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ORIGINAL ARTICLE

Effectiveness of Leksell gamma knife hypophysectomy on cancer-related intractable pain – a single-center experience

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Abstract

OBJECTIVES: Hypophysectomy is a method used in analgesia in patients with painful bone metastases. The pain relief after this procedure is not pathophysiologically fully understood. In only a few studies Leksell gamma knife (LGK) was used for radiosurgical hypophysectomy. In our study, we performed the LGK hypophysectomy in patients with intractable cancer-related pain due to bone metastases and evaluated the impact of this method on pain relief.
METHODS: From 1994 to 2020 we enrolled 20 patients with the diagnosis of disseminated carcinoma. All patients underwent radiosurgical hypophysectomy on LGK. The maximum dose was 150-200Gy. The dose to the optic pathway was 9,8Gy on average.
RESULTS: Six patients died before the first follow-up and we did not receive any posttreatment information from 4 patients. In all the rest 10 evaluated patients pain relief was achieved (0-50% of pre-procedural pain). The hypophysectomy effect lasted for the rest of their lives (the mean follow-up period was 12,6 months). In three patients we observed hormonal disbalance - hypocortisolism and diabetes insipidus with good response to substitutional therapy, one patient developed a temporary abducens nerve palsy. No other adverse events were observed.
CONCLUSION: Our results suggest that the LGK hypophysectomy is an effective and safe procedure to reduce cancer-related intractable pain, especially in bone metastases of hormonally dependent tumors.

Abbreviations:

LGK - Leksell gamma knife
Gy - gray
VAS - Visual Analogue Scale

INTRODUCTION

The prevalence of cancer noticeable increases nowadays despite sophisticated oncological prevention, screening, and treatment options. (Wild 2020) Two-thirds of patients with advanced cancer are prone to bone metastases. (Reale *et al.* 2001) Intractable cancer-related pain due to bone metastases significantly impacts the quality of life and its treatment remains challenging. (Rodriguez *et al.* 2019) More than 70% of patients in an advanced stage of cancer are treated with opioids and despite it, 30% of them suffer from medical refractory pain. (Wild 2020) Opioid therapy is also related to moderate and serious side effects such as nausea, sedation, constipation, physical dependence, tolerance, and respiratory depression.(Benyamin *et al.* 2008) Surgical treatment of bone metastases is expanding but still has limitations in indications and the improvement of quality of life in these patients. (Manabe *et al.* 2004)

Hypophysectomy in the treatment of intractable cancer-related pain was introduced in 1953 by Luft and Olivercona who performed this surgical procedure via an endonasal transsphenoidal approach with excellent pain relief but with high morbidity and mortality.(Luft & Olivecrona 1953) In 1978 LaRossa *et al.* presented 15 patients with breast cancer with bone metastases after endonasal transsphenoidal hypophysectomy. (LaRossa *et al.* 1978) All of these patients had pain level decrease 24 hours after the surgical intervention. It was also proved that only transection of the pituitary stalk leads to pain relief and decreases the risk of hormonal disbalance. (Ehni & Eckles 1959) Tindall published excellent results of hypophysectomy in patients with carcinoma of the pancreas, ureter, testes, and adrenal gland. (Tindall *et al.* 1977) Levin reported a 93% reduction of cancer-related pain after chemical hypophysectomy. (Levin *et al.* 1980) Moricca supported this result with 98,1% success of chemical hypophysectomy. (Miyazaki *et al.* 1978) Similar results were achieved by cryohypophysectomy or the application of Yttrium90. (Conway & Collins 1969; Fergusson & Hendry 1971; Morales *et al.* 1971; Rozsíval *et al.* 1975) Dvorak and Rozsival performed hypophysectomy using thermocoagulation with excellent results. (Rozsíval *et al.* 1975; Dvorák & Dvorák 1987) All these methods were accompanied by a relatively high complication rate. Between 1954 and 1972 Levy et. al presented a radiosurgical hypophysectomy in 183 patients with breast cancer. In 1972 Backlund *et al.* described the first radiosurgical hypophysectomy using a Leksell gamma knife (LGK) and confirmed this method as efficacious and safer than previous invasive methods. (Backlund *et al.* 1972; Levy *et al.* 1991) From this time there are only a few studies of radiosurgical hypophysectomy and this method became neglected in oncological palliative medicine. (Misfeldt 1977; Lipton *et al.* 1978; Levy *et al.* 1991) Nowadays there is a renaissance of this method due to the increase of patients with malignant diagnoses and prolonged survival of patients with cancer.

