ABSTRACT

Objective. We sought to evaluate the efficacy and feasibility of superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy (hereafter RADPLAT) for head and neck squamous cell cancer (hereafter HNSCC) patients with retropharyngeal lymph node (hereafter RPLN) metastasis.

Study Design. Retrospective case series review

Setting. University medical center in Japan

Subjects and Methods. Ten HNSCC patients with RPLN metastasis treated by RADPLAT were analyzed.

Results. The ascending pharyngeal artery was targeted for the treatment of RPLN metastasis in 9 patients. The median total dose of cisplatin was 26.6 mg/m2 (mean, 31.5 mg/m2; range, 11.7-87.9 mg/m2). In the remaining patient, the RPLN was supplied by the ascending palatine artery. As grade 3 and 4 adverse effects, leukopenia was observed in three, mucositis in four and nausea in one patient. No neurological complications were observed in any patients. Metastatic RPLNs were evaluated as a complete response in all patients. There was no recurrence of RPLN metastasis in any patients. Four patients remain alive without any evidence of disease and six patients died of disease. The 5-year overall survival rate was 50%.

Conclusions. We have shown that superselective intra-arterial cisplatin infusion for RPLNs was a feasible and

effective approach for HNSCC patients with RPLN metastasis.

INTRODUCTION

Retropharyngeal lymph node (RPLN) metastasis is considered to be a significant predictor of poor prognosis for patients with head and neck squamous cell carcinomas (HNSCCs) [1,2]. RPLN dissection is relatively simple and takes only a few minutes when performed electively. On the other hand, gross involvement of the RPLNs by the tumor can make the operation difficult and, at times, not feasible [3].

Recently, superselective intra-arterial chemotherapy in combination with concomitant radiotherapy (RADPLAT) has been performed for patients with locally advanced HNSCC and has been reported to result in a favorable outcome, preserving function and improving survival [4,5]. We considered RADPLAT to be applicable to the treatment of RPLN metastasis and, therefore, assessed the efficacy and feasibility of this non-surgical treatment for HNSCC patients with RPLN metastasis.

MATERIALS AND METHODS

Patients. Two hundred thirty-five patients with untreated HNSCCs underwent RADPLAT in Hokkaido University Hospital, Japan between September 1999 and July 2012. In this study, we analyzed ten patients who

had RPLN metastasis. The primary tumor sites were the hypopharynx in six, the maxillary sinus in two, and the oropharynx in two patients. Eight patients were diagnosed with Stage IVA, one with Stage IVB, the remaining patient with stage III. Other detailed characteristics are shown in Table 1. T and N classifications were defined according to the American Joint Committee on Cancer (AJCC) staging system 2010. Patients visiting our hospital before 2009 were restaged according to the AJCC 2010. The tumor stage was determined on the basis of patient history, physical examination, chest X-rays, as well as computed tomography and/or magnetic resonance imaging (MRI) and/or positron emission tomography - computed tomography.

Approval for this study was obtained from the institutional review board at Hokkaido University. Completion of the survey was regarded as implied consent for participation.

Radiotherapy. The irradiation plan during the period 2006–2012 was 40 Gy in 20 fractions of 2 Gy over four weeks for the primary site and involved nodal areas, immediately followed by a boost of 26-30 Gy in 13-15 fractions to the primary cancer over an additional three weeks (total dose, 66-70 Gy) (Figure 1.). Between 1999 and 2005, the primary site and involved nodal areas were irradiated with 40 Gy in 16 fractions of 2.5 Gy over four weeks, with a boost irradiation of 25 Gy in 10 fractions to the primary tumor over an additional 2.5 weeks (total dose, 65 Gy).

Chemotherapy. Cisplatin (100-120 mg/m^2 per week for four weeks) was infused through a microcatheter placed

angiographically to selectively encompass only the dominant blood supply of the targeted tumor (Figure 1.). Cisplatin infusion mainly targeted the primary tumor, RPLNs and sometimes metastatic lymph nodes. At the same time, sodium thiosulfate (20-24 g) was given intravenously to neutralize cisplatin toxicity [6]. All arterial catheterizations were accomplished transcutaneously through the femoral artery, and the catheters were removed immediately after infusion. To encourage the rapid excretion of the cisplatin, 8 L of lactated Ringer's solution was given over a 24-h period. A 5-HT3-receptor antagonist was given to all patients before arterial infusion to minimize nausea and vomiting. Chemotherapy was completed during the first four weeks of treatment, provided that patients responded well in the early treatment period and received three arterial infusions.

