Clinicopathological Study of Primary Intraosseous Squamous Cell Carcinoma of the Jaw and a Review of the Literature

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Abstract

Background: Primary intraosseous squamous cell carcinoma (PIOSCC) is a rare malignant odontogenic tumor that originates from odontogenic epithelial remnants. It is often difficult to definitively diagnose PIOSCC, and hence, extraction or surgical treatment is performed prior to initial diagnosis in most cases. In the present study, we aimed to examine new insights into and prognostic factors of PIOSCC patients admitted to our department.

Methods: We extensively reviewed the records of patients who underwent radical surgery for PIOSCC between January 2001 and December 2014.

Results: Among all the cases of OSCC, the frequency of PIOSCC was 1.45%. The 2-year relapse-free survival (RFS) and overall survival (OS) rates were found to be 50.0% and 41.6% in all cases, respectively. Three patients underwent surgery or tooth extraction prior to the initial diagnosis; in fact, intervention prior to initial diagnosis was found to be a significantly poor prognostic factor for RFS and OS. In contrast, patients who were not treated before the initial diagnosis was made, did not exhibit any loco-regional recurrence.

Conclusions: The treatment of PIOSCC should be similar to that for oral cancer with clinical stage T3N0 or higher in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines. In addition, the cases of PIOSCC that are not treated prior to the initial diagnosis are more likely to obtain a good prognosis.

Key words: Primary intraosseous squamous cell carcinoma, extraction, prognostic factor

Introduction

The World Health Organization (WHO) in 2005 described that ameloblastic carcinomas and primary intraosseous squamous cell carcinoma (PIOSCC) are odontogenic carcinomas that originate from odontogenic epithelial remnants[1]. Although the pathogenesis of PIOSCC remains unclear, chronic inflammation from an odontogenic infection has been hypothesized as a key factor in carcinogenesis.[2] A comparison of PIOSCC and mucosal OSCC suggested that the carcinogenic process may be markedly similar, but that both tumors exhibit different sets of oncogenes and tumor markers, which would indicate different genetic pathways.[3]

In 2005, the WHO indicated 3 subcategories of PIOSCC: a solid tumor that invades the marrow spaces and induces osseous resorption, squamous cancer that arises from the lining of an odontogenic cyst, and a squamous cell carcinoma in association with other benign epithelial odontogenic tumors.[1] Waldron and Mustoe proposed a different classification that has been widely accepted; however, certain more recently described types of odontogenic epithelial malignancies are not included.[4] It is often difficult to definitively diagnose PIOSCC as the lesions need to be distinguished from alveolar carcinoma that could invade the bone from the overlying soft tissues or from tumors that have metastasized to the jaw from a distant site and from primary tumors of maxillary sinus origin.[5]

The overall prognosis for patients with PIOSCC is reportedly poor. The primarily causes for this poor prognosis include the vague symptoms and aggressive behavior of tumor cells, which lead to tumor growth, frequent local recurrence and lymph node metastasis.[6-9] However, the WHO 2005 report[1,10] and National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines[11] have not described the T classification of PIOSCC in detail or the standard therapy for this condition; moreover, several other

clinical features of PIOSCC remain unclear.

In the present study, we reviewed cases of PIOSCC that underwent radical surgery, and elucidated certain novel insights and prognostic factors.

Materials and Methods

Patients

We retrospectively reviewed the records of patients who underwent radical surgery for PIOSCC between January 2001 and December 2014, and those who were followed for >1 year. This study was approved by the independent ethics committee of our hospital. Tumor stage was classified according to the TNM classification of the International Union Against Cancer,[10] whereas histologic tumor differentiation was defined according to the WHO classification.

All the study patients underwent extensive pretreatment evaluation, including physical examination, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US). The diagnostic criteria of PIOSCC included the absence of an initial connection with the overlying mucosa or skin and the exclusion of metastasis from a distant primary site or association with another odontogenic tumor or maxillary sinus. In addition, the information obtained from clinical findings was thoroughly evaluated.

Statistical analysis

The relapse-free survival (RFS) and overall survival (OS) rates were calculated by using the Kaplan-Meier method and compared by using the log-rank test. P values of < 0.05 were considered significant.

Results

Patient characteristics

The clinicopathological characteristics of the patients are summarized in Table 1. During the 11-year period between January 2001 and December 2014, 6 of 414 patients (1.45%) were diagnosed with PIOSCC, including 5 male and 1 female patient. The mean patient age was 71 years (range, 59–81 years). The chief complaints included non-healing of the extracted socket, pain and swelling, or swelling with sensory disturbance of the region. Three patients underwent surgery or tooth extraction prior to the initial diagnosis, and the duration after surgery was either 1 month or 2 months. Positive nodes were detected in 4 patients, although distant metastasis was not observed in any of the patients on imaging. A panoramic examination indicated the presence of a radiolucent lesion in all the cases, and the lesion borders were found to be well-defined in 2 cases (Fig 1A and B), irregular in 3 cases (Fig 2A and B), and non-evaluable in 1 case. The greatest dimension of the lesions ranged from 25 to 56mm. Biopsy was performed in 5 patients, and the duration between biopsy and surgery ranged from 8 to 36 days.

Treatment and outcome

The treatment courses of the patients are summarized in Table 2. Initial treatment involved the excision of the primary tumor at the time of neck dissection or excision only in all the cases; thereafter, postoperative radiotherapy (RT; total 66Gy) with or without concurrent chemotherapy (60-100mg/m^2 Cisplatin [CDDP]) was performed in patients with adverse risk features according to the NCCN Clinical Practice Guidelines. Pathological lymph node metastasis was detected in 3 patients, and positive extracapsular spread (ECS) was observed in 1 patient. Recurrence or distant metastasis

was noted in 3 patients, and salvage surgery was required in 2 patients. After the surgery, since 2 patients had unresectable recurrent tumors, systemic chemotherapy (400 mg/m^2 for the first injection and 250mg/m^2 Cetuximab, 60-80mg/m^2 Paclitaxel) was performed. Since 1 patient had unresectable recurrent tumors and multiple distant metastases, palliative treatment was performed. Three patients died because of local failure, regional failure, or distant metastasis. At present, the remaining 3 patients are being closely followed (duration of follow-up, 12–74 months). Three patients did not exhibit any evidence of the disease at the final follow-up.

RFS and OS rates

The 2-year RFS and OS rates were found to be 50.0% and 41.6% in all cases, respectively (Fig 3). Moreover, the patients were classified into 2 different groups: (Group A) intervention group, wherein surgery or extraction was performed prior to the initial diagnosis; and (Group B) non-intervention group, wherein no surgery or extraction was performed prior to the initial diagnosis. The RFS and OS rates were examined between the groups. The 1-year RFS rates in the intervention and non-intervention groups were 0% and 100%, respectively (P = 0.0246; Fig 4A), and a significant correlation in this value was observed between the groups. Moreover, the 1-year OS rates in the intervention and non-intervention groups were found to be 66.7% and 100%, respectively (P = 0.052; Fig 4B).

