on tumor bed was > 60 Gy (p = .003). No statistically significant correlation between RT volumes or techniques and late toxicities was found.

Table 4
Late toxicities.

Characteristic	
Skin fibrosis	43 (33)
None	76 (59)
G1	8 (6)
G2	2 (2)
G3	
Neck swelling	94 (73)
None	35 (27)
G1	
Trismus	115 (89)
None	13 (10)
G1	1 (1)
G2	
Dysphagia	115 (89)
None	11 (9)
G1	3 (2)
G2	
Xerostomia	60 (46)
None	59 (46)
G1	10 (8)
G2	
Note: all data are presented as No (%).	

Patterns of failure: local control

Actuarial LC rates at 2, 5 and 10 year were 79%, 70% and 67% (median LC was not reached).

Univariate analysis showed that better KPS at diagnosis, more favorable HS, well differentiated PGT, less advanced pathological stage and the absence of nodal disease are related with better LC. Multivariate analysis confirmed DG and pathological stage as independent predictors of better LC.

Patterns of failure: overall, cancer specific and metastases free survival

Actuarial OS rates at 2, 5 and 10 year were 90%, 74% and 64% respectively with a median OS of more than 22 years.

Actuarial CSS rates at 2, 5 and 10 years were 93%, 82% and 76% respectively (median CSS was not reached).

Actuarial MFS rates at 2, 5 and 10 years were 88%, 83% and 80% respectively (median MFS was not reached).

Univariate analysis revealed that better KPS at diagnosis, more favorable histological subtype, higher DG, less advanced pathological stage and absence of nodal disease are related with better OS. Subsequent multivariate regression analysis confirmed only low grade disease and less advanced pathological stage as predictors of better survival. Figure 1 depicts OS according to DG.

Univariate analysis showed that better KPS at diagnosis, more favorable histological subtype, higher DG, less advanced pathological stage and the absence of nodal disease induced better CSS rates. Multivariate analysis confirmed only DG and the nodal disease as predictors of better CSS. Figure 2 shows the relationship between CSS and HS.

Univariate analysis showed that better KPS at diagnosis, more favorable histological subtype, higher DG, less advanced pathological stage and the absence of nodal disease are related with better MFS rates. Multivariate analysis confirmed that only the absence of nodal disease has a favorable impact on MFS.

Table 5 and Table 6 show the details of univariate and multivariate analysis.

Table 5
Univariate analysis for patients and disease characteristics and treatment outcomes.

Characteristics		*LC*		*p*		*OS*		*p*		*CSS*		*p*		*MFS*		*p*
	2 y	*5 y*	*10 y*		*2 y*	*5 y*	*10 y*		*2 y*	*5 y*	*10 y*		*2 y*	*5 y*	*10 y*	
Crude rate	79	70	67	-	90	74	64	-	93	82	76	-	88	83	80	-
KPS at diagnosis KPS > 80 KPS ≤ 80	84 70	78 54	78 46	.001	98 77	86 52	79 36	.000	98 84	90 67	87 54	.000	96 84	90 68	90 50	.000
Histology ACC MEC AdCC SDC NOS ACC CAexPA SCC PA Others	100 83 77 47 63 70 67 76 92	89 78 68 28 54 58 67 76 77	89 78 54 19 54 58 67 76 77	.003	100 89 93 71 81 100 71 100 96	100 73 79 40 55 67 43 100 83	100 68 63 32 40 44 14 100 70	.000	100 89 93 84 87 100 83 100 96	100 76 86 47 66 87 62 100 92	100 76 75 37 58 58 62 100 77	.005	100 95 82 56 63 100 67 100 96	100 95 82 34 55 100 67 100 84	100 95 71 22 55 100 67 100 84	.000

Characteristics		*LC*		*p*		*OS*		*p*		*CSS*		*p*		*MFS*		*p*
DG	87	84	81	.000	97	89	82	.000	97	95	95	.000	95	95	91	.000
LG	63	47	43		80	48	38		88	58	49		74	62	57	
HG																
Pathological stage	88	81	81	.000	98	86	77	.000	98	92	87	.000	92	89	89	.000
Stage I-III	60	41	31		71	42	27		82	55	42		71	57	43	
Stage IV																
Nodal disease	90	80	78	.000	97	82	75	.000	98	91	86	.000	96	93	91	.000
pN0	50	38	32		71	42	27		79	49	39		58	43	37	
pN+																