In this single-center study, we performed the radiosurgical LGK hypophysectomy in patients with intractable cancer-related pain due to bone metastases and evaluated the impact of this method on pain relief.

METHODS

Between 1994 and 2020 we enrolled 20 patients (12 females, 8 males), mean age was 59,4years (46-73) who suffered from cancer-related pain and fulfilled two

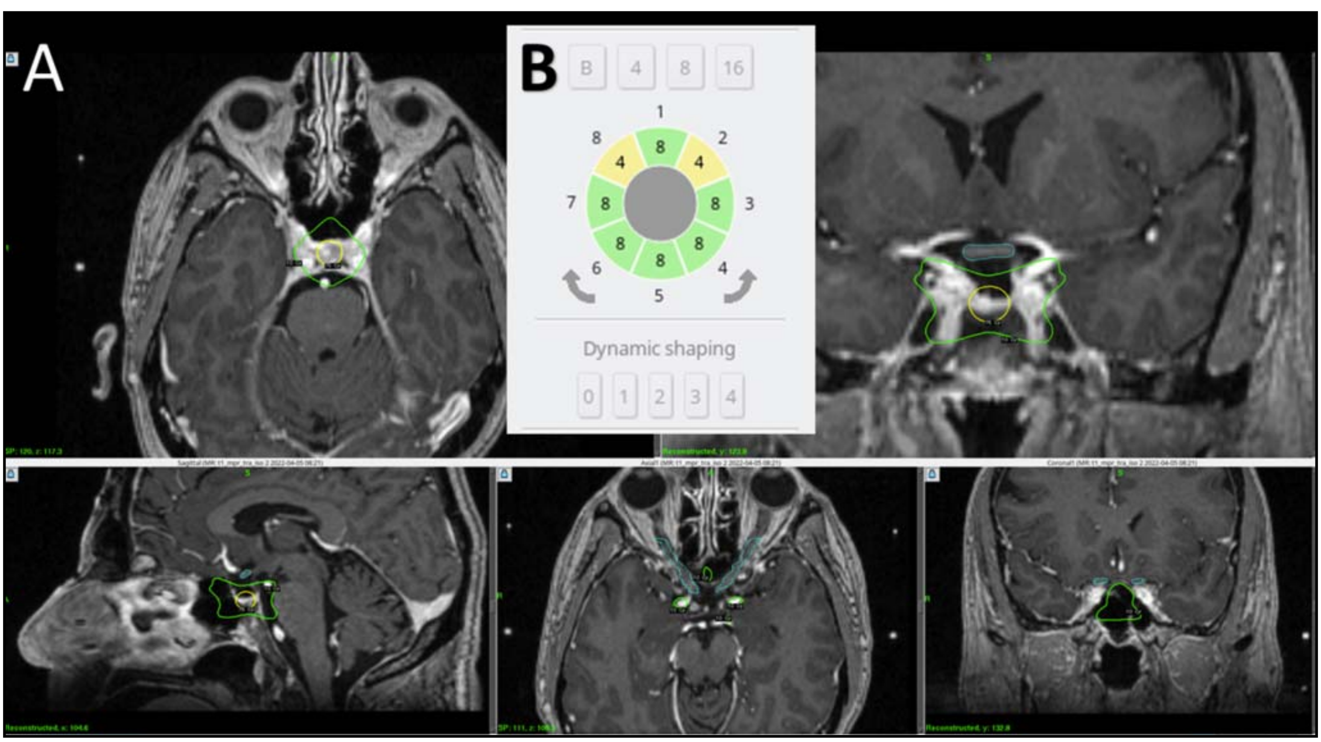

Fig. 1. A: Example of treatment plan; green line - 10Gy isodose; blue line – optic tract contour; yellow line - 50% isodose (75Gy), the maximal dose to the optic tract is 6,7Gy; B: Collimators setting used for hypophysectomy to minimize a dose on the optic tract