Histopathological findings

The surface of the tumor was covered by non-ulcerative mucosa without moderate to severe dysplasia or carcinoma in all cases (Fig 5A). With regard to the differentiation of PIOSCC according to the WHO classification, 3 cases exhibited a

well-differentiated tumor, 2 cases exhibited a moderately differentiated tumor, and 1 case exhibited a poorly differentiated tumor. In cases where the PIOSCC arose from cystic lesions, the lesions exhibited hypokeratinizing tumor cells that formed relatively round or ovoid tumor nests with a palisading arrangement of basal cells (Fig 5B). Although the sequences between the cyst epithelium and tumor epithelium were not clear, this tumor was confirmed as a PIOSCC originating from odontogenic cysts because cytokeratin 19 immunohistochemical staining yielded positive results in the tumor cells but not in the oral mucosa (Fig 5C). In cases where the PIOSCC arose de novo, the growth of tumor cells was observed in the bone marrow of the mandible (Fig 5D). This tumor was not associated with any cystic component and appeared to arise de novo.

Discussion

Both the WHO 2005 report and NCCN Clinical Practice Guidelines have not provided detailed information regarding PIOSCC, and hence, further insights and data on prognostic factors could help better understand the condition and develop novel treatments. In the present study, we aimed to elucidate new insights and the prognostic factors of PIOSCC.

PIOSCC is a rare malignant odontogenic tumor that accounts of <2% of all cases of oral SCC.[12,13] The most common site of PIOSCC ranges from the retromolar region to the ramus of the mandible; the ratio of occurrence at the mandible and maxilla has been found to be 4:1.[7,14] In the present study, we detected 6 cases of PIOSCC in a series of 414 cases of oral SCC; the ratio of occurrence at the mandible and maxilla was similar in these cases.

The radiologic findings of PIOSCC are varied, including radiolucent appearance,

well-defined lesions with cortical preservation, small or massive amounts of bone resorption, and more aggressive forms with irregular borders.[15] Kaffe et al reported that the radiologic borders of PIOSCC were defined, but non-corticated, in 57% of cases and diffuse in 43% of cases; hence, this feature could be used as a criterion for diagnosis.[14] To our knowledge, no cases of root resorption or tooth displacement have been reported thus far. In the present study, we noted 3 cases with diffuse and irregular borders and 2 cases with defined borders that were non-corticated.

With regard to the histopathologic features of PIOSCC, tumors that arise from the cystic component reportedly show well-differentiated keratinizing carcinomas. In contrast, tumors with de novo origin show less-differentiated keratinizing or non-keratinizing carcinomas.[16] In the present study, however, the histopathologic features were not associated with the site of origin.

Most studies, including case reports, have indicated that the prognosis of PIOSCC is poor.[6-9,16] One of the reasons underlying this poor prognosis is that the PIOSCC symptoms are vague, and usually involve pain, swelling, and sensory paralysis in the lower lip; moreover, except for cases that are detected incidentally during radiography, the tumor cells in these cases have already invaded the extra jawbone prior to the initial diagnosis.[6,7,14] In the present study, none of the cases exhibited tumor cells that were strictly confined to the jawbone.

Furthermore, the rate of metastasis in cases of PIOSCC is reported to be 18.1–51%,[6,7,9,17] with marked differences between tumors of de novo (36.5%) and cystic origin (4.4%).[9] In the present study, 3 cases were diagnosed as pN (+) and were found to have tumors of de novo origin. In addition, in PIOSCC cases, the local recurrence rate is reportedly 50–60%,[6,18] whereas the 5-year survival rate is reportedly 30–40%,[7,8] with a 2-year survival rate of 40–68%.[6,7,18] In the present study, local recurrence was only

observed in 1 case and the RFS and OS rates were similar among the cases.

The NCCN Clinical Practice Guidelines have not described any standard therapy for PIOSCC. However, since the survival rate is consistent with that of other stage IV oral cavity lesions,[7,8] we believe that the treatment should be similar to that for oral cavity cancers with clinical stage T3N0 or greater. Thus, in the present study, surgery and postoperative RT, with or without concurrent chemotherapy, was performed for high-risk cases, including those with extracapsular spread of lymph node metastasis and positive margins. Elective neck dissection is generally recommended even in patients not diagnosed with cervical lymph node involvement because the reconstruction of hard tissues is required in most of these cases.

PIOSCC is often misdiagnosed as periodontitis or pericoronitis based on the imaging findings, and hence, tooth extraction or surgical treatment is commonly performed prior to the initial diagnosis. In these cases, the extracted socket exhibited non-healing, followed by pain, swelling, and sensory paralysis.[9,19,20] However, no assessment of the error rate of the preoperative diagnosis of PIOSCC has been performed. To our knowledge, preoperative dental operations were performed in 30 of 53 cases (56.6%).[6,8,9,14,18,20-23] In contrast, the error rate for SCC of the gingiva have been reported to be 25.5% (26 of 102 cases).[24] Although preoperative dental operations are considered to be significantly associated with a poor prognosis in patients with OSCC,[24] no investigations of the prognosis of PIOSCC have been performed thus far. A review of previous reports classified 12 of 53 cases who were followed up for > 12 months and could be evaluated into an intervention group and non- intervention group; none of the 6 cases in the non-intervention group exhibited any evidence of disease, whereas 3 of the remaining cases in the intervention group exhibited a poor prognosis.[8,9,14,18,20-22] In the present study, marked differences in the RFS and OS rates were observed between the

intervention group and non-intervention group. The patients who did not undergo treatment prior to the PIOSCC diagnosis exhibited no recurrence. These results suggested that preoperative dental operations in PIOSCC may be a potential prognostic factor. In the intervention group, 2 cases presented with cystic type on radiographs and the other case had been followed for only 12 months. Hence, there may be some biases against the clinical outcome. However, as tumor cells in all the cases had ruptured through the jaw and into the peripheral soft tissues on both radiography and histopathology, there were minimal differences based on the extent of the disease.

Thus, we discussed novel insights about PIOSCC and the prognostic factors. Nevertheless, the study has 2 major limitations, including its retrospective nature and the small number of cases. Moreover, there were some biases that were inherent in these studies, including the data recorded by the authors. The management of our department in PIOSCC has been uniformed to reduce biases associated with retrospective study design. In addition, the incidence of PIOSCC is very low among all the cases of OSCC. Hence, an intergroup study with a further number of cases is needed.

In conclusion, based on the clinical features of PIOSCC, we believe that the treatment of this condition should be similar to that of oral cancers with clinical stage T3N0 or greater. Moreover, the lack of any intervention prior to the initial diagnosis in PIOSCC cases could possibly achieve a better prognosis, particularly if the diagnosis is made early and an adequate surgical strategy is adopted.

Conflicts of interest statement

None declared.

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Figure legends

Figure 1. Radiographic (A) and Computed tomography (B) findings showing well-defined borders of the lesions.

Figure 2. Radiographic (A) and Computed tomography (B) findings showing irregular border of the lesions.

Figure 3. Kaplan-Meier survival curve of the relapse-free survival (RFS) and overall survival (OS) rates.