Note: all data are expressed as %. KPS = Karnofsky Performance Status, ACC = acinic cell carcinoma, MEC = mucoepidermoid carcinoma, AdCC = adenoid cystic carcinoma, SDC = salivary duct carcinoma, NOS AC = not otherwise specified adenocarcinoma, CA ex PA = carcinoma ex pleomorphic adenoma, SCC = squamous cell carcinoma, PA = pleomorphic adenoma, DG = differentiation grade, LG = low grade, HG = high grade.

Table 6
Multivariate analysis for prognostic factors.

Variable	*Outcome*	*HR*	*CI (95 %)*	*p*
Differentiation grade: HG vs. LG	LC	3.079	1.238–7.659	.016
	OS	2.632	1.207–5.743	.015
	CSS	5.67	1.566–20.534	.008
Pathological stage: stage IV vs stage I-III	LC	3.122	1.391–7.011	.006
	OS	4.278	2.066–8.86	.000
Pathological stage: pN+ vs pN0	CSS	3.393	1.377–8.357	.007
	MFS	8.83	3.278–23.787	.000

Note: HG = high grade, LG = low grade, LC = local control, OS = overall survival, CSS = cancer specific survival, MFS = metastasis free survival, HR = hazard ratio, CI = confidence interval.

Discussion

Current therapeutic approach to PGT includes surgery (as radical as possible) and radiotherapy [10, 11]. As already mentioned, PGT are a group of rare and extremely heterogeneous diseases. Prognosis of patients in terms of LC and survival outcomes depends on several clinical and pathological features and can be very different. It is then mandatory to identify features possibly simplifying the choice of the best treatment option for every patient.

In an historic paper by Theriault (1986) [16], 10 year recurrence-free survival rates were 62% and 22% respectively, in patients treated with surgery and in those treated with surgery + PORT. Cause-specific survival was independently related with these prognostic factors: histology, tumor stage, lymph node metastases, age and damage to the facial nerve. More recently, Chen et al. (2007) [17] reported that loco-regional recurrence rate for patients with high risk PGT receiving exclusive surgery could be as high as 63% in the subgroups of patients that presented at least one of the following

characteristics: lymph-nodal metastases, high grade disease, stage T3-T4 disease, positive margins [17]. The authors concluded that PORT should be carefully considered for patients with high risk PGT. Another paper by Mendenhall et al. (2005) reported that surgery + PORT induced better LC at multivariate analysis when compared with RT alone [18] in patients with high risk disease (defined as the presence of close or positive resection margins, high grade disease, lymph-nodal metastases, perineural or endothelial-lined space invasion).

Our data are consistent with those present in literature and confirm the importance of the prognostic factors mentioned before. In our series, 10-year LC was 67% for patients treated with surgery + PORT: pathological stage and DG were confirmed as independent predictors of loco-regional recurrence. Results in terms of survival outcomes were also comparable. Worst survival rates are in fact related with high grade and locally advanced disease. Both advanced T stage and nodal involvement impact negatively on survival. Multivariate analyses did not confirm HS as predictors of survival most likely due to the small numbers of patients in each subgroup. Nevertheless, survival outcomes of subgroups are consistent with current literature data [6].

In our series, 10-year MFS was 80%. Univariate analysis confirmed the worst MFS rates linked to the aggressive HS (SDC and NOS AC), to HG and to locally advanced disease. Furthermore, in our cases the presence of nodal disease resulted as the only predictor of MFS at multivariate analysis. Treatment strategies for patients diagnosed with distant metastases were also variable: chemotherapy (especially doxorubicin based), surgery, RT or a combination of treatments was preferred at clinician's discretion. A wait-and-see strategy was chosen in two cases.

