


Sentinel Node Biopsy for Conjunctival Melanoma; Single Centre Experience and Review of Current Literature

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Barbara Peric, MD, PhD^{1,2} , Spela Leiler, MD³, Gregor Hawlina, MD, PhD^{2,4}, Boris Jancar, MD¹, Marko Snoj, MD, PhD^{1,2}, and Andraz Perhavec, MD, PhD^{1,2}

Abstract

Purpose: To evaluate the role of sentinel lymph node (SLN) biopsy in patients with conjunctival melanoma (CjM).

Study design: Retrospective observational cohort study and literature review.

Subjects: Slovenian patients with CjM are included in the study.

Methods: Prospectively collected data of CjM patients treated from June 2005 to December 2016 were retrospectively analyzed.

Main outcome measures: The numbers of SLN biopsy procedures, positive and false positive SLN, and local and regional relapses have been described together with overall survival.

Results: From June 2005 until December 2016, 24 patients with CjM were treated. The median follow-up time was 65.3 months. The mean Breslow thickness was 1.5 mm (sd = 1.8 mm), and ulceration was present in 29% of cases. Altogether, 14/24 (58%) SLN biopsy procedures were performed. SLN was positive in 2/14 (14%) cases. The estimated 5-year overall survival (OS) of the group was 72.5%, with a median survival of 151 months (95% CI 77–224). From January 2013 to January 2020, five (5/140, 3%) authors reported results comparable to our study.

Conclusion: Our results confirm that CjM is a rare disease with approximately 14% of positive SLN. At the moment, there are no firm conclusions regarding who would benefit most from SLN biopsy or whether or not CLND should be offered. Data from literature emphasize the need for consistent and uniform staging and future multicentric studies.

Keywords

conjunctival melanoma, sentinel node biopsy, lymphadenectomy, survival

Introduction

Conjunctival melanoma (CjM) is the second most common primary malignancy of the ocular surface and constitutes 5% of all the melanomas of the eye. It occurs with an annual incidence of 0.2–0.7/1.000.000.^{1,2} Tumors are common among the Caucasian population and the elderly.³

This rare tumor emerges from atypical melanocytes in the basal layer of the epithelium.⁴ The most important risk factors are conjunctival melanocytic intraepithelial neoplasia or

¹Institute of Oncology Ljubljana, Ljubljana, Slovenia

²Faculty of Medicine, University of Ljubljana, Slovenia

³Eye Hospital, University Medical Centre, Ljubljana, Slovenia

⁴Eye Hospital, University Medical Centre, Ljubljana, Slovenia

Corresponding Author:

Barbara Peric, Institute of Oncology Ljubljana, Zaloska 2, Ljubljana 1000, Slovenia.

Email: bperic@onko-i.si



primary acquired melanosis (PAM), previous nevi, and UV exposure.⁵

Although there are similarities between clinical appearance and association with UV exposure, CjM presents itself differently in biological behavior in comparison to cutaneous melanoma; for example, it is associated with higher recurrence rates after primary therapy.⁶ The overall frequency of a local recurrence is estimated to be approximately 40%.⁴

Analogous to cutaneous melanoma, CjM is believed to have spread to regional lymph nodes in 19% of cases at the time of discovery. The first regional lymph nodes affected by nodal spread are usually pre-auricular, and rarely submandibular or deep cervical.³ Tumor thicknesses of >2 mm and large basal diameter but also non-epibulbar location, positive resection margins, orbital extension, nodular tumours, “de novo” emergence, and ulceration are associated with a higher risk of nodal metastases.^{1,7-9}

Since sentinel lymph node (SLN) biopsy gives important prognostic information in the case of cutaneous melanoma, the same procedure was proposed for CjM patients. Indeed, it has been shown that positive SLN correlates significantly with death from CjM.¹ Detection of subclinical micrometastases in regional lymph nodes followed by completion lymph node dissection (CLND) of the neck was thought to offer CjM patients a survival advantage.⁸ Although the procedure has been widely used, the efficacy of this approach in CjM is not completely clear due to the low incidence of the disease and frequency of SLN positive cases.^{2,4,11}

Interestingly, in recent years, our understanding of the importance of CLND after positive SLN biopsy has been comprehensively altered based on the results of two prospective randomized trials which showed that CLND offers no survival benefits when compared to follow-up US scans for patients with cutaneous melanoma.^{12,13}

Evidence of cutaneous melanoma raises the question of whether CLND should be offered to patients with CjM in order to improve regional control and perhaps even survival. Due to a lack of randomized prospective studies, the only available data addressing the topic of SLN biopsy in CjM comes from clinical registries and researchers’ reports.

