Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Tumour seeding in the surgical pathway after resection of skull base chordoma

Marco Krengli[a,b,c,*], Arturo Poletti[d], Eleonora Ferrara[a,b], Piero Fossati[c,e]

[a] Division of Radiotherapy, University Hospital "Maggiore della Carità", Novara, Italy
[b] Department of Translational Medicine, University of "Piemonte Orientale", Novara, Italy
[c] Centro Nazionale Adroterapia Oncologica (CNAO), Pavia, Italy
[d] Department of Otorhinolaryngology, Humanitas Research Hospital, Rozzano, Milan, Italy
[e] Department of Radiotherapy, Istituto Europeo di Oncologia (IEO), Milan, Italy

ARTICLE INFO

Article history:
Received 29 July 2015
Received in revised form
22 October 2015
Accepted 19 February 2016
Available online 21 March 2016

Keywords:
Surgery
Tumour seeding
Surgical pathway recurrence
Skull base chordoma

ABSTRACT

Aim: The aim of this study is to review the clinical series in which tumour seeding was reported after skull base surgery for chordomas.

Background: The occurrence of implantation of cancer cells during surgical procedures for the removal of chordoma is a rare event described by a number of authors in a few patient series and case reports.

Materials and methods: Literature search was performed by PubMed and Scopus by using the words "surgical tumour seeding, tumour implantation, surgical pathway recurrence, skull base chordoma, and clivus chordoma".

Results: Six retrospective series and 7 case reports were included in the analysis. In total, 34 patients are described with pathway recurrence, 30 at a single site and 4 at multiple sites.

In the 5 largest chordoma series, the rate of occurrence of surgical seeding ranged from 1.3% to 7.3% (3.9%). In the 34 patients diagnosed with tumour seeding, the most frequent surgical approach was trans-nasal/trans-sphenoidal, that was used in 12 cases. The median time from primary treatment to surgical pathway tumour seeding ranged from 7 to 78 months. Data of the treatment of seeding are available in 26/34 patients. All of them underwent a new surgery, 6 received additional external beam radiotherapy, and 2 intraoperative radiotherapy.

Conclusions: The risk of surgical seeding should be taken into consideration when deciding on the surgical approach and the planning treatment volume for postoperative radiation therapy. The surgical pathway should be included in follow-up studies to diagnose this peculiar type of treatment failure possibly at an early phase.

* *Corresponding author at*: Chair of Radiotherapy, University of "Piemonte Orientale", Via Solaroli 17, 28100 Novara, Italy. Tel.: +39 0321 3733424; fax: +39 0321 3733698.
E-mail address: krengli@med.unipmn.it (M. Krengli).

http://dx.doi.org/10.1016/j.rpor.2016.02.005

1. Background

Chordoma is a rare cancer arising from notochord remnants. Its incidence is 0.08 per 100,000 with predominance of male and a peak between 50 and 60 years. Chordoma occurs at skull base in 30–40% of cases.[1,2] Although it is usually a slow growing cancer and looks relatively benign histologically, it is locally aggressive and frequently recurs following treatment. Normally, surgical resection is the first line treatment. The "en bloc" resection aims at local control but is usually difficult to achieve, due to the close proximity of this tumour to critical structures such as brainstem, cranial nerves, and major intracranial vessels. Radiation therapy is used to sterilize surgical field and treat residual, recurrent or unresectable disease. Local recurrence is the most common form of treatment failure, local recurrence free survival at 5 years being in the range of 17–33% in historical series treated by conventional radiotherapy and 50% in more recent series treated by stereotactic radiotherapy.[3–5] Particle therapy, mainly by protons, has substantially improved local control and long term outcome.[3,6,7] Chordoma has also the potential to metastasize to regional lymph nodes, distant sites and cerebrospinal fluid.[1,2,7,8] A rare and peculiar pattern of failure is tumour seeding along the surgical access pathway that is reported in less than 5% of cases.[8] These sites, such as the nasal cavity and surrounding soft tissue, are often outside the treatment field of radiation and can be subject to iatrogenic tumour implantation.