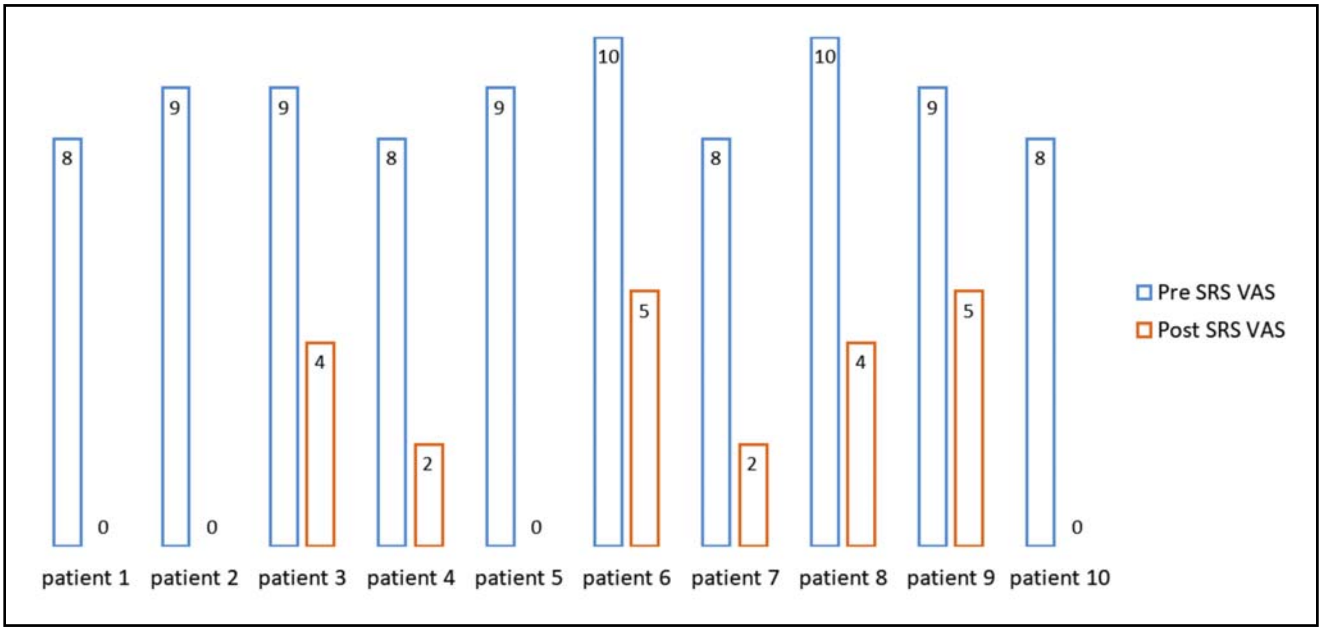

Fig. 2. Graph of pain relief in followed-up patients. SRS – stereotactic radiosurgery; VAS – visual analog scale.

inclusion criteria: 1) pain related to bone metastases; 2) insufficient effect of previous analgetic treatment. The primary tumor histology included breast cancer (45%; 9), prostate cancer (25%; 5), lung cancer (15%; 3), rectal cancer (5%; 1), laryngeal cancer (5%; 1) and kidney cancer (5%; 1).