As expected, the time lapse from the first diagnosis to the time of appearance of metastases was extremely wide ranging from 1 month to almost 15 years (median time 17 months) and it well represents the different biological behaviors of different PGT. Similarly, CSS after the diagnosis of distant metastases was equally various and ranged from 0 to 73 months. Pattern of distant failures are presented in Fig. 3.

Given the recent extraordinary increase in the use of stereotactic ablative radiotherapy (SABR) in many different clinical settings, we reviewed the medical records of these patients to determine if, retrospectively, some of them could have benefitted from this approach. In fact, PGT are known for their relatively slow growing distant metastases and lungs, liver and bones are the most frequent sites of secondary spread (and this is confirmed in our series) [8]. At least theoretically, this represents an optimal biological rationale for treating these patients with SABR because slow growing diseases are more sensitive to high doses per fraction [19] and contemporarily lungs, liver and bones are common sites of SABR for other primary or secondary tumors [20, 21, 22] in many radiation oncology departments. Moreover, recent data from the SABR-COMET [23, 24] by Palma and colleagues, although not including PGT in their trial, demonstrated a survival benefit in patients treated with SABR to oligometastases compared to palliative standard of care. In our series, only a few patients could have benefitted from SABR because in most cases the secondary spread was diagnosed at a relative late stage and therefore polimetastatic and the patients underwent chemotherapy (upfront or at further progression) with unsatisfying results.

Unfortunately, to date there are not enough data to sustain the hypothesis that some selected patients, if subjected to a more intensive follow up, could have had a survival benefit with SABR but in our opinion this approach should be further examined in the next future due to his strong biological rationale. Current international guidelines recommend life-long FU for all the patients treated for PGT and, maybe, for patients at high risk a more intensive radiological FU could determine a survival benefit.

No statistically significant correlation was found among PORT techniques, volumes or total dose and survival outcomes. To the best of our knowledge, also this is consistent with present literature data.

The most serious adverse event of PGT treatment is probably facial nerve paralysis which is often temporary but can sometimes be permanent (to our knowledge it is still unclear whether PORT could worsen the post-surgical recovery or not) [25]. Other more or less common side effects of treatment included Frey's syndrome (i.e. sweating and flushing in the preauricular area), xerostomia, trismus, dermatitis/fibrosis, dysgeusia, dysphagia, radiation-induced hearing impairment, bone necrosis [26, 27, 28]. In our series, radiation treatment courses were generally well tolerated. In fact, the only severe (≥ G3) toxicities reported were acute mucositis and dermatitis (20% and 9% respectively). PORT total dose only affected acute mucositis and acute/late xerostomia whereas no statistically significant correlation was found between PORT volumes or techniques and toxicities.

Of course, we are well aware of the main limitations of this study: first of all, the lack of a comparison group treated with surgery only; secondly, several surgical data, especially those belonging to patients treated in the early 90's, were not available: more details regarding the surgical handling of the neck would be extremely interesting in a paper like this, as also concomitant chemotherapy indications and administration would. Yet, we think that this paper can still add some important information to the current literature about radiation therapy in parotid gland cancer, since it is, to our knowledge, one of the largest single Institution experience.

Conclusions

In conclusion, PGT are a mixture of different diseases with different behavior. Since the rarity and the heterogeneity of PGT, multidisciplinary approach should be mandatory to better select patients that could benefit from different treatment strategies. Surgery still plays a key role in these diseases whereas PORT should be strongly considered for patients with high risk of loco regional recurrences. This paper confirms that pathological stage and DG are the main prognostic factors in PGT and patients with locally advanced and/or poorly differentiated diseases should be encouraged to receive PORT. Unfortunately, a significant fraction of these patients (about 20% in this series, which is in line with current literature) dies due to systemic progression (particularly to the lungs): PGT are often chemotherapy-resistant diseases due to their slow evolution and the role of molecular targeted therapies should be further investigated. To date, to the best of our knowledge there is no strong evidence for target therapy in PGT [29]. Nevertheless, many oncologists suggest molecular analyses (for example next-generation sequencing) for patients with metastatic PGT: this could help finding some HS carrying driver mutations potentially treatable with new drugs. Similarly, trials considering more intensive follow up and SABR for oligometastatic patients should be considered.