Figure 4. Relapse-free survival (RFS; A) and overall survival (OS; B) rate curve showing a worse prognosis for patients in the intervention group than for those in the non-intervention group (P = 0.0246, P = 0.053, respectively). Group A, no intervention; Group B, intervention. The differences between the 2 groups are evaluated using the log-rank test.

Figure 5. Representative histopathological features of primary intraosseous squamous cell carcinoma. A, The surface of the tumor is covered with non-cancerous oral mucosa (hematoxylin and eosin stain, original magnification ×40). B, Hypokeratinizing tumor cells form tumor nests with a palisading arrangement of basal cells (hematoxylin and eosin stain, original magnification ×400). C, Positive staining for cytokeratin 19 is seen in the tumor nest (original magnification ×40). D, Growth of tumor cells is observed in the bone marrow of the jaw (hematoxylin and eosin stain, original magnification ×40).

Table 1: Clinical characteristics of 6 patients with PIOSCC

Case	Age/Sex	Primary site	Chief complaint	Treatment before diagnosis	Duration after treatment (Month)	X-ray findings	Greatest dimension (mm)	Duration between biopsy and surgery (Day)
1	79/M	Maxillary molar	Pain/ Swelling	None	-	Cystic	25	36
2	59/M	Mandibular molar	Non healing/ Trismus	Osteotomy	1	Non-evaluable	Non-evaluable	None
3	76/M	Mandibular molar	Pain/ Swelling	Extraction	2	Invasive	45	28
4	66/M	Maxillary incisor	Swelling/ Sensory disturbance	None	-	Cystic	28	12
5	65/M	Mandibular molar	Pain/ Swelling	None	-	Invasive	56	20
6	81/F	Maxillary premolar	Non healing	Extraction	2	Invasive	38	8

Table 2: Treatment courses of 6 patients with PIOSCC

Case	Initial treatment	RT or CCRT regimen	Histopathology	The number of pN	ECS	Recurrence and distant metastasis	Salvage treatment	Prognosis
1	Surgery (+RND)	None	Well	0	-	None	None	NED 74 months
2	Surgery (+mRND) + CCRT	66Gy + CDDP240mg/m^2	Poorly	3	Positive	Skull base, Supraclavicular fossa, sternal notch	Palliative care	Died of LF 9 months
3	Surgery (+mRND) + RT	66Gy	Well	1	Negative	Contralateral neck	mRND C-mab +TXL	Died of NF 16 months
4	Surgery (+mRND)	None	Moderately	0	-	None	None	NED 20 months
5	Surgery (+mRND)	None	Moderately	1	Negative	None	None	NED 12 months
6	Surgery	None	Well	None	-	Bilateral neck and Lung	mRND C-mab+ TXL	Died of DF 15 months

* mRND, modified radical neck dissection; DM, distant metastasis; NED, no evidence of disease; LF, local failure; NF, neck failure; DF, distant failure