2. Aim

The aim of this study is to perform a review the literature about the occurrence and the natural history of tumour seeding after a surgical approach for skull base chordoma.

3. Material and methods

Literature search was performed by PubMed and Scopus by using the following words: surgical tumour seeding, tumour implantation, surgical pathway recurrence, skull base chordoma, and clival chordoma. No limits of time period were used. Only English-language studies were included. Only studies with tumour seeding related to surgical procedures for skull base chordoma were included. No selection basing on type of studies was adopted. Abstracts from scientific meetings were considered when relevant, i.e. including large series of skull base chordoma. Case reports were considered as well.

4. Results

From literature search, we found 6 retrospective series and 7 case reports of patients who experienced surgical pathway recurrence after excision of skull base chordomas[9–21] (Table 1). No prospective trials were found. Five out of 13 series included not only skull base but also cervical spine tumours. An abstract was also considered since it specifically updated the results on skull base chordoma of one of the largest series about skull base and cervical chordoma.[20]

In total, 34 patients were described with pathway recurrence, 30 at a single site and 4 at multiple sites: one patient with 4 sites, another patient with 3 sites and two patients with 2 sites.

Postoperative radiotherapy was mainly delivered by protons or protons/photons.

In the 5 largest chordoma series coming from 4 different institutions, the rate of occurrence of surgical seeding ranged from 1.3% to 7.3% (median 3.9%). Considering the total number of patients affected by skull base chordoma from these 5 series, the mean incidence of surgical seeding was 2.7% (25/930). In the 34 cases with 39 sites of surgical seeding, the surgical approaches were as follows: trans-nasal/trans-sphenoidal in 12 cases, cervical skin and soft tissues in 5 cases, trans-maxillary in 2 cases, trans-oral in 6 cases, trans-petrosal in 1 case (3 sites), infra-temporal or trans-condylar in 2 cases, rhinoseptal in 2 cases, trans-latero nasal and temporo-zygomatic in 1 case, at the level of craniotomies in 4 cases and in the abdominal wound after a procedure for tissue graft in one case.

The median time from primary treatment to surgical pathway tumour seeding reported in the 3 large series ranged from 12.5 to 78 months and the same time in the 7 case reports ranged from 7 to 72 months.

Data concerning treatment of seeding were available in 26 out of 34 patients. All of them underwent a new surgery, 6 received external beam radiotherapy, and 2 intraoperative radiotherapy.

Three articles described the series from MGH.[9,10,20] The most recent one[20] includes 8 patients with 11 sites of surgical seeding observed in a series of 203 cases of clivus chordoma (3.9%) who underwent 302 surgical procedures: 7 after 187 trans-facial approaches (3.7%), 2 after 101 craniotomies (2.0%), and 2 after 14 infratemporal approaches (14.3%). The authors reported 5 and 10 years overall survivals rates worse for the 8 cases with surgical seeding compared to the other 195 patients. Of the 8 cases with surgical seeding, 3 (37.5%) developed systemic metastases, compared to 5/195 (2.6%) cases without surgical seeding.

Fischbein et al.[11] reported on 3 patients out of 70 (4.3%) operated for skull base chordoma at the University of California, San Francisco, who recurred along the surgical pathway. All the three patients, aged 33–47, were operated by trans-sphenoidal approach in two cases and by trans-oral approach followed by external spheno-ethmoidectomy for recurrence in one case. All three patients were treated postoperatively by proton beam radiation therapy. Tumour seeding occurred in the nasal cavity in the first two cases and in the ethmoid region in the third case. All the three patients required further surgery associated with radiation in 2/3. They remained without tumour progression after 2–4 years after the treatment for tumour seeding.

Arnautovic et al.[12] reported surgical seeding in 6 out of 82 patients (7.3%) operated for chordoma of the skull base and cervical spine at the University of Arkansas. The 6 patients were aged from 14 to 52 years and 5 of them had undergone postoperative radiotherapy with protons in 3 cases and photons in 2. All the 6 patients had received 2–8 surgical procedures for their primaries and recurrences. Five developed a single site of seeding, including the site of abdominal wound

Table 1 – Series of skull base chordoma patients with surgical pathway recurrence.