Abbreviations

PGT: parotid gland tumors, PORT:post-operative radiation therapy, HS:Histological subtypes, DG:differentiation grade, LC:loco-regional control, OS:overall survival, CSS:cancer specific survival, MFS:metastases free survival, KPS:Karnofsky Performance Status, SGC:salivary gland cancers, MEC:mucoepidermoid carcinoma, AdCC:adenoid cystic carcinoma, ACC:acinic cell carcinoma, SDC:salivary duct carcinoma, SCC:squamous cell carcinoma, PA:pleomorphic adenoma, CA ex PA:carcinoma ex-pleomorphic adenoma, FU:follow up, NOS AC:not otherwise specified adenocarcinoma, LG:low grade, HG:high grade, RT:radiation therapy, SABR:stereotactic ablative radiotherapy.

Declarations

The study has been properly submitted to the local ethical committee (Spedali Civili di Brescia, Ethical Committee, reference number: NP 4146).

Consent for publication:

not applicable.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions:

- Study concepts: DT
- Study design: LT, PB
- Data acquisition: MLB, AG, GC, AA
- Quality control of data and algorithms: DA
- Data analysis and interpretation: MB
- Statistical analysis: MM, RM
- Manuscript preparation: FR, AM
- Manuscript editing: FB, LS
- Manuscript review: SMM