The aim of our study was to evaluate the frequency of regional lymph node metastases of CjM patients in Slovenia and to compare our results with available literature data.

Methods

For this retrospective observational cohort study with a systematic review of the available literature, data of Slovenian CjM patients were analyzed. Analysis of prospectively collected data from the Institute of Oncology Ljubljana clinical registry and the national Cancer Registry was performed. Patients with CjM treated from June 2005 to December 2016 were included.

All patients were initially diagnosed and treated at the Eye Hospital of the University Medical Centre of Ljubljana, where

primary tumors were excised. All CjM specimens were examined by two experienced pathologists specialized in melanocytic lesions. After tumor removal and confirmation of CjM, if indicated, SLN biopsy was performed at the Institute of Oncology Ljubljana within 6 weeks following tumor resection. The indications were as follows: tumour thickness > 1 mm in 5 patients, non-limbal location in 4 patients, > 1 mitosis/mm² in 3 patients, and in two cases it was performed after local recurrence. The procedure was performed according to standard recommendations including subconjunctival injection of 0.2 mL of Technetium-99m (Tc-99m) and dynamic and static imaging with a gamma camera (lymphoscintigraphy). After lymphoscintigraphy, the SLN was surgically excised with the assistance of a sterile, handheld gamma probe through a 3 cm incision placed over the area of high radioactivity. No touch technique was used with regard to the node. Blue dye subconjunctival injections were used in earlier cases and later omitted due to the danger of residual blue staining. The excised SLNs were histologically evaluated using a “bread loaf” approach. In case adjuvant treatment of the primary tumor was required (wider local excision or strontium-90 (Sr90) beta radiotherapy of the tumour bed), it was performed at the time of the SLN biopsy.

In case of positive SLN, CLND was performed which included superficial parotidectomy and lymph nodes levels I to V according to the American Head and Neck Society classification.¹⁷ The procedure was also performed in cases of clinically detected metastatic lymph nodes.

After the SLN biopsy, patient progress was followed according to a schedule: a clinical exam every 3 months for the first 2 years, then every 6 months until the fifth year, and thereafter by an ophthalmologist every 6 months. Local recurrence was defined as the recurrence of histologically proven invasive CjM. Regional and distant metastases were identified clinically and/or via US, MRI, PET-CT, or CT, and confirmed with fine needle aspiration biopsy (FNAB) followed by histological examination of the removed lymph nodes. Follow-up was closed on March 14, 2020. The clinical records of all consecutive patients were reviewed with regard to age, sex, time of diagnosis, tumor location at presentation, regional and distant metastases at presentation, time of SLN biopsy, and outcome of interest (local recurrence, regional metastases, distant metastases, death from CjM, and death from any other cause). Histopathological records for each patient were reviewed for tumor thickness, presence of ulceration, and mitotic rate. Patients were staged according to the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th edition)*, and pathological criteria were used for primary tumor definition.

Clinicopathological characteristics were summarized as frequencies and percentages for categorical and means for continuous variables. Overall survival (OS) was defined as the interval from the date of diagnosis to the date of death, and was censored for the last follow-up date. The survival curve was plotted using the Kaplan–Meier method. The analysis was

conducted using IBM SPSS software version 26, and P -value $< .05$ was considered statistically significant.

The literature review was conducted using advanced searches of the PubMed biomedical literature database with the following indicators; (conjunctiva AND melanoma) OR conjunctival melanoma AND (sentinel node biopsy OR epidemiology OR incidence OR genetic). A manual search was also performed for articles referenced in bibliographies that were not initially retrieved by the search, as well as in specific areas in which information was lacking. All articles published in English between January 2013 and January 2020 were reviewed and the most suitable were included in the study comparison.