Fig. 1 A

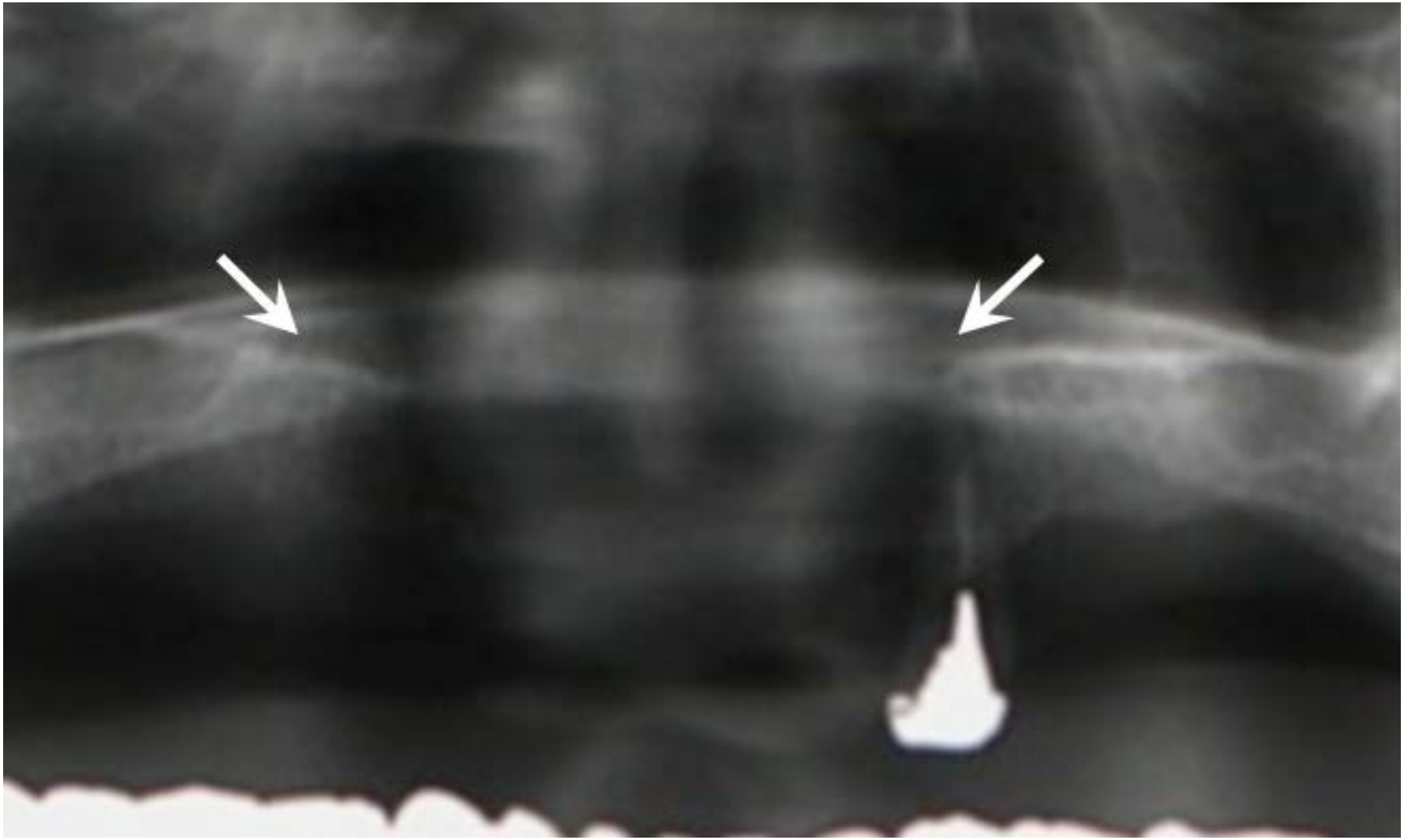

Fig. 1 B

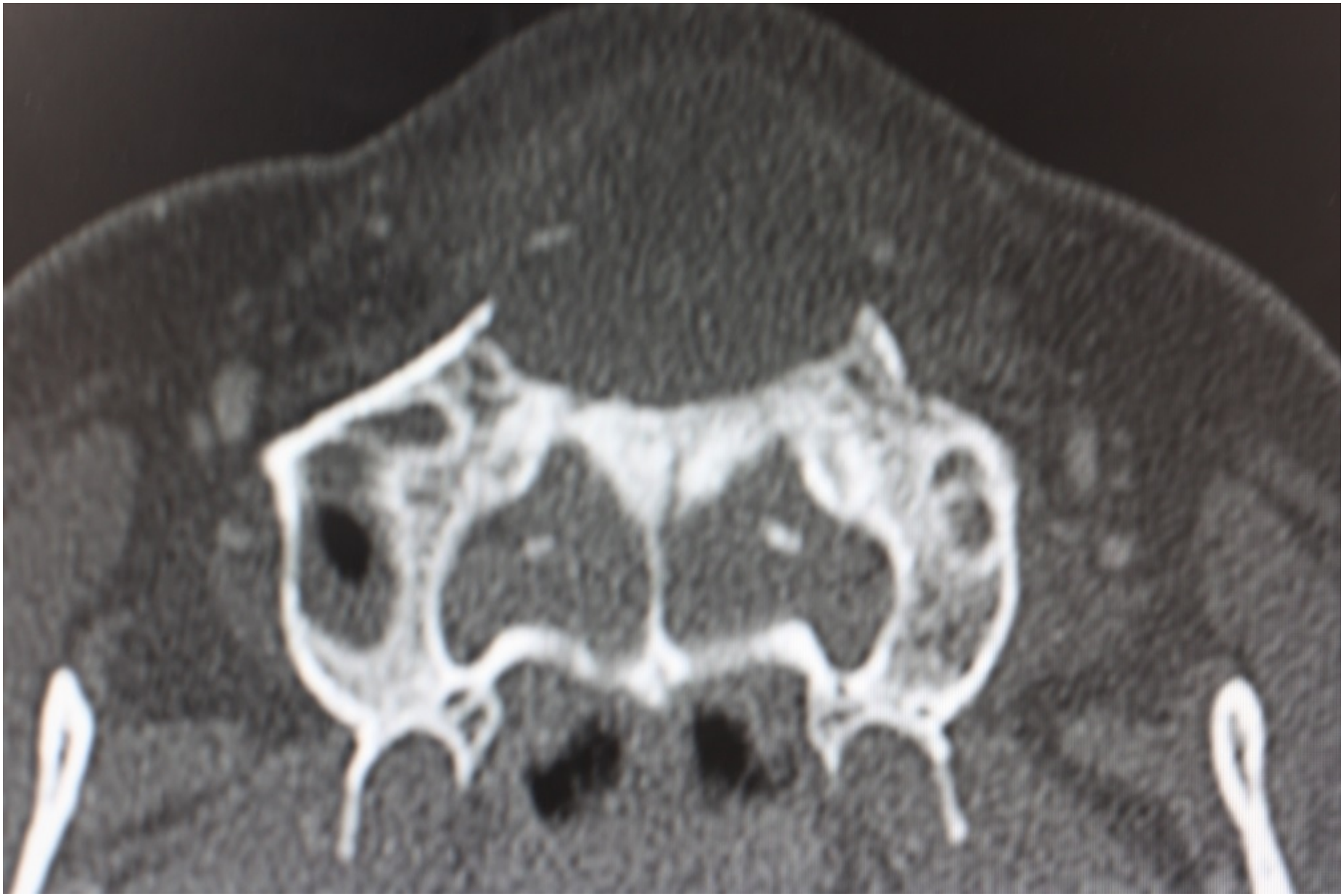

Fig. 2 A

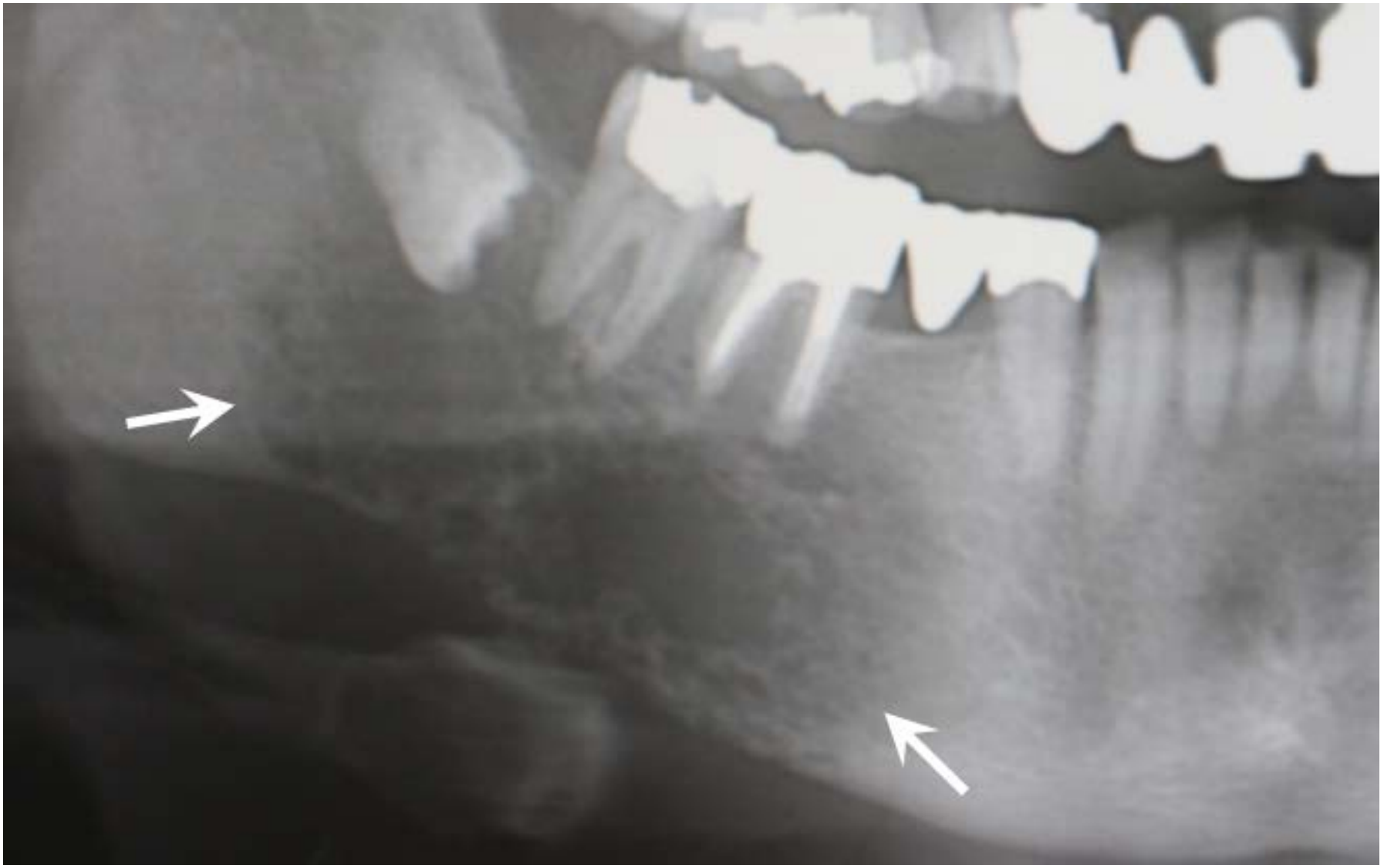

Fig. 2 B