Author	Primary site	No. pts with surgical pathway recurrence	Surgical approach	Postoperative radiotherapy	Surgical pathway recurrence site	Median time to recurrence (months)	Treatment at recurrence
Austin et al.[9]	CS	2/141 (1.4%)[a]	NA	Protons/photons	2 Neck	NA	NA
Fagundes et al.[10]	SB and CS	All: 3/204 (1.4%) SB: 2/153 (1.3%) CS: 1/51 (2.0%)	NA	Protons/photons	1 Hard palate; 1 Nasal cavity; 1 Neck	NA	Surgery, EBRT
Krengli et al.[20]	SB	8/203 (3.9%)	Sublabial-transseptal-transsphenoidal; Transmaxillary; Transoral; Fronto-temporal craniotomy; Infratemporal-transcervical	Protons/photons	3 Nasal cavity; 1 Infratemporal fossa; 1 Palate; 1 Skin (cervical scar); 1 Two sites (palate, fronto-temporal craniotomy); 1 Four sites (nasal septum, right and left craniotomies, subcutaneous tissue in maxillary region)	25 (range, 14–58)	Surgery, chemo, RT
Fischbein et al.[11]	SB	3/70 (4.3%)	Transsphenoethmoidal; Sublabial-transsphenoidal; Transoral	Protons	1 Nasal incision site; 1 Nasal septum; 1 Ethmoid	32 (range 24–42)	Surgery, IORT, RT
Arnautovic et al.[12]	SB and CS	6/82 (7.3%)	Transmaxillary; Transnasal; Transnasal; Cervical; Transoral; Transpetrosal	Protons/photons in 5/6 pts	1 Maxillary sinus; 1 Nasal cavity; 1 Septum/maxilla; 1 Neck soft tissue; 1 Abdominal wound; 1 Petrous apex; Retroauricolar area; tentorium	12.5 (range, 5–15)	NA
Kinoshita et al.[13]	SB	1, case report	Fronto-temporal craniotomy	NA	Craniotomy site; meningeal spread	7	Surgery
Van Lierop et al.[14]	SB	1, case report	Transoral-transpalatal	Yes	Hard–soft palate	24	Surgery
Boyette et al.[15]	SB	1, case report	Transoral; transcondilar with C-shape retroauricolar incision	NA	Parotid region	48	Surgery
Zener et al.[16]	SB	1, case report	Transcervical, transoral, transparotid and endoscopic intranasal exposure	Yes	Neck (cervical incision)	54	Surgery
Zemmoura et al.[17]	SB	1, case report	Sublabial-transnasal-transseptal	Yes	Maxillary bone	31	Surgery
Hines et al.[18]	SB	1, case report	Transnasal-transseptal	Gamma-knife	Nasal cavity	24	Na
Iloreta et al.[19]	SB and CS	1, case report	Endoscopic nasal and trans cervical	Protons	Neck (cervical incision)	72	Surgery
Vogin et al.[21]	SB and CS	All: 5/371 (1.3%) SB: 5/310 (1.6%) CS: 0/61	Transnasal-left temporal-left cervical; Transpalatine-transmaxillary-left temporal Rhinoseptal Trans-latero nasal and temporo-zygomatic	Protons/photons	2 Philtrum 1 Ethmoid 1 Nasal septum 1 Pterional and left temporal muscle	57	Surgery, protons

Abbreviations: pts: patients; SB: skull base; CS: cervical spine; NA: not available; chemo: chemotherapy; EBRT: external beam radiotherapy; IORT: intraoperative radiotherapy.

[a] 2 chordoma recurrences in 141 cases of chordoma and chondrosarcoma.

for tissue graft, and one patient developed up to 17 different seeding sites. The authors reported that 2 patients died of tumour recurrence during subsequent follow-up.