On the day of the treatment, we applied a Leksell stereotactic G-frame on the head of the patient parallelly to the optic pathway in local anesthesia. All patients underwent MRI scans (1,5 Tesla, T1 weighted images in axial and coronal planes with 1.0mm slice thickness and T2 weighted images in the coronal plane with 2.0mm slice thickness). Using LGK Perfexion, we created a treatment plan using Leksell Gamma Plan software (Elekta instrument). 50% isodose involved the whole pituitary gland. The 8mm collimator was used. We modified collimators in segments 2 and 8 to 4mm in diameter to maximal reduce the dose on the optic tract. (Fig.1B) The maximum dose was on average 176Gy (150-200Gy). The maximum dose on the optic pathway was 9,8Gy (7-15Gy). (Fig.1A) Patients were discharged the same day with a scheduled follow-up 2 months after the treatment.

The pain was evaluated before the treatment and after the treatment on regular follow-ups (the first was two months after the procedure). We used the Visual Analogue Scale (VAS) and the percentage of remaining pain (%) for pain level measurement.

RESULTS

From 20 patients we included 10 patients in our retrospective analysis (7 females and 3 males). Six patients died in a consequence of the cancer progression before the first follow-up so the effect could not be evaluated. We did not receive any information from four patients after the treatment. Six of the ten patients suffered from breast cancer, two from prostate cancer, and two from lung cancer. In all 10 patients, we achieved a pain reduction, which resulted in an average of 24% (0-50%) of remaining pain. (Fig. 2 and Tab. 1)

The mean follow-up was 12,6 months (2-34months). The pain level decrease was achieved from 2 to 4 weeks after the procedure and was permanent, no pain recurrence from bone metastases was observed.

In two patients hypocortisolism was present with the need for substitutional therapy 5 and 12 months after radiosurgical hypophysectomy. In one patient the diabetes insipidus occurred 3 months after the treatment with the success of substantial therapy. One patient developed temporary abducens nerve palsy with full recovery after 5 months. No other adverse events were observed.

DISCUSSION

This study evaluates the effect of radiosurgical LGK hypophysectomy on pain relief in patients with intractable cancer-related pain with multiple bone metastases. Our study confirms, that LGK hypophysectomy is an effective and safe treatment modality in this group of patients where the effect of analgesic treatment was insufficient.

The analgesic mechanism of radiosurgical hypophysectomy remains poorly understood. (Chernov *et al.* 2021) Because of its effect on hormonally dependent bone metastases, the disruption of hormonal pathways was the first theory. (Yanagida *et al.* 1979; Ramirez & Levin 1984) This theory does not explain the immediate pain relief (hours) in many patients. Moreover,

Tab. 1. Patient's characteristics

Patient No	Sex	Age at SRS	Primary tumor	KPS	Pain localisation	Pre-SRS pain (VAS)	Post-SRS pain (VAS)	Pain reduction (% of remaining pain)	FU (months)
1	F	57	breast cancer	80	thoracic spine	8	0	0	26
2	F	50	breast cancer	80	cervicocranial junction	9	0	0	24
3	F	54	breast cancer	80	thoracic and lumbar spine	9	4	50	6
4	M	65	prostate cancer	90	lumbar spine	8	2	20	13
5	M	58	prostate cancer	80	lumbar spine	9	0	0	34
6	F	59	breast cancer	80	thoracic spine	10	5	50	5
7	M	59	lung cancer	60	lumbar spine and hip	8	2	20	3
8	F	51	breast cancer	80	cervical and thoracic spine	10	4	50	10
9	F	67	lung cancer	70	sacrum	9	5	50	2
10	F	68	breast cancer	60	thoracic and lumbar spine	8	0	0	3
ø		**58,8**		**76**		**8,8**	**2,2**	**24**	**12,6**

F – female; M – male; SRS – stereotactic radiosurgery; KPS – Karnofsky performance scale; VAS – visual analogue scale; FU – follow-up

pain relief persists despite tumor growth and normal function of the pituitary gland, and patients with non-hormonal tumors also experienced pain relief. (Levin *et al.* 1980; Ramirez & Levin 1984; Hayashi *et al.* 2003) Another theory considers an increased activity of pre-pro-opiomelanocortin (precursor to β-endorphin) as the reason for pain relief after hypophysectomy which was supported by a higher level of β-endorphin in cerebrospinal fluid and blood. Nevertheless, this elevation takes only 72 hours, and administration of naloxone after LGK hypophysectomy did not influence the analgesic effect of the procedure. (Yanagida *et al.* 1979) Recent theory suggests that the hypothalamus and its afferent nociceptive pathways have a key role in pain relief. (Larkin *et al.* 2020) To better understand the pathophysiological changes after hypophysectomy more studies still have to be done.