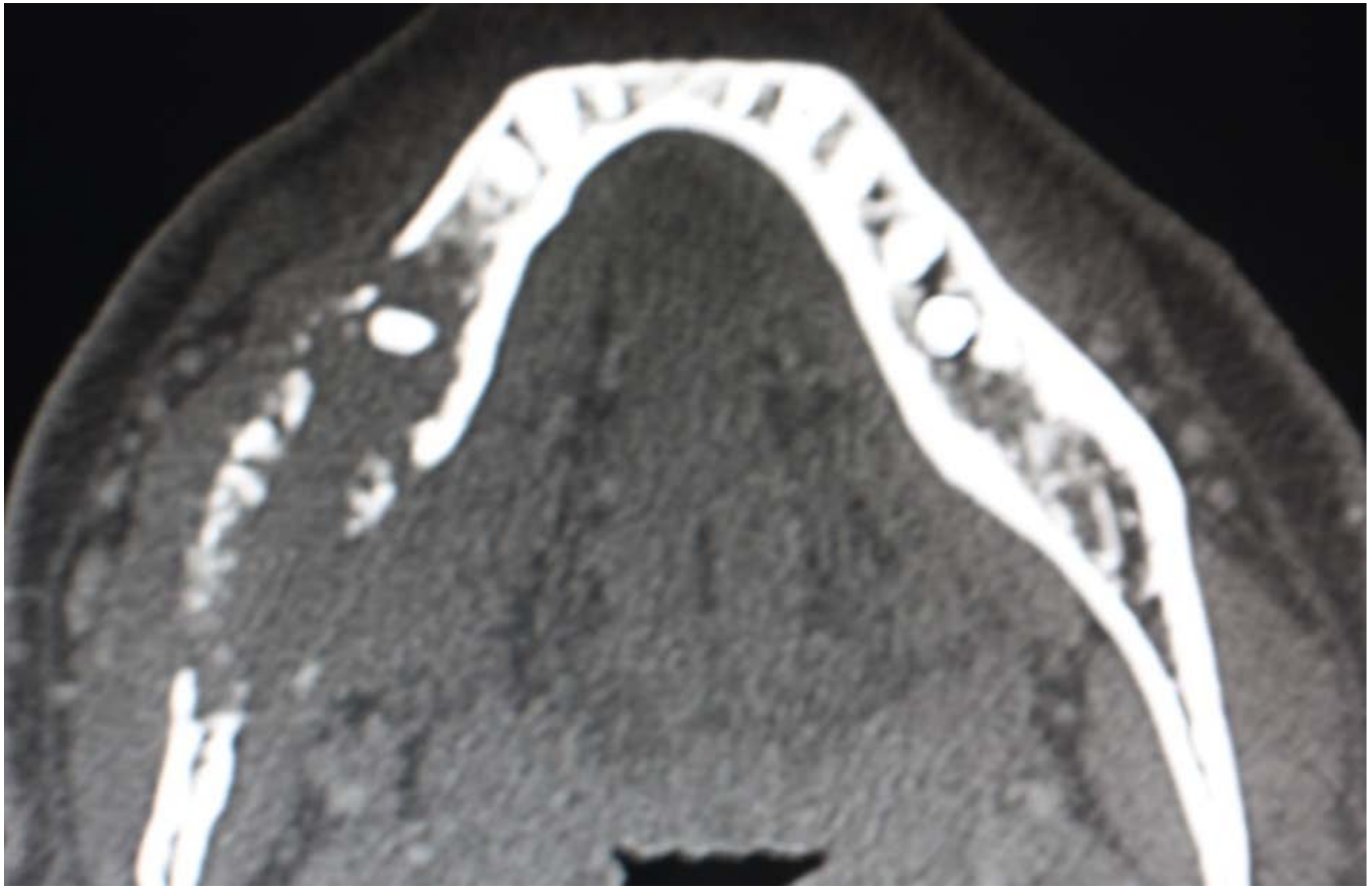

Fig. 3

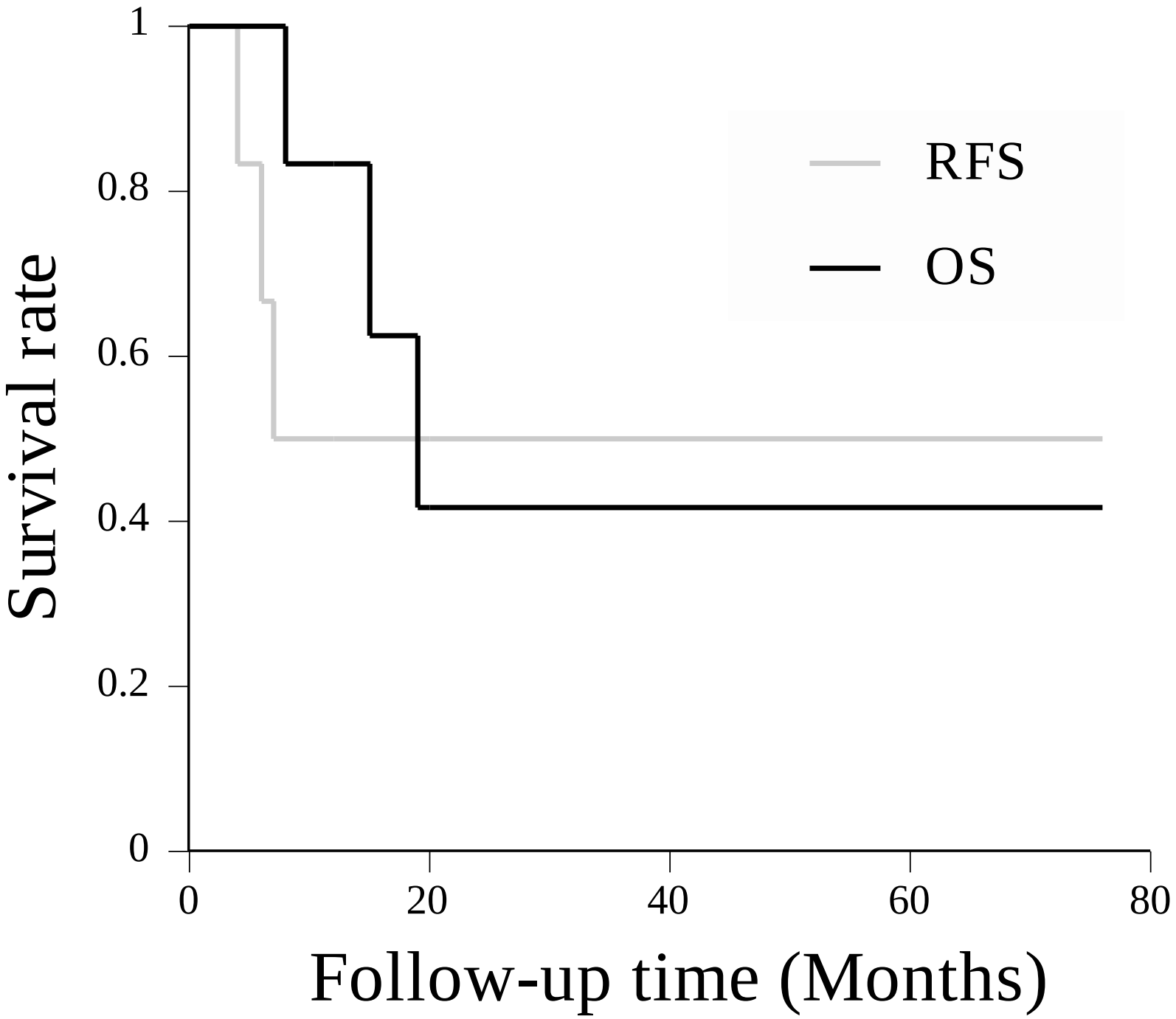
1
0.8
0.6
0.4
0.2
0
Survival rate
0
20
40
60
80
Follow-up time (Months)
RFS
OS