Results

From June 2005 until December 2016, 24 patients with CjM were treated at the Institute of Oncology Ljubljana. The mean age at the time of CjM diagnosis was 60.8 years. There were 17 (71%) female and 7 (29%) male patients. All primary tumors were treated with wide local excisions by the ophthalmologist. In 15/24 (62.5%) patients, the disease affected the left eye, while 9/24 (37.5%) patients had right eye CjM. The locations of the tumor were as follows: limbus in 7/24 (29%) cases, bulbar in 13/24 (54%) cases, tarsal in 3/24 (12%) cases, and unknown in 1/24 (4%) case.

Mean tumor thickness was 1.5 mm (sd = 1.8 mm) and ulceration was present in 7/24 (29%) cases. In 4/24 (17%) the information was unavailable. PAM was noticed in 9/24 (37%) cases.

In total, 14/24 (58%) SLN biopsy procedures were performed, while eleven patients did not undergo the SLN biopsy and in one case the procedure was repeated due to a new primary tumor.

Residual blue staining of conjunctiva was noticed for a few days in all the patients with whom blue dye was used (8/14). In one case transient paresis of the marginal mandibular nerve was reported (1/14, 7%).

The removed SLN was positive in 2/14 (14%) cases. Metastases measured 0.3 mm and 0.6 mm. After completion of lymph node dissection, no other metastases were discovered (60 and 35 lymph nodes were removed).

Regional lymph nodes were clinically detected and removed during follow-ups for two patients with no previous SLN biopsy (2/24, 8%). Altogether, lymph node metastases were discovered in 4 patients (4/24, 17%).

The median follow-up time was 65.3 months. During that time, four patients (4/24, 17%) developed distant metastases. Four patients (4/24, 17%) had local recurrence on conjunctiva that required reoperation and/or radiotherapy.

At the time of the completion of the study, 15 patients were alive (15/24, 62%) and 9 (37%) patients had died. Five patients died due to CjM (5/24, 21%), one of the patients died due to direct intracranial invasion, and four patients died due to systemic disease. One of the patients with systemic disease had a positive SLN with CLND, and one had previous regional

disease and no SLN biopsy. A summary of the results is presented in Table 1.

The estimated 5-year overall survival (OS) of the group was 72.5%, with a median survival of 151 months (95% CI 77–224). There was no survival difference between female and male patients ($P = .321$). The Kaplan–Meier survival curve of patients is shown in Figure 1.

The PubMed literature search resulted in 356 articles related to CjM. Out of 140 articles published in a 6-year period from January 2013 to January 2020, four (5/140, 3%) reported results comparable to our study. Three studies also had comparable methodologies (Esmaeli, Pfeiffer, and Cohen), while one did not use SLN biopsy as the standard procedure (Brouwer).^{1,8,11,14} Finally, we compared our results with published meta-analysis (Wong).⁴ The summary of the literature search and a comparison to our results are presented in Table 2.

Table 1. Clinicopathological characteristics of the 2005–2016 CjM cohort.

AJCC 8th pT	T1a	T1b	T2a	T2b	Unknown	T3a	T3b
No	15	0	2	0	2	2	3
PAM present	8	/	/	/	/	0	0
Mitoses $>1/\text{mm}^2$	4	/	/	/	/	1	3
Ulceration							
Yes	2	/	/	/	0	1	3
No	11	/	/	/	1	0	0
Unknown	2	/	0	/	1	1	0
SLNB							
Yes	8	/	/	/	2	1	2
No	7	/	/	/	1	1	1
SLN positive							
Yes	1	/	/	/	0	0	0
No	7	/	0	/	2	1	2
Reg	1	/	0	/	1	0	0
Local	1	/	0	/	1	1	1
Distant	2	/	0	/	0	1	1
CjM death	2	/	0	/	0	2	1

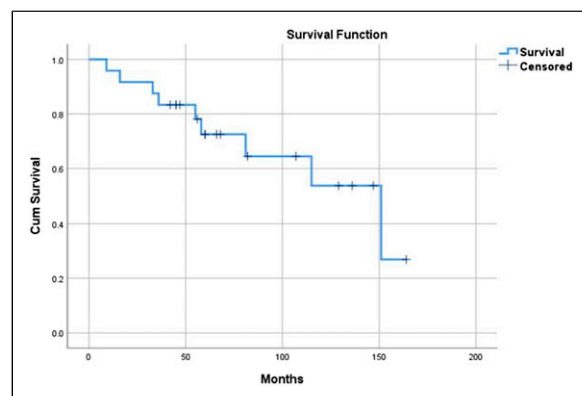


Figure 1. Survival of Slovenian CjM patients.