Vogin et al.[21] reported surgical seeding in 5 out of 371 patients (1.3%) operated for chordoma of the skull base and cervical spine at different institutions from France, Italy, Spain and United Kingdom and treated with proton therapy at the Institut Curie Proton Centre in France. Median age was 45 (range 12–58). All of the five patients had spheno-occipital primary chordoma operated and treated with a combination of photon and proton post-operative irradiation (67–74 Gy, 2 Gy/fraction). During the initial irradiation, the area of relapse had received 30 Gy or less. Two patients developed a single seeding site and three patients developed 2 different seeding sites. All cases underwent a second surgery and 3 of them received a new proton therapy course (median dose 59.4 Gy). At a median follow-up of 64 months (range 29–84), two patients died of tumour recurrence.

5. Discussion

Needle track or surgical pathway recurrence is a rare but well recognized complication of biopsy and surgery of a variety of neoplasms, including endometrium, cervix, lung, colon-rectal and ovary cancers. The frequency of this event varies in different studies in relation to the site of tumour, histology, type of surgical approach and technique. Probably, the true incidence of the surgical seeding is not well known, but it seems to be an uncommon event, with an overall incidence rate of 5% or less, that rarely results in identifiable metastases.[22–27] Concerning skull base tumour sites, Moore et al.[23] reported an actuarial risk of incisional relapse of 3% at 1 year in a series of 70 patients treated for sinonasal malignancies with midface and anterior skull base surgery.

The possible mechanism of surgical pathway recurrence may be a direct implantation of tumour cells at the time of the surgical procedure or also a haematogenous spread to this particular location in which the increased blood flow and concentration of unknown chemotactic factors may increase the likelihood of tumour cells implantation. This dissemination and concomitant seeding of neoplastic cells may occur at different times: preoperative rupture (spontaneous or traumatic), biopsy (needle or open) or during surgery (rupture of the capsule or removal of the tumour in piecemeal). Factors that can influence the likelihood of tumour cells implantation can be host immune surveillance, number and characteristics of tumour cells, and the presence/absence of blood flow once separated from the main tumour mass.[11,15,19]

Concerning skull base chordoma, surgical seeding represents a relatively rare complication and in some cases can be difficult to distinguish among recurrence, second primary and true surgical implantation. Fishbein et al.[11] suggested a definition of surgical recurrence pathway in reference to chordoma. They defined surgical recurrence pathway as located along the path of surgical access and separated from the primary tumour bed by a significant amount of normal tissue, i.e. more than 2.5 cm, if there is no demonstrable lymphatic or perineural pathway of spread and if no distant metastases are present at time of a surgical pathway failure. They also suggested that the time from primary surgery to the development of surgical pathway recurrence should be taken into account, even though no clear time interval is known.

We found in the literature a description of 34 patients with surgical pathway recurrence. In the analysed series, only one patient did not fully meet the previously described criteria. Indeed, the case report by Kinoshita et al.[13] described the case of subcutaneous localization of chordoma in the site of the previous craniotomy in a patient with meningeal dissemination. In such a case, we could also hypothesize that the meningeal infiltration could have determined the invasion of craniotomy site where the tissue and vascular architecture were substantially altered and could favour the tumour cells implantation.

Literature data are difficult to analyse because of their retrospective nature, the variety of surgical approaches used, and the frequent lack of detailed information. However, from the available series, we found a mean incidence of surgical pathway recurrence of 2.7%. This data is quite similar to that reported in the previous literature review published by Iloreta et al.[19]

In all the published series,[9–21] patients underwent open surgery, mainly by anterior approaches through transnasal/trans-sphenoidal or transoral pathways, that could be considered procedures of higher risk.

In order to prevent surgical tumour seeding, different techniques and measures have been recommended. Arnautović et al.[12] suggested to coat the walls of operative tunnel with fibrin glue and large cotton patties before tumour removal and change the set of instruments and gloves after tumour removal and before performing tissue closure.