Evaluation of response and toxicity. Responses were evaluated by clinical examination, together with CT and/or MRI studies at 6-8 weeks after the completion of therapy. A complete response was defined as a total resolution of the tumor. Toxicities during RADPLAT were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0. All patients were closely observed during the follow-up period, the median of which was 49 months (range, 5-138 months).

Statistical analysis. The Kaplan-Meier method was applied for analysis of the survival rate. The time of interest for the survival rate was the period from the start of treatment to death. JMP Pro 10.0.2 statistical software (SAS Institute, Cary, NC) was used for the statistical analysis.

RESULTS

RADPLAT. Intra-arterial chemotherapy was performed a median of 4 times (range, 3–4 times; mean, 3.6 times). All patients underwent a full course of irradiation without interruption (median, 66 Gy; range, 65-70 Gy). We determined the targeted artery by the selective IA computed tomographic angiography, which ensures that all compartments of the RPLN metastasis were supplied by the targeted artery. In 9 of 10 patients, cisplatin was infused into the ascending pharyngeal artery to the RPLNs. In the remaining patient, cisplatin was infused into the ascending palatine artery to the RPLNs. Infusion into the artery supplying the RPLNs was conducted an average of 2.6 times (range, 1-4 times). When the RPLNs responded well and/or the ascending pharyngeal arteries got too narrow to insert microcatheters, no further infusion was performed. The median cumulative dose of cisplatin administrated to the ascending pharyngeal artery was 25.2 mg/m^2 (mean, 35.0 mg/m^2; range, 11.7-87.9 mg/m^2). In the remaining patient, cisplatin was infused into the ascending palatine artery, which is a branch of the facial artery, to the RPLNs. In this patient, as the ascending palatine artery was too narrow for a microcatheter to be inserted, cisplatin was infused into the main branch of the facial artery to the RPLNs as well as the primary tumor.

Adverse effects. As grade 3 and 4 adverse effects, leukopenia was observed in three (30%), mucositis in four (40%) and nausea in one (10%) patient. In one patient (No. 2), osteonecrosis of the maxilla was observed at 15 months after RADPLAT, requiring total maxillectomy and the reconstruction of the maxilla using a free flap

transfer. No neurological complications were observed in any patients.

Clinical outcomes. A complete response was achieved in the RPLNs in all patients after RADPLAT. No recurrence of RPLN metastasis was observed among the 10 patients. Four patients remain alive without any evidence of disease. Two patients died of recurrent primary diseases, and two patients died of distant metastases. A further two patients died of recurrent nodal diseases, although the RPLNs were successfully controlled. The 5-year overall survival rate was 50% (Figure 2.). Table 1 shows the details and outcomes for the ten patients. All of the four surviving patients, who have no evidence of disease, are capable of oral intake without feeding-tube support. Further, one patient who required surgery due to osteonecrosis of the maxilla as mentioned above also underwent tracheostomy during the perioperative period, however, the remaining three patients did not require tracheostomy during the follow-up period.

DISCUSSION

Since Ballantyne reported that RPLN metastases is associated with poor prognosis in patients with pharyngeal wall cancer [7], several reports have suggested that the control of neck metastases, distant metastases, and survival rates are significantly associated with RPLN metastases [1,7-10]. Ballantyne conducted a retrospective study of 34 patients with SCC of the pharyngeal wall. Metastasis to the RPLNs was detected by microscopic examination in 15 (44.1 %) of the 34 patients, and RPLN involvement was associated with a significantly poorer

survival rate [7]. McLaughlin et al. found the overall incidence of radiologically positive RPLN among 774 patients with SCC of the nasopharynx, oropharynx, hypopharynx, or supraglottis to be 9% [1]. The 5-year disease-free survival (DFS) rate (35 vs. 58 %; p = 0.0004) and overall survival rate (29 vs. 44 %; p = 0.0001) were significantly lower in the RPLN-positive group than in the non-RPLN metastasis group.

RPLNs are considered to act as the first echelon of lymphatic drainage for the nasopharynx, paranasal sinuses, oropharynx and hypopharynx [7,12,13]. Metastatic involvement of the lateral retropharyngeal nodes may lead to secondary invasion and compression of the carotid sheaths [14]. Actually, there are several reports that advocate the dissection of the RPLNs during initial surgery in advanced tumors of the oropharynx, hypopharynx and cervical esophagus [9-11,14-16]. However, therapeutic RPLN dissection is technically challenging because of the limited surgical field and adhesion of the RPLNs to the surrounding tissue [14]. Even if surgery can be undertaken, the surgical procedure can result in severe post-operative complications, including bleeding and swallowing dysfunction due to lower cranial neuropathy.