Table 2. SLN procedure for CjM; summary of the results.

Author, title	Perić	Pfeiffer et al. (2017) [including patients from Savar et al. (2009)]	Esmaeli et al. (2019)	Cohen et al. (2013)	Brouwer et al. (2018)	Wong et al. (2014) meta-analysis
Follow-up	65.3 (median, months)	63 (median, months)	46.6 (median, months)	20 (median, months)	70.2 (mean, months)	1.9 (mean, years)
No. of cases	24	31 (out of all 51 patients with ocular axonal melanoma)	88	22 (4 with injection failure)	70	56 (4 with injection failure)
Males	7 (29%)	21 (41%)	32 (36%)	11 (50%)	35 (50%)	N/A
Females	17 (71%)	30 (59%)	56 (64%)	11 (50%)	35 (50%)	N/A
Mean age at diagnosis (years)	60	62	62	59	60.3	Not specified
Location of tumour	Limbus 7/24 (29%), bulbar 13/24 (54%), tarsal 3/24 (12%), and unknown in 1/24 cases (4%)	Bulbar 27%, palpebral 10%, and both 8% (out of all 51 patients with ocular axonal melanoma)	Not specified	Non-epibulbar	Not specified	Not specified
Requirements for SLNB	Hist. invasive CjM + ulceration, no distant metastases	No signs of metastasis, >17 years, hist. confirmed CjM, >1 mm thick or ulceration	Not specified	>2 mm thick, unfavourable location (forniceal, caruncular or tarsal conjunctiva) and recurrent melanoma	Not performed by standard. Instead, US every 6 months and in case of susp. finding cytological examination	>1 mm, exclusion of regional and distant metastasis, and histological ulceration
No. of SLNBs	14/24 (58%)	All	31/88 (35%)	All	All	All
SLNB positive	2/14 (14%)	4/31 (13%) (in CjM group)	4/31 (13%)	2/18 (11%)	2/18 (11%)	9/52 (17%)
SLNB false negative	None	2/27 (7%)	Not specified	None	None	4/43 (9%)
Injection failure	None	1/51 (2%)	Not specified	4/22 (4%)	4/22 (4%)	4/56 (7%)
Complications of SLNB	Transient blue staining in patients where blue dye was used (8/14, 57%) and transient marginal mandibular nerve palsy (1/14, 7%)	Transient facial nerve palsy (6%), haematoma of the neck (2%), and stitch abscess (2%)	Not specified	Transient blue staining (23%) and transient facial nerve palsy (6%)	Transient blue staining (23%) and transient facial nerve palsy (6%)	Transient blue staining (31%) and transient facial nerve palsy (6%)
No. of local relapses	4/24 (17%)	N/A	14/88 (16%)	1/2 (50%) (from SLNB+)	20 (29%)	40% (307/770)
No. of regional relapses	4/24 (17%)	6/31 (19%)	5/88 (6%)	1/2 (50%) (from SLNB+)	7 (10%)	19% (140/734)
No. of systemic relapses	4/24 (17%)	At least 1/31	16/88 (19%)	5/22 (23%)	9 (12%); 4/9 without prior regional disease	19% (141/734)

(continued)

Table 2. (continued)