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Figures

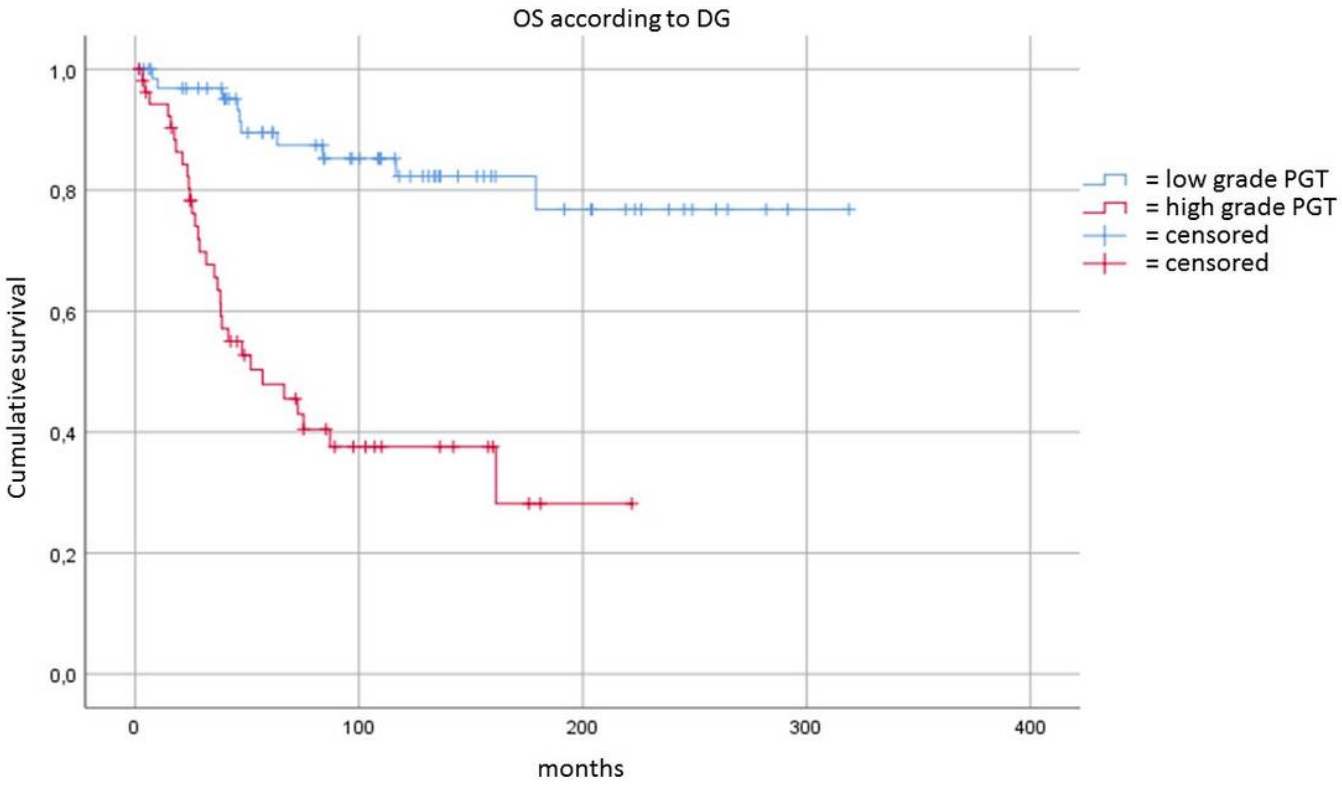

Figure 1

OS and DG