Recently, there have been several reports on the effectiveness of RADPLAT for local advanced HNSCC [4-6,17,18], although a multicenter, randomized phase 3 trial comparing RADPLAT and intravenous chemoradiation did not show the superiority of RADPLAT to intravenous chemoradiation for locally advanced HNSCC [19,20]. We consider that RADPLAT can be applied to the treatment of RPLN metastases by injecting cisplatin to the vessels feeding RPLN metastases, but none has ever reported the efficacy and feasibility of this

procedure.

In the current study, RPLNs were evaluated as complete response after RADPLAT in all ten patients and none showed any recurrence of RPLN metastasis. The ascending pharyngeal artery is usually the smallest of the arteries that diverge from the external carotid artery and is generally considered to feed the RPLNs [21]. Low-dose cisplatin infusion is thought to be sufficient for the eradication of RPLNs because the ascending pharyngeal artery is narrow and RPLN metastasis is usually quite limited in comparison with lymph node metastases in level I-V.

The ascending pharyngeal artery is also known to supply the lower cranial nerves and this procedure has an associated risk of lower cranial neuropathy [22], although none of the patients suffered severe complications, including lower cranial neuropathy, in the present study. It is known that the ascending pharyngeal artery diverges into two branches, the pharyngeal trunk and the meningeal trunk. The former feeds the RPLNs, while the latter bifurcates into branches, enters the jugular foramen and hypoglossal canal, and feeds the lower cranial nerves [21]. In this study, the catheter was inserted selectively into the pharyngeal branch, located in the distal portion of the bifurcation between the pharyngeal and meningeal trunks, in order to prevent the cisplatin from flowing backward into the meningeal trunk. As a result, we could achieve the infusion of cisplatin to the RPLNs while minimizing the risk of complications such as lower cranial neuropathy.

With regard to treatment outcomes, four patients died because of locoregional disease other than RPLN, and two patients died due to distant metastasis without RPLN metastasis in this study. The 5-year overall survival rate was 50%. Although it is impossible to compare the tumor sites and draw any conclusions regarding survival, the 5-year overall survival rate was reported to be 30-53% for patients with oropharynx and hypopharynx with RPLN metastasis who had underwent RPLN dissection [11,23]. Therefore, RADPLAT, which achieved a 5-year overall survival rate of 50% and a good control rate for RPLN, is considered to be one of the opinions for patients with RPLN metastasis. Although RADPLAT is not a standard treatment because it requires expertise in interventional radiology, the aforementioned randomized phase III trial in The Netherlands found that in an unplanned subgroup analysis there were significantly higher local and locoregional control rates and disease-free survival for RADPLAT for large (>30 mL) lateralized tumors [19,20]. RPLN metastasis is usually small but difficult to remove due to its location; however, RADPLAT when performed by a well-skilled interventional radiologist can achieve control of RPLN metastasis with fewer complications, which suggests that RADPLAT may play a role in the treatment of HNSCC with RPLN metastasis. Furthermore, some recent reports suggest that induction chemotherapy can prevent distant metastases of HNSCC [24,25], so RADPLAT following induction chemotherapy might improve the survival for HNSCC patients with RPLN metastasis. Further study is, however, required to further confirm this.

In conclusion, the results of this study suggested that RADPLAT is a novel and effective approach for the control

of RPLN metastasis. We believe that RADPLAT is a treatment of choice for patients with RPLN metastasis, in that it can aid in preserving organ function as well as patient quality of life.

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Conflict of interest: None.

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Table 1.

Table 1. Details of the nine patients who received SSAI for retropharyngeal lymph node metastasis