Fig. 4 A

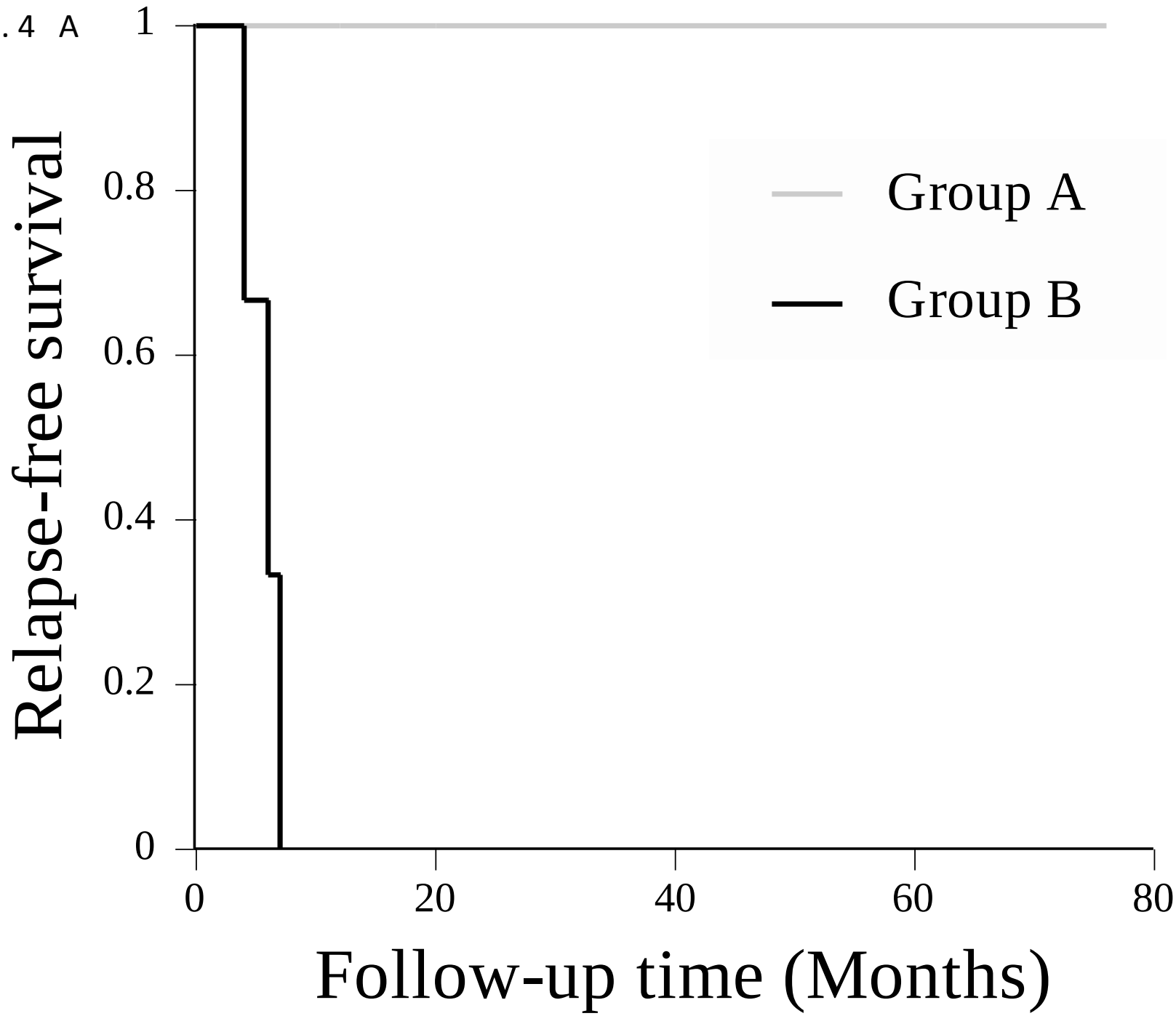
Relapse-free survival
1
0.8
0.6
0.4
0.2
0
0
20
40
60
80
Follow-up time (Months)
Group A
Group B