Author, title	Peric	Pfeiffer et al. (2017) [including patients from Savar et al. (2009)]	Esmaeli et al. (2019)	Cohen et al. (2013)	Brouwer et al. (2018)	Wong et al. (2014) meta-analysis
Primary treatment	Wide local excision (24/24) followed by Sr-90 brachytherapy (21/24)	Wide local excision	Not specified	Wide local excision (24/24) followed by adjuvant cryotherapy was performed in (12/22), β -radiotherapy (strontium 90) in 6/22, and MMC .04% (1/22)	Wide local excision followed by adjuvant cryotherapy (7/70), chemotherapy (1/70), ruthenium plaque (11/70), strontium brachytherapy (21/70), or iridium brachytherapy (2/70)	Wide excision (+/- adjuvant cryotherapy, topical chemotherapy, or radiotherapy)
SLN biopsy + lymphadenectomy	2 CLND		Not specified		1st: Underwent superficial parotidectomy and radical dissection of the lymph node chain. 2nd: Palliative regional radiotherapy to the neck due to frailty. The patient died due to systemic CjM	Subsequent lymphadenectomy demonstrated benefits of prolonged distant disease-free survival and overall survival
Survival	5-year OS: 72.5%, mean survival of 113 months (95% CI 88–138)	5-year OS: 79% (out of all 51 patients with ocular and axillary melanoma)	Positive SLN associated with increased risk of death from disease, HR = 6.24, 95% CI: 1.25–31.13	17/18 patients survived during the follow-up period, no 5-year survival reported	5-year OS: 72%, melanoma-related survival 90%	5-year OS: 74–86%
Conclusions	The benefits of performing SLN biopsy in CjM patients are questionable	SLN biopsy is safe and identifies nodal micrometastasis in approximately 20% of cases	Authors found a significant correlation between SLN status and disease-related death, highlighting the opportunity to offer additional treatment to patients with a positive SLN.	SLN biopsy is a safe procedure and should be considered for the staging of patients with high-risk conjunctival melanoma	Despite no use of SLN biopsy, recurrence rates are similar. Instead, US follow-up every 6 months has been performed	The role of lymphoscintigraphy and SLN biopsy is highly debatable to date, as improvement in survival with this technique has not yet been established

Discussion

With this retrospective observational study, we have added another 24 CjM cases to existing reports of this rare melanocyte tumor. The number of cases diagnosed in Slovenia from 2005 to 2016 is no surprise since the rarity of the disease has previously been noted by other authors.^{4,7,8,14} Since an incidence of 0.15-0.78/100.000 has been reported recently, the number of diagnosed patients in this study is slightly higher than expected.² The fact that 42% of the patients were diagnosed in the last 3 years could indicate that the incidence of the disease is rising in Slovenia.

Fourteen patients (58%) had SLN biopsies performed during that period. The number of procedures is relatively low considering other reports; Pfeiffer and Esmali reported 31 cases, Cohen 22 SLN biopsy procedures, and Wong's meta-analysis included data from 52 patients.^{1,4,8,14} Only the results reported by Cohen featured prospectively collected data; all the other researchers relied on retrospective results.^{1,8,14}

When attempting to compare the results of previous reports to our findings, various obstacles are encountered. Though the age and distribution of patients are quite similar, the median follow-up times range from 20 to 65 months in different studies. However, the main obstacle is unclear or missing staging (TNM according to the AJCC Cancer Staging Manual) and various indications for SLN biopsy procedure. While some advocate SLN biopsy in the case of histological confirmation of CjM with no signs of distant metastases, and tumor thickness of at least 1 mm or presence of ulceration, others recommend it for tumor thickness of >2 mm, non-limbal location, and recurrence after previous PAM removal.^{5,8,14}

In our group of patients undergoing SLN biopsy, only half of them reached tumor thickness of >1 mm, and biopsy was proposed to others due to high mitosis count, unfavorable tumor location, or invasive CjM discovered after previous PAM removal. Despite such factors, which have been associated with higher risk of metastases in the past, the number of positive SLN was low, only 2/14 (14%). The percentage of positive SLN is still quite similar to other reports, where it varies from 11 to 17%.^{4,8,14} Both SLN-positive patients had tumor thickness of >1.5 mm and >10 mitosis/mm², which indicates that the risk of disease progression to regional lymph nodes increases with tumor thickness and mitoses, similar to cutaneous melanoma. These results concur with the proposal that SLN biopsy should be offered based on the presence of at least two of the high-risk features: non-limbal location, >2 mm thickness, ulceration, and >1 mitotic figure per mm².⁴ Tumor thickness of >2 mm, presence of ulceration, positive SLN, and mitotic rate were all recently associated with lower disease-specific survival or increased risk of death from disease.¹

The triple technique of SLN detection employed correctly identifies the SLN in 99% of cases.¹⁵ Failure of the method is associated with false negative (FN) rate. One of the important risk factors of the failure to retrieve the correct node in cases of

cutaneous melanoma is due to tumors located in the head and neck region.¹⁶ Although FN rate is not always reported, Pfeiffer and Wong described the FN rate of 7–9% of CjM cases.^{4,8} We managed to detect the SLN in all our patients in the preauricular or submandibular regions with no FN results.