Pain relief was achieved in all our analyzed patients (10 from 20) and persisted the whole life. We are in accordance with previous studies from Backlund *et al.*, Hayashi *et al.* and Kwon *et al.* who evaluated the effect of LGK hypophysectomy in similar series of patients (8; 9 and 7 patients). (Backlund *et al.* 1972; Hayashi *et al.* 2002; Kwon *et al.*) Moreover, in previous studies, radiosurgical hypophysectomy was effective even in the treatment of non-hormonal cancer pain without bone metastases and non-malignant thalamic pain. (Hayashi *et al.* 2003; Chernov *et al.* 2021) The effect occurs from several hours to four weeks after the treatment which is much earlier than in other indications for LGK radiosurgery. (Backlund *et al.* 1972; Liscák & Vladyka 1998; Hayashi *et al.* 2002; Golanov *et al.* 2020) Permanent duration of pain relief is the advantage over the other analgetic radiosurgical methods (e.g., cingulotomy and thalamotomy). (Roberts & Pouratian 2017)

The maximum dose on the pituitary gland has been applied from 150 to 250Gy. (Backlund *et al.* 1972; Liscák & Vladyka 1998; Hayashi *et al.* 2002; Kwon *et al.*) In our study, the maximum dose was on average 176Gy which is close to the lower limit of the range. This result confirms that the maximum dose of 150Gy may be sufficient for pain relief and there is no need to elevate the maximum dose over this limit. The dose to the optic tract was 9,8Gy on average and no visual complication was reported. Other critical structures obtained much less dose than their tolerance.

Despite the relatively high administrated dose, we recorded only a few side effects of irradiation. Hormonal disbalance occurred in three patients. One patient developed diabetes insipidus 3 months after the treatment with the success of substantial therapy. In two patients hypocortisolism was present with the need for substitutional therapy 5 and 12 months after hypophysectomy. One patient developed temporary abducens nerve palsy with full recovery after 5 months. The higher incidence of hormonal disbalance in the study of Backlund *et al.* might be caused by a higher maximum dose which was 200-250Gy. (Backlund *et al.* 1972) In a study of Hayashi, no side effects occurred and in the study of Kwon, only one patient with pre-existing panhypopituitarism get worse. (Hayashi *et al.* 2002; Kwon *et al.*) In these two studies, the maximum dose was up to 200Gy. No other side effect was present.

In our study, the mean follow-up was 12,6 months and the longest follow-up was 34 months. In previous studies, the maximal follow-up was 12 months. (Larkin *et al.* 2020) Four of the ten patients in our study have lived more than 12 months after the hypophysectomy with permanent pain levels decreased from 50% to 100%. Two patients suffered from breast cancer and two from prostate cancer. This highlights that LGK hypophysectomy is well established in hormonally dependent bone metastases. Unfortunately, patients with lung, kidney, rectal and laryngeal cancer died due to primary disease before the first follow-up, or we did not receive any information from them after the treatment. That is the reason why we could not evaluate the effectiveness of this procedure for non-hormonally dependent tumors.

The main limitation of this retrospective study is the low number of patients included and that we obtained sufficient data to analyze from only half of the patients. In the majority of these patients, we have a short follow-up. These main limitations are due to the fact that hypophysectomy is still a rare indication for patients in an advanced stage of oncological disease. These patients are in a poor clinical status with short survival.

In conclusion, our study confirms radiosurgical hypophysectomy as an effective and safe palliative method for pain relief in patients with multiple bone metastases of hormone-dependent cancers who suffer from intractable medically refractory pain.

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