Case No.	Age	Sex	Primary lesion	T	N	Radiation dose (Gy)	Chemot herapy (Times)	Total dose of cisplatin (mg/m^2)	Chemother apy to RPLN (Times)	Total dose of cisplatin targeting RPLNs (mg/m^2)	Recurre nce of RPLNs	Maximum diameter of RPLN (mm)	Outcome (observation period after chemotherapy)
1	63	M	hypopharynx	3	2b	66	4	364	3	32.6	-	18(ipsi-) 16(contra-)	dead (neck) (19m)
2	68	M	maxillary sinus	4a	2c	70	4	447	3	16.8	-	13	NED (61m)
3	66	F	maxillary sinus	3	1	65	3	275	1	11.7	-	10	dead (neck) (66m)
4	62	M	hypopharynx	3	2c	66	3	361	3	87.9	-	20	dead (primary) (11m)
5	58	M	hypopharynx	2	2b	70	4	370	2	43.7	-	13	NED (85m)
6	59	M	hypopharynx	3	2b	66	3	335	2	21.7	-	8	dead (primary) (5m)
7	66	M	oropharynx	4a	2b	66	3	336	2	28.0	-	8	dead (distant) (37m)
8	67	M	hypopharynx	4b	3	70	4	409	4	25.2	-	15	dead (distant) (9m)
9	53	M	hypopharynx	2	2b	70	4	453	3	47.2	-	11	NED (67m)
10	61	F	oropharynx	3	2b	65	3	310	3	-*	-	17	NED (138m)

SSAI: superselective intra-arterial chemotherapy, RPLN: retropharyngeal lymph node

NED: no evidence of disease, dead (primary): dead of primary disease, dead (neck): dead of neck disease, dead (distant): dead of distant metastasis

*Cisplatin was infused into the ascending palatine artery to the RPLN.

Figure Legends

Fig. 1 Treatment schedule of RADPLAT.

RT: radiotherapy, AI: intra-arterial chemotherapy

Fig. 2 Overall survival rates (using the Kaplan-Meier method)

Fig. 3 Gadolinium-enhanced magnetic resonance imaging (Gd-MRI) findings for a 58-year-old male with a left pyriform sinus cancer that was classified as T2N2b are shown.

Fig. 4 Pretreatment Gd-MRI findings for a patient (No. 5) with hypopharyngeal cancer with metastatic retropharyngeal lymph nodes (RPLNs).

Fig. 5 A lateral subtraction angiogram showing that the left retropharyngeal node was supplied by the left ascending pharyngeal artery. The arrow indicates the enhanced metastatic retropharyngeal node. Cisplatin was infused from a catheter positioned at ▲.

Fig. 6 Gd-MRI findings as two months after RADPLAT. (a) The RPLN metastasis has disappeared. (b) Complete

response has been achieved for the primary lesion. The patient remains alive without any evidence of disease after a follow-up of 85 months.

Treatment schedule

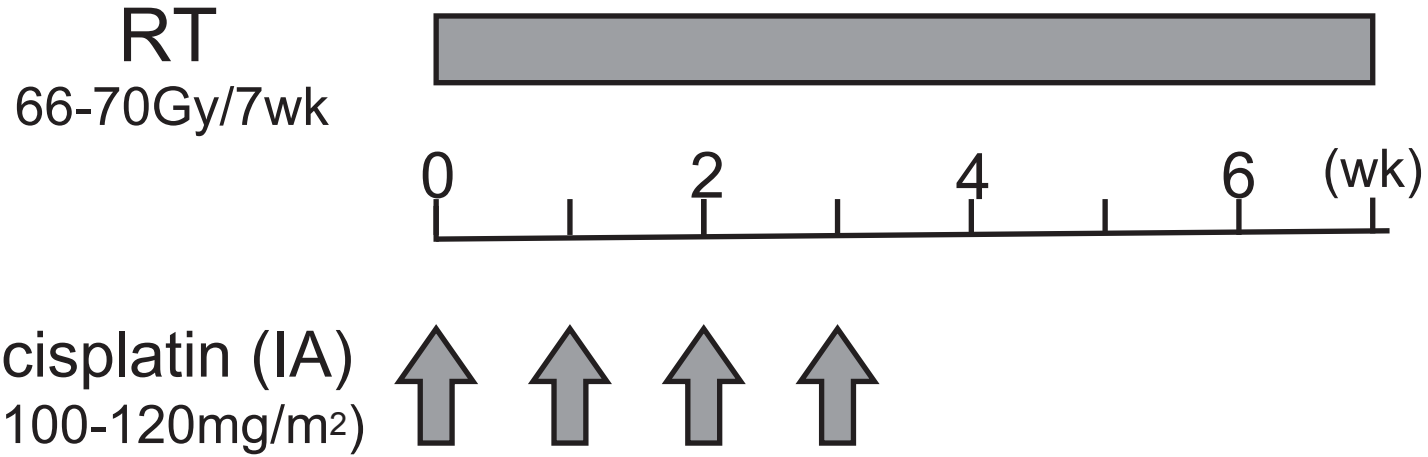


Figure 1