In the last years, the improvement of endoscopic techniques offers an alternative to open surgery for resection of skull base chordomas; the main indication is for centrally located lesions or as an adjunct to craniotomy for more extensive tumours.[28] The endoscopic endonasal approach offers the advantage of a direct and shorter surgical corridor, magnified visualization but limited exposure of adjacent site to the tumour. However, on the other hand, piecemeal resection, which is usually performed by this technique, could increase the chance of tumour seeding. Thus far, no cases of surgical seeding are reported after endoscopy; however, more data and longer follow-up are needed to assess the incidence of tumour implantation in surgical pathway after this technique.[19,28]

From the available data of the largest series and the case reports,[9–21] the postoperative radiation volume did not include, in principle, the surgical path and the site of surgical seeding was found outside the radiation fields or in the low dose volumes. Some authors suggested the inclusion of biopsy and surgical pathways in the radiotherapy field in order to reduce the risk of recurrence[12,14] but the inclusion of the entire surgical access path in radiation therapy field still remains a controversial issue as suggested by the recent consensus meeting because of the risk of toxicity related to treating a large target volume to high radiation dose[8] considering the low occurrence rate of surgical seeding that ranges from 1.3% to 7.3% in the reported series. In this regard, multidisciplinary discussion could be helpful to identify those cases at higher risk of tumour seeding due to tumour location and complexity of the surgical procedure. On the other hand, consensus was

reached on the need of imaging follow-up including not only the primary site, but also the area at risk of potential tumour seeding.[8]

6. Conclusions

Surgical seeding recurrence is an uncommon form of treatment failure following surgical excision of clivus chordomas with only a few cases reported in the literature. This peculiar type of treatment failure should be taken into consideration when deciding on the appropriate surgical approach and defining the planning treatment volume for postoperative radiation therapy. Moreover, the surgical pathway should be included in follow-up radiology studies to diagnose these lesions possibly at an early phase.

Conflict of interest

None declared.

Financial disclosure

None declared.

Acknowledgment

The authors would like to thank Norbert Liebsch, MD, PhD, from Massachusetts General Hospital, Boston, MA, USA for his suggestions and comments.