The specific node location can lead to injection failure and certain postoperative complications.⁴ In our cohort, palsy of the mandibular branch of the facial nerve was present in one case, which accounts for 7% of nerve damage. We did not experience injection failure. The complication rate was similar to other reports where transient nerve damage was described in 6% of cases and injection failure in 7% of cases.^{4,8,14}

FN lymph nodes are discovered due to regional relapses during follow-up or due to CLND. Though data of regional relapses are usually presented by authors and vary from 6 to 19%, data about CLND are scarce.¹⁴ We performed CLND in both patients with positive SLN and in both cases histology revealed no additional metastatic lymph nodes.

The issue of CLND in CjM patients is controversial, as the results of two prospective studies in cases of cutaneous melanoma have shown that there was no survival difference between the group of patients with cutaneous melanoma who had CLND due to positive SLN, and those who had the procedure after regional relapse.^{12,13}

Positive SLN was associated with an increased risk of death from disease (HR = 6.24, 95% CI 1.25–31.13).¹ However, by treating cutaneous melanoma patients, we have learned that the size of metastatic deposits in SLN also correlates with prognosis. It has been well established that micrometastatic disease (<0.1 mm) is associated with similar survival rates as negative SLN in case of cutaneous melanoma. Even tumor deposits of sizes <1 mm have a good prognosis with 85% 5-year survival.¹⁷ In our cohort, both patients with positive SLN had CLND due to metastases of <1 mm, and in both cases, histology revealed no additional metastatic lymph nodes. Even though SLN metastases indicate an increased risk of death, it is difficult to conclude whether and which patients should proceed with CLND. Another possibility for patients with positive SLN could be US follow-up.¹⁵

In our study, 17% of patients had a regional spread of the disease and the same number of patients had distant metastases. Results are similar to other reports (regional disease 10–19% and systemic 19–23%),^{4,8,11,14} A slightly lower percentage of regional disease (6%) was reported by Esmali.¹⁰ One interesting observation to note is that out of 5 patients who died due to CjM, only two had had previously clinically or pathologically detected regional lymph node metastases.

The estimated 5-year OS of our group of patients was 72.5%, with no differences between male or female patients. The estimate is in concordance with a composition of five large studies, which revealed 5-year survival rates between 74% and 86%, with one study reporting a 5-year estimate of CjM-related deaths of 7%.^{4,8,11,14}

Information about SLN is one of the most important prognostic factors in cutaneous melanoma that enables clinicians

to decide which patients need adjuvant targeted therapy or immunotherapy.^{15,16} Recently, successful use of programmed cell death 1 (PD-1) inhibitors has been reported in metastatic CjM.¹⁰ Based on this, it has been proposed that CjM patients with positive SLN, and thus increased risk of death, could also be candidates for adjuvant systemic treatment.¹

We are aware of the limitations of our study as a retrospective analysis of a small population of CjM patients. However, we present national data and not only a single-center experience. Adding a pathological T category according to the AJCC 8th edition enabled us to focus only on invasive melanoma and to exclude the possible bias of in situ lesions. Tumor staging and reporting of ulceration in our group of patients could prove invaluable for future meta-analysis of SLN biopsy in CjM.

Conclusion

In conclusion, our results confirm that CjM is a rare disease with approximately 14% of positive SLN. Currently, there are no firm conclusions regarding who could benefit most from SLN biopsy and whether or not CLND should be offered. Data from literature emphasize the need for consistent and uniform staging and future multicentric studies.

Appendix

Abbreviations

CI confidence interval
 CjM conjunctival melanoma
 CLND completion lymph node dissection
 CT computer tomography
 FNAB fine needle aspiration biopsy
 MRI magnetic resonance imaging
 OS overall survival
 SLN sentinel lymph node
 US ultrasound

Declaration of conflicting interests

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Ethics approval

The study was conducted in accordance with recommendations of Ethical Committee at The Institute of Oncology Ljubljana (NAV–613–8010–Ver 10 / February 20, 2020) and the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki.

Informed consent

All patients provided written informed consent including study participation prior to treatment.

ORCID iD

Barbara Peric  <https://orcid.org/0000-0001-7228-8267>.

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