Fig. 4 B

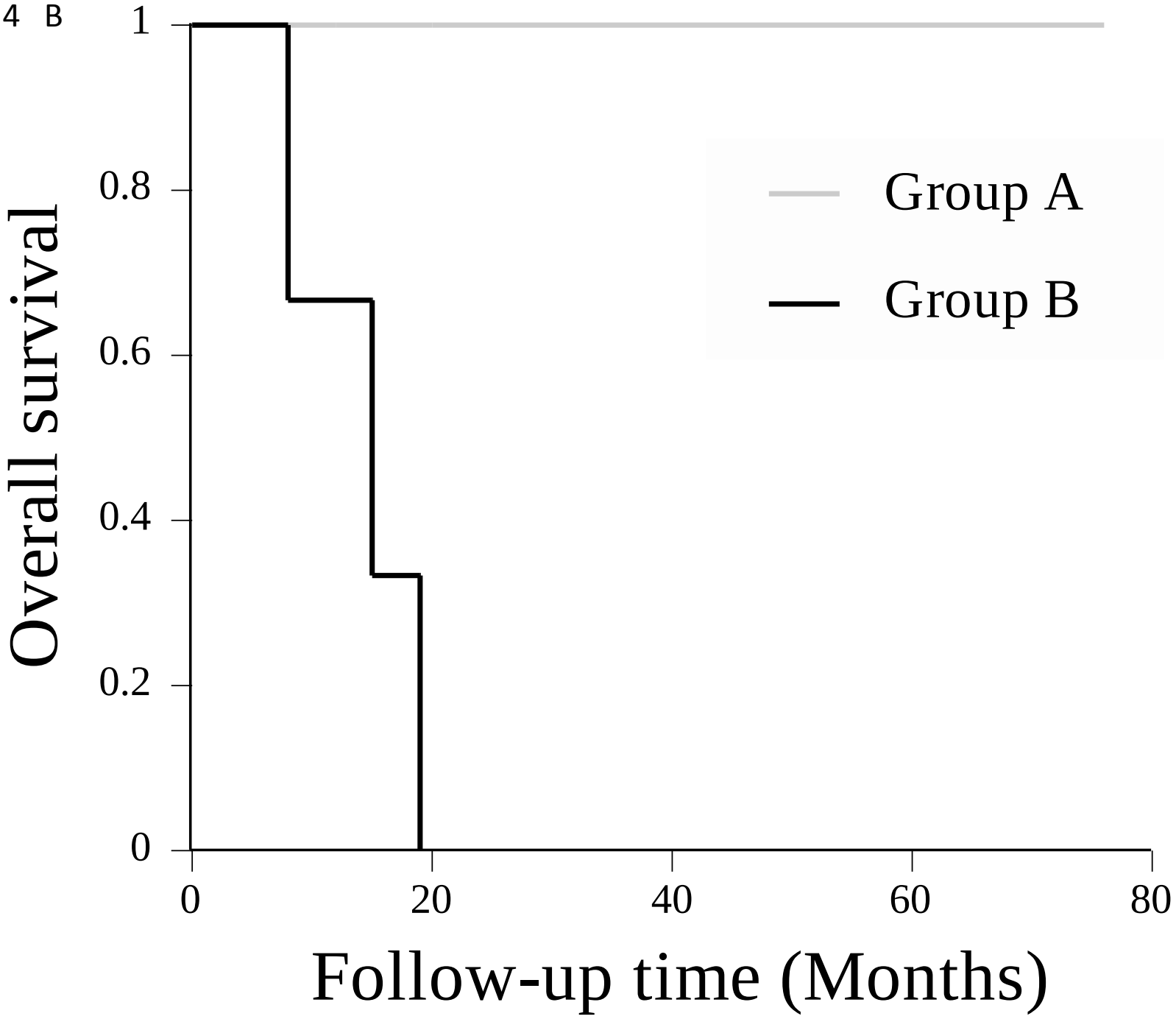
Overall survival
1
0.8
0.6
0.4
0.2
0
0
20
40
60
80
Follow-up time (Months)
Group A
Group B