REFERENCES

1. Walcott BP, Nahed BV, Moheyeldin A, Coumans JV, Kahle KT, Ferreira MJ. Chordoma: current concepts, management, and future directions. *Lancet Oncol* 2012;**13**:e69–76.
2. Jones PA, Aghi MK, Muzikansky A, Shih HA, Barker FG. Outcomes and patterns of care in adult skull base chordomas from the Surveillance, Epidemiology, and End Results (SEER) database. *J Clin Neurosci* 2014;**21**:1490–6.
3. Jereczek-Fossa BA, Krengli M, Orecchia R. Particle beam radiotherapy for head and neck tumours: radiobiological basis and clinical experience. *Head Neck J Sci Spec* 2006;**28**:750–60.
4. Debus J, Schultz-Ertner D, Shad L, Essig M, Thillmann CO, Wannenmacher M. Stereotactic fractionated radiotherapy for chordomas and chondrosarcomas of the skull base. *Int J Radiat Oncol Biol Phys* 2000;**47**:591–6.
5. Rangel-Castilla L, Russin JJ, Spetzler RF. Surgical management of skull base tumors. *Rep Pract Oncol Radiother* 2016;**21**:325–35.
6. Mazzoni G, Krengli M. Historical development of the treatment of skull base tumours. *Rep Pract Oncol Radiother* 2016;**21**:319–24.
7. Tzortzidis F, Elahi F, Wright D, Natarajan SK, Sekhar LN. Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chordomas. *Neurosurgery* 2006;**59**:230–7.
8. Stacchiotti S, Sommer J, Chordoma Global Consensus Group. Building a global consensus approach to chordoma: a position paper from the medical and patient community. *Lancet Oncol* 2015;**16**:e71–83.
9. Austin JP, Urie MM, Cardenosa G, Munzenrider JE. Probable causes of recurrence in patients with chordoma and chondrosarcoma of the base of skull and cervical spine. *Int J Radiat Oncol Biol Phys* 1993;**25**:439–44.
10. Fagundes MA, Hug EB, Liebsch NJ, Daly W, Efird J, Munzenrider JE. Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. *Int J Radiat Oncol Biol Phys* 1995;**33**:579–84.
11. Fischbein NJ, Kaplan MJ, Holliday RA, Dillon WP. Recurrence of clival chordoma along the surgical pathway. *Am J Neuroradiol* 2000;**21**:578–83.
12. Arnautović KI, Al-Mefty O. Surgical seeding of chordomas. *J Neurosurg* 2001;**95**:798–803.
13. Kinoshita T, Okudera T, Shimosegawa E, et al. Chordoma with postoperative subcutaneous implantation and meningeal dissemination: MRI. *Neuroradiology* 2001;**43**:763–6.
14. Van Lierop AC, Fagan JJ, Taylor KL. Recurrent chordoma of the palate occurring in the surgical pathway: a case report. *Auris Nasus Larynx* 2008;**35**:447–50.
15. Boyette JR, Seibert JW, Fan CY, Stack Jr BC. The etiology of recurrent chordoma presenting as a neck mass: metastasis vs. surgical pathway seeding. *Ear Nose Throat J* 2008;**87**:106–9.
16. Zener R, Jacquet Y, Wong JW, Enepekides D, Higgins KM. A rare case of surgical pathway implantation of clival chordoma presenting as a neck mass. *J Surg Case Rep* 2011;**2011**(1):3.
17. Zemmoura I, Ben Ismail M, Travers N, Jan M, François P. Maxillary surgical seeding of a clival chordoma. *Br J Neurosurg* 2012;**26**:102–3.
18. Hines JP, Ashmead MG, Stringer SP. Clival chordoma of the nasal septum secondary to surgical pathway seeding. *Am J Otolaryngol* 2014;**35**:431–4.
19. Iloreta AM, Nyquist GG, Friedel M, Farrell C, Rosen MR, Evans JJ. Surgical pathway seeding of clivo-cervical chordomas. *J Neurol Surg Rep* 2014;**75**:e246–50.
20. Krengli M, Liebsch L, Harsh G, Hug EB, Munzenrider JE, Suit HD. Tumor implantation during skull base surgery. In: *Proceedings II International Skull Base Conference*. 1996.
21. Vogin G, Calugaru V, Bolle S, et al. Investigation of ectopic recurrent skull base and cervical chordomas: the Institut Curie's Proton Therapy Center experience. *Head Neck* 2015, http://dx.doi.org/10.1002/hed.24199.
22. Yokoi K, Miyazawa N, Imura G. Isolated incisional recurrence after curative resection for primary lung cancer. *Ann Thorac Surg* 1996;**61**:1236–7.
23. Moore MG, Lin DT, Deschler DG, Wang JJ, Chan AW. Risk of incisional recurrence after midface and anterior skull base surgery in sinonasal malignancies. *Skull Base* 2011;**21**:87–92.
24. Joshi SC, Sharma DN, Khurana N, Mohanta PK, Bahadur AK. Endometrial carcinoma with recurrence in the incisional scar: a case report. *Int J Gynecol Cancer* 2003;**13**:901–3.
25. Chen TP, Liu HP, Lu HI, Hsieh MJ, Liu YH, Wu YC. Incidence of incisional recurrence after thoracoscopy. *Surg Endosc* 2004;**18**:540–2.
26. Gunderson LL, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following curative surgery for adenocarcinoma of the rectum. Clinicopathologic correlation and implications for adjuvant therapy. *Cancer* 1974;**34**:1278–92.
27. Smith EH. Complications of percutaneous abdominal fine-needle biopsy. Review. *Radiology* 1991;**178**:253–8.
28. Chibbaro S, Cornelius JF, Froelich S, et al. Endoscopic endonasal approach in the management of skull base chordomas-clinical experience on a large series, technique, outcome, and pitfalls. *Neurosurg Rev* 2014;**37**:217–24.