Original paper

# Role of irradiation in combined treatment of head and neck paragangliomas at the Centre of Oncology in Krakow between 1970–2005

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**Aim of the study** is to evaluate the results of postoperative radiotherapy of paragangliomas, prognostic factors and causes of treatment failure.

**Material and methods:** Forty-four patients (39 females and 5 males) aged 20 to 74 years were treated for paraganglioma between 1970 and 2010 at the Centre of Oncology in Kraków. Patient survival probability was estimated with the Kaplan-Meier method. Log-rank tests and Cox proportional hazard model were used in univariate and multivariate analysis, respectively.

**Results:** The most common locations of paragangliomas were the following: the ear, carotid body and internal jugular vein bulb. Forty (91%) out of them were benign and 4 – malignant. All patients underwent surgery followed by adjuvant radiotherapy. The delivered dose ranged from 50 to 72 Gy, the mean dose was 60 Gy. Five-year overall survival was 84%. Five-year relapse-free survival was 84%, either. The multivariate analysis has shown that the dose in an independent prognostic factor for the overall survival. The univariate analysis has shown significantly higher 5-year overall survival in patients who received a dose of 60 Gy or higher – 92% vs. 70% in patients who received a dose lower than 60 Gy.

**Conclusions:** Postoperative radiotherapy with doses higher than 60 Gy in patients with paragangliomas is associated with longer overall survival.

**Key words:** head and neck tumours, paragangliomas, chemodectoma, radiotherapy.

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## Introduction

Paragangliomas are rare, non-malignant tumours, originating from neuroectodermal cells. About 5% of these tumours may show malignant potential. The most common four locations of paraganglioma within the head and neck are the following: the carotid artery bifurcation, the lower ganglion of the vagus nerve, the tympanic cavity (the most common tumour of the middle ear) and the upper bulb of the internal jugular vein [1]. The location of paragangliomas is determined by developmental processes associated with the embrional migration pathway of neural crest cells. Sporadically, paragangliomas were also reported in such locations as larynx, trachea, lung, orbit, nasopharynx, paranasal sinuses or even the omentum. Only in 1–3% of patients paraganglioma is a hormonally active tumour secreting catecholamines and their metabolites [2–4].

Paragangliomas are slowly growing, hard and painless tumours, with rich vascularity, and are surrounded by a thin capsule. The signs and symptoms depend on tumour location and its growth rate. If the tumour is located in the ear, the most common signs and symptoms are as follows: hypoacusis; tinnitus; otoscopy changes, such as pink colour, bulging and pulsation of the tympanic membrane; tumour in the acoustic meatus, paralysis of the facial, vagus, accessory and sublingual nerves, and headache; and if the tumour is located within the neck, hoarseness, haemoptoe, steadily growing tumour in the upper neck, dyspnoe, tachycardia and skin reddening may be experienced [2, 5].

A breakthrough in the diagnostics of paragangliomas has come along with the development of imaging methods. At present, the diagnosis is based on ultrasound, computed tomography, magnetic resonance imaging and carotid arteriography [6, 7].

Biopsy is avoided in the majority of cases due to the risk of bleeding.

Positive family history is found in 10-30% of patients and is connected with a 2-fold increase of the risk of multifocality. On the other hand, 30% of the head and neck paragangliomas are of hereditary nature with an autosomal dominant pattern of inheritance with incomplete penetrance. Mutations within genes PGL1, PGL3, PGL4 (responsible for coding of 3 subtypes of succinate dehydrogenase) predispose to paraganglioma occurrence [2–4].

The current local staging classification is the Glasscoc and Jackson classification of the year 1981 or a classification proposed by McCabe and Fletcher [2].

The treatment of paragangliomas depends on the tumour location and stage of the disease.

The standard of care in patients with early paragangliomas is preoperative tumour embolisation and subsequent surgery. Modern operation techniques allow for surgery procedures associated with increasing probability of cure. Local relapse is observed in 0 to 5.5% of patients [8]. The risk of cranial nerve (VII, IX, X, XI and XII) injury is 10% to 40%, and in single paragangliomas of the cervical glomus it rises up to 100% [2, 3, 8–10].