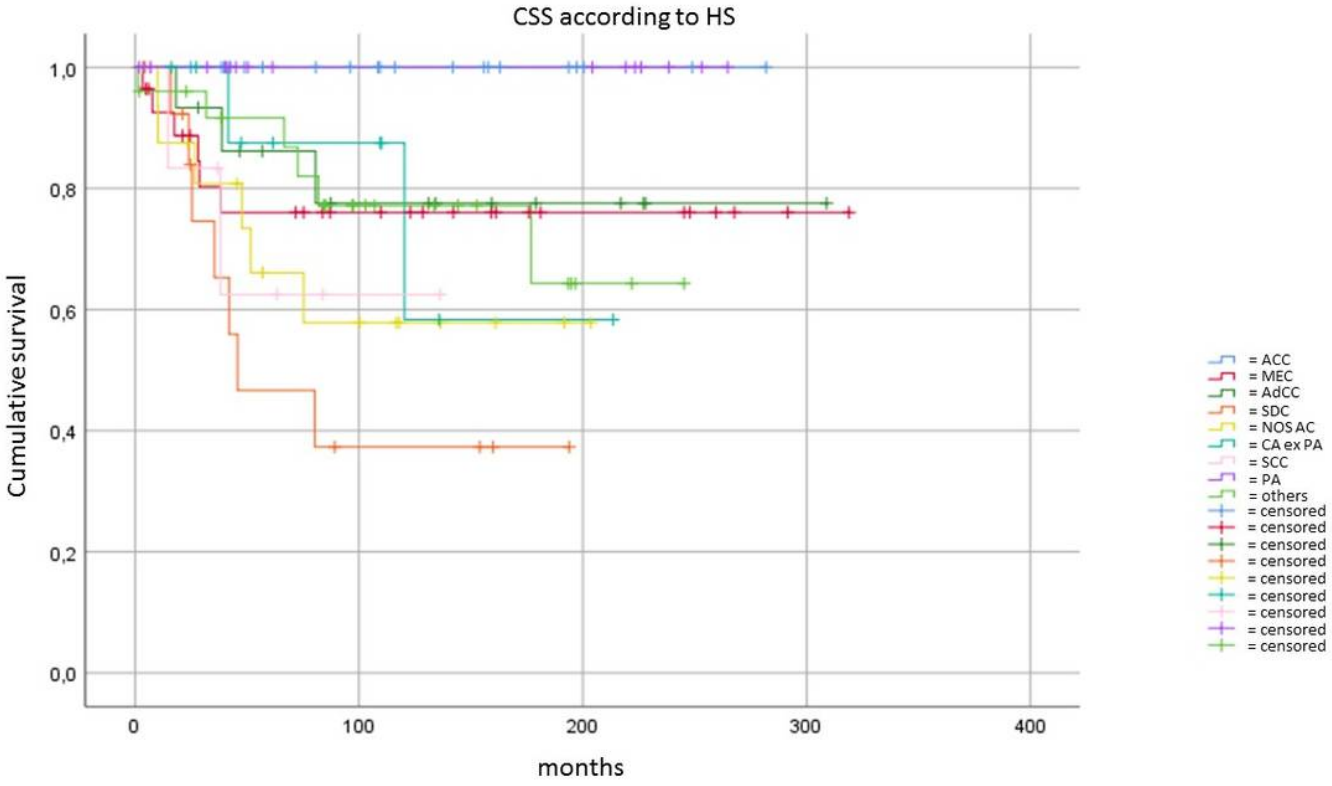

Figure 2

CSS and HS

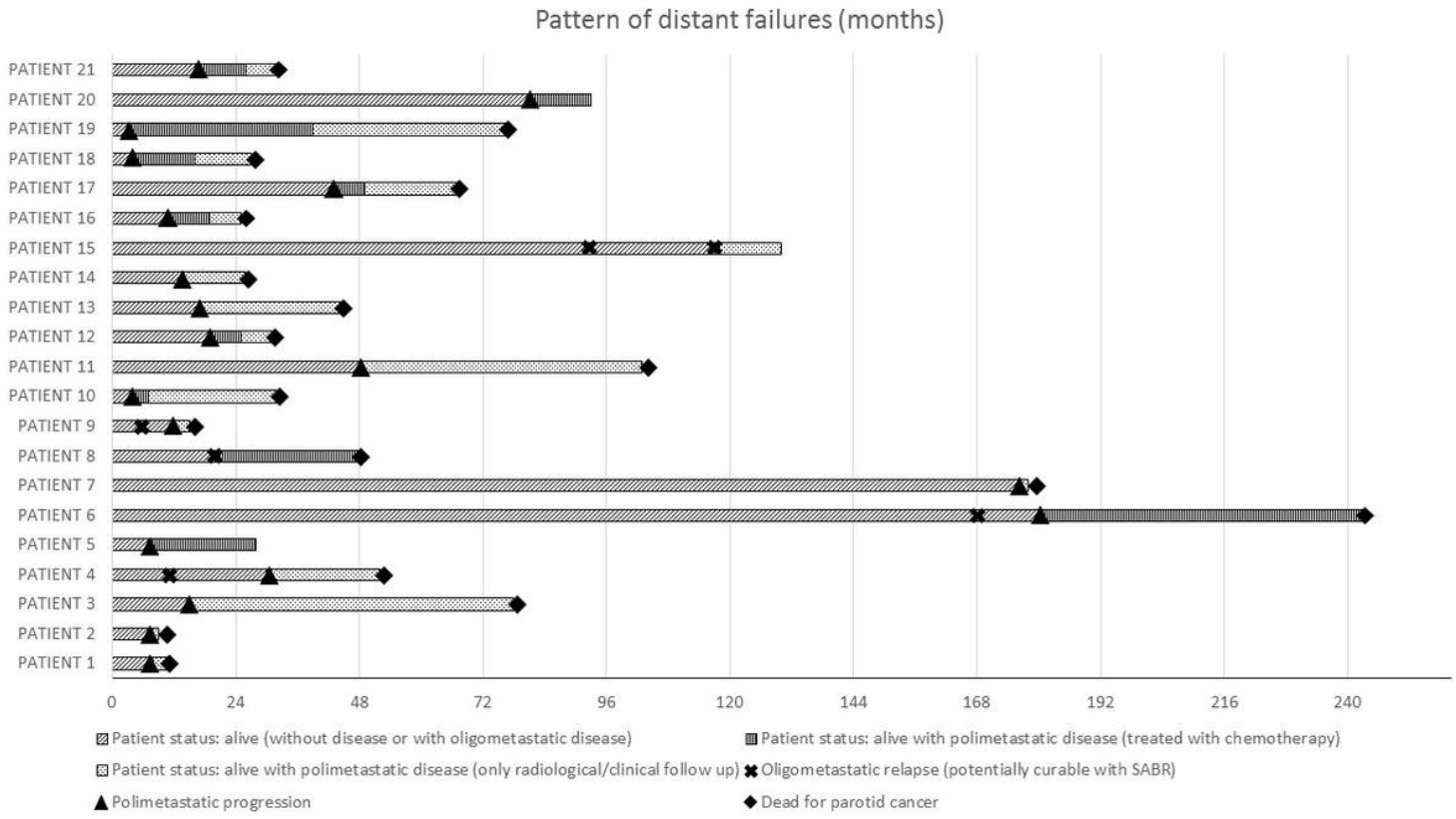

Figure 3

Pattern of distant failures