Fig. 5 A

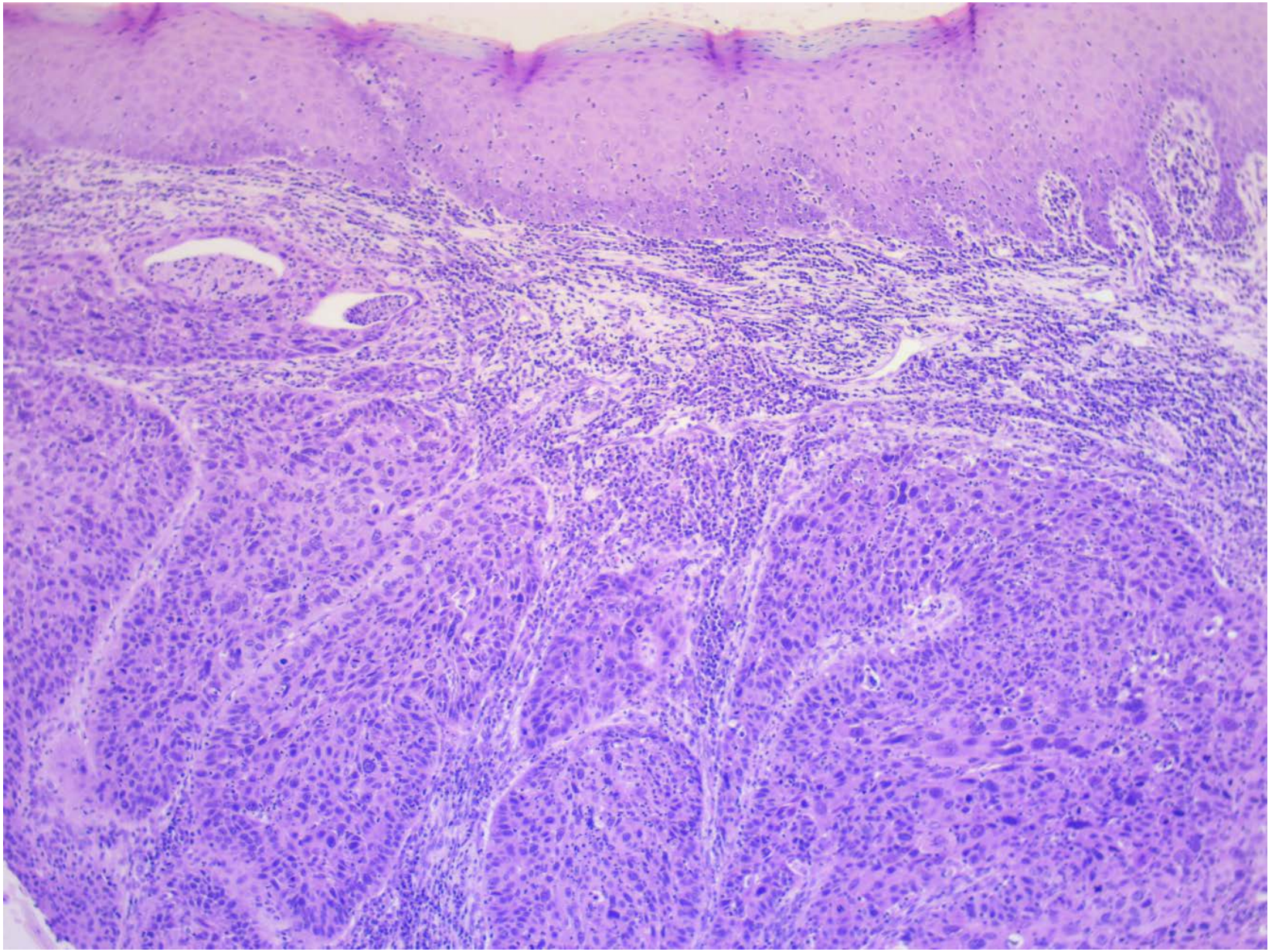

Fig. 5 B

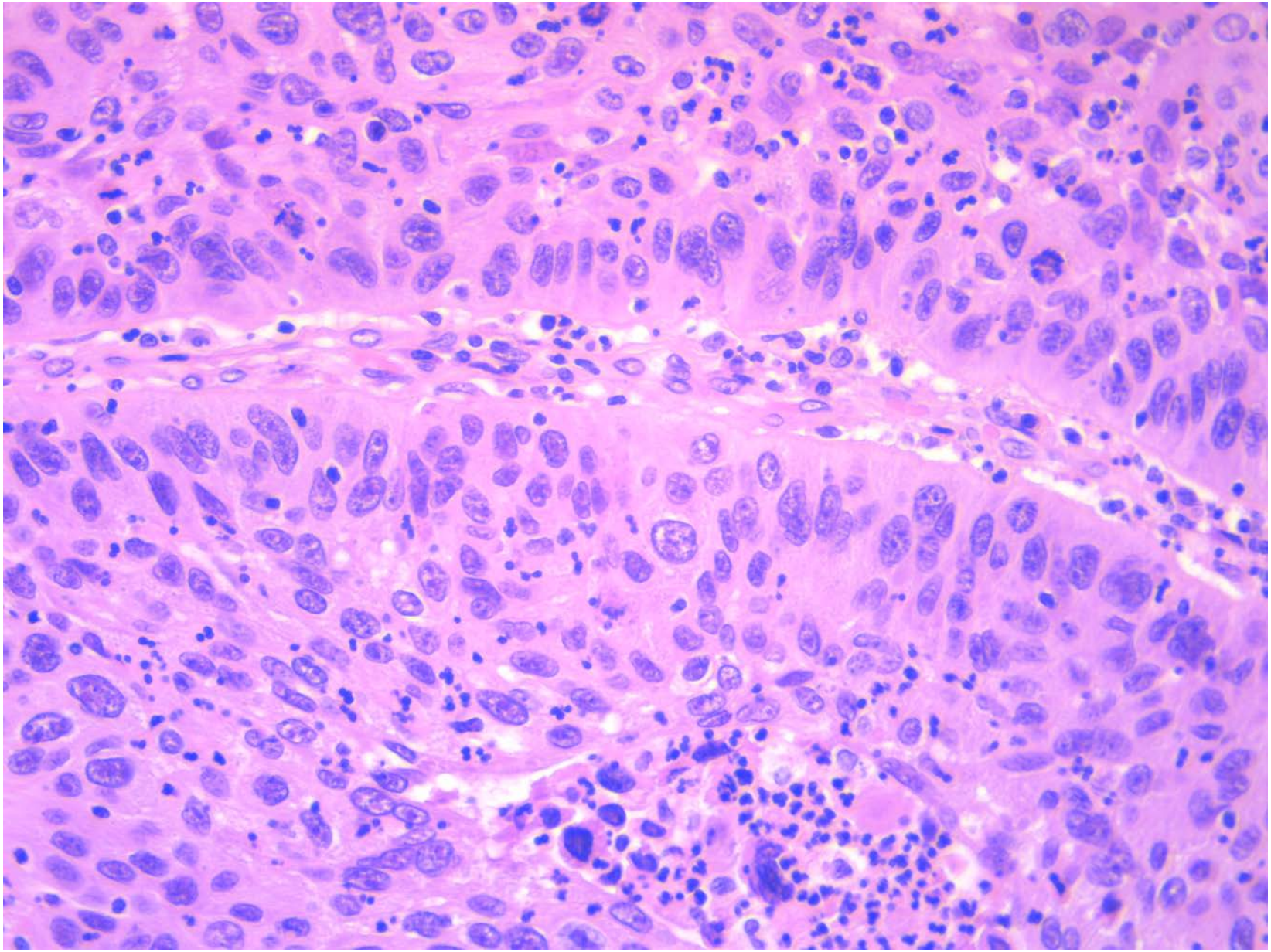

Fig. 5 C

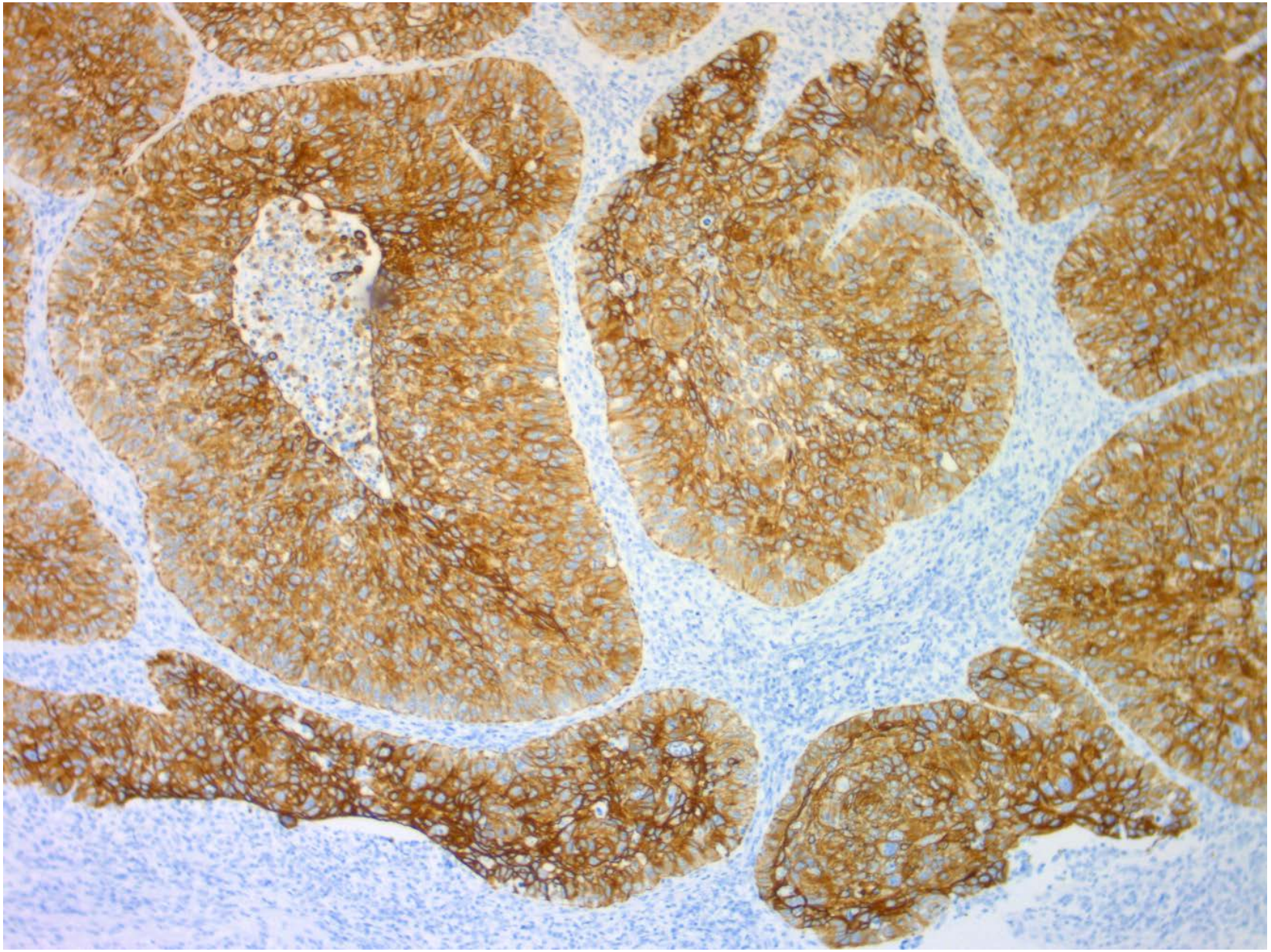

Fig. 5 D