Radiotherapy appeared to be an equivalent treatment method, as compared to surgery, due to the risk of haemorrhage during surgery. Obliterative action of ionising radiation against rich vascular network of these tumours as well as the cases where surgery would be associated with serious complications due to the size and location of the tumour are also arguments in favour of radiotherapy [3, 8, 11].

Radiotherapy is commonly used as single modality treatment in locally advanced paragangliomas or as adjuvant treatment after incomplete resection [2, 8, 12]. There are reports describing the use of preoperative radiotherapy in patients with locally advanced tumour to enable performance of surgery [2].

A newer method is stereotactic radiotherapy which is curative in about 95% of patients with 8% of neurological complications, such as cranial nerve neuropathy, transient in nature in the majority of cases [8, 11, 13, 14].

The purpose of this work is to evaluate radiotherapy and other treatment methods in the management of paraganglioma and analysis of prognostic factor and failure pattern.

## Material and methods

Forty-four patients (39 females and 5 males) treated in the Centre of Oncology in Krakow between 1970 and 2005 for a paraganglioma were included in the analysis.

Patients' age ranged from 20 to 74 years. The median age was 44 years.

Forty patients were diagnosed with benign tumours, in 4 cases malignant tumours were found.

Paragangliomas were most commonly located in the middle ear (65%), carotid body (15%) and internal jugular vein bulb (9%). In isolated cases tumours were located elsewhere (the orbit, the mediastinum, the retroperitoneal space, the base of the skull).

The duration of symptoms ranged from 1 month to 180 months (mean: 49 months) and was longest when paraganglioma was located in the ear. The symptoms varied according to tumour location. The most common symptoms when the tumour was located in the ear were tinnitus, hearing worsening, deafness and discharge from the ear.

One case of family occurrence of the paraganglioma was noted. Surgery was performed in all patients. In 4 (9%) cases this was a complete resection. In 32 (73%) of patients tumour resection was grossly incomplete, in 8 (18%) of patients – microscopically incomplete.

Postoperative irradiation was performed in all patients.

In 40 patients radiotherapy was indicated because of incomplete resection or tumour malignancy. The interval between the surgery and the start of radiotherapy ranged from 3 to 43 weeks (the median interval was 8 weeks).

All patients were irradiated with use of megavoltage therapy; in 30 patients the cobalt beam was used, 9 patients were irradiated with combined electron – photon beam technique and 5 of them were irradiated with a photon beam. Two oblique beams with wedge filters was the most common technique used – in 42 patients. In 2 patients the technique of two opposite field was used. The [delivered] doses ranged from 18 to 72 Gy, mean dose was 60 Gy in 30 fractions, 2 Gy per fraction.

Overall survival (OS) and disease-free survival (DFS) were the outcome measures in this study. The probability of patients' survival, calculated from the date of surgery to the date of the last follow-up assessment or to the date of patient's death was estimated with the Kaplan-Meier method. Log-rank tests and Cox proportional hazard model were used in univariate and multivariate analysis, respectively.

The following parameters were evaluated in the univariate analysis: age, sex, type of surgery, completeness of resection, time from the surgery to the start of radiotherapy, duration of symptoms, total dose, location and type of the tumour.

*P*-value < 0.05 was assumed as the threshold of statistical significance.

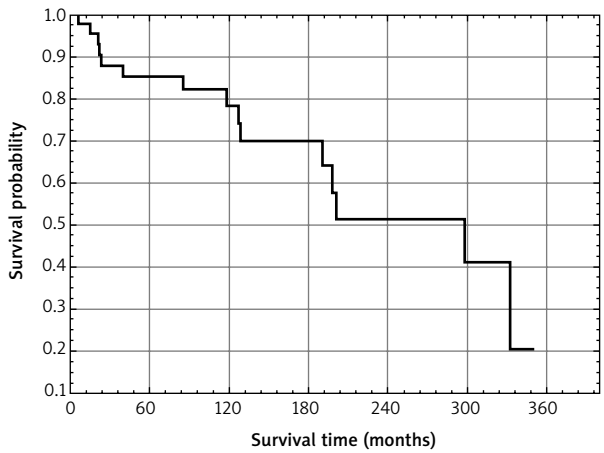


**Fig. 1.** Overall survival

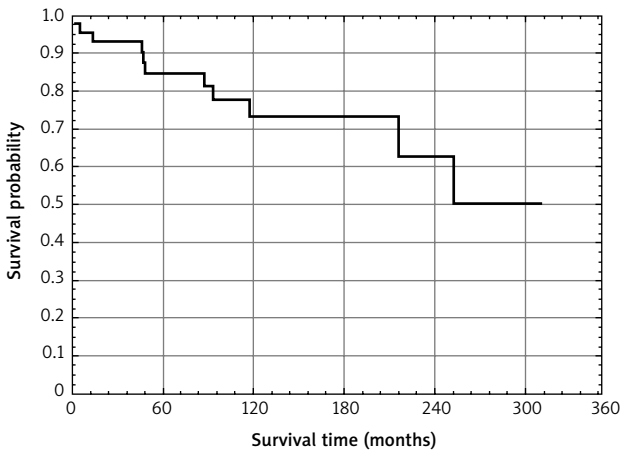


**Fig. 2.** Disease-free survival

Analysis of failure patterns and evaluation of early complications were also performed.

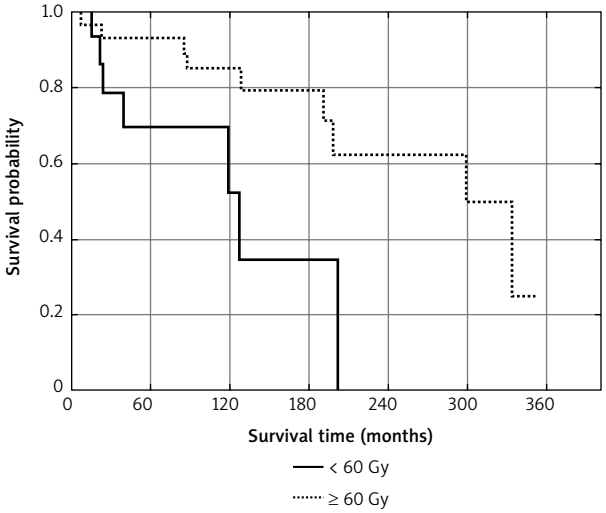


**Fig. 3.** Disease-free survival by total dose

## Results

The follow-up ranged from 3 to 330 months (the median: 104 months).

Five-year overall survival was 84%, 5-year disease-free survival was 84%, which is shown in Figs. 1 and 2.

The univariate analysis has shown significantly better overall survival ($p = 0.02$) in patients who received a dose of 60 Gy or higher (92%) and in patients who received a dose lower than 60 Gy 5-year overall survival was 70% (Fig. 3 and Table 1).

Tumour malignancy significantly affected both overall and relapse-free survival.

Patients who underwent microscopically incomplete surgery had a higher rate of overall survival (100%), as compared to the patients in whom the surgery was grossly incomplete (84%), however this difference was not statistically significant. Patients aged 44 years or less had insignificantly ($p = 0.1$) better overall survival (95%) than patients older than 44 years (74%).

The other variables included in the univariate analysis had no prognostic value with respect to both overall and disease-free survival.

**Table 1.** Univariate analysis of prognostic factors (significant bolded)

| Prognostic factors | Number of patients | % | 5 year DFS% | 5 year OS% |
|---|---|---|---|---|
| Total group | 44 | 100 | 84 | 84 |
| Gender | | | | |
| female | 39 | 89 | 88 | 82 |
| male | 5 | 11 | 60 | 100 |
| Age | | | | |
| > 44 years | 23 | 48 | 84 | 74 |
| ≤ 44 years | 21 | 52 | 84 | 95 |
| Histological subtype | | | $p < 0.0002$ | $p < 0.002$ |
| no data | 2 | 5 | **100** | **100** |
| benign | 38 | 86 | **90** | **88** |
| malignant | 4 | 9 | **0** | **50** |
| Duration of symptoms before treatment | 22 | | | |
| > 36 months | 22 | 50 | 89 | 90 |
| ≤ 36 months | | 50 | 79 | 79 |
| Completeness of operation | | | | |
| R0 | 4 | 9 | 50 | 50 |
| R1 | 8 | 18 | 100 | 100 |
| R2 | 32 | 73 | 84 | 84 |
| Time between operation and the beginning of radiotherapy | | | | |
| < 8 weeks | 20 | 45 | 78 | 80 |
| ≥ 8 weeks | 24 | 55 | 90 | 90 |
| Radiation dose | | | | **$p = 0.02$** |
| < 6000 | 17 | 39 | 71 | **70** |
| ≥ 6000 | 27 | 61 | 92 | **92** |

*NA – not applicable*

The multivariate analysis has shown that the dose is an independent prognostic factor for the overall survival (Table 2).

Five patients died due to paraganglioma, 1 due to another tumour. There were also 3 deaths due to non-cancer causes and 5 – due to unknown causes. Local progression was found in 8 (18%) patients, metastatic spread of the disease – in 2 (5%) persons. The median time to progression in this group of patients was 48 months. Tumour metastases were found in lungs and bones. No cases of secondary tumours were found.

The treatment was well tolerated. Xerostomy was found in 20% of patients.

**Table 2.** 5-year OS multivariate analysis of prognostic factors

| | Variable | Relative risk | *p* |
|---|---|---|---|
| **OS** | Radiotherapy dose | 0.24 | 0.01 |

## Discussion

The design of the study is at the same time its limitation: this is a series of cases treated in one centre over a period of 35 years with various treatment techniques. Paragangliomas are rare tumours thus a prospective clinical study to evaluate their treatment is infeasible. Literature data come only from retrospective case series [8, 12, 15–24].

Another limitation resulting from the length of the analysed period is missing imaging diagnostics [computed tomography (CT), magnetic resonance imaging (MRI)] in the majority of cases. For this reason tumour stage was excluded from analysis.

Patients' characteristics do not differ from those presented in the literature. The highest incidence of paragangliomas is noted between the 4$^{th}$ and the 6$^{th}$ decades of life [2, 4, 21].

The rate of relapse-free survival after conventional adjuvant radiotherapy is about 80–100% [5, 8, 12, 21, 24]. The results obtained in our Centre of Oncology fall within this range. When using conventionally fractionated radiotherapy, the recommended dose is 45–60 Gy [2, 12, 24]. In our material, in the univariate analysis we have shown a statistically significant effect of the dose on the overall survival. Patients who received a dose of 60 Gy and higher have better disease-free survival and better prognosis. Konefal *et al.* have demonstrated that the recurrence rate is higher for the doses lower than 41 Gy [17]. Others suggest that the doses above 45 Gy are associated with increased complications without lowering the risk of tumour relapse [24].

Late sequele of radiotherapy are the following: xerostomy, dental caries, hair loss, bone necrosis, middle ear inflammation, brain tissue necrosis, secondary tumours [2, 12, 24]. In our material we have observed xerostomy in 20% of patients. Konefal *et al.* report a complication rate of 4% in patients treated with surgery or curative radiotherapy [17].

Conclusion: our own results as well as the reports published to date show that radiotherapy is an effective method of treatment in patients with paragangliomas.

Precise dynamic radiotherapy techniques introduced on a large scale in the recent years: RT3D (tridimentional conformal radiotherapy), RST (stereotactic radiotherapy), IMRT (intensity modulated radiotherapy), and last but not least the progress in patient position verification/correction during irradiation (image guided radiotherapy – IGRT) allow to maintain and possibly improve the level of cure with concurrent maximal protection of the critical organs.

*The authors declare no conflict of interest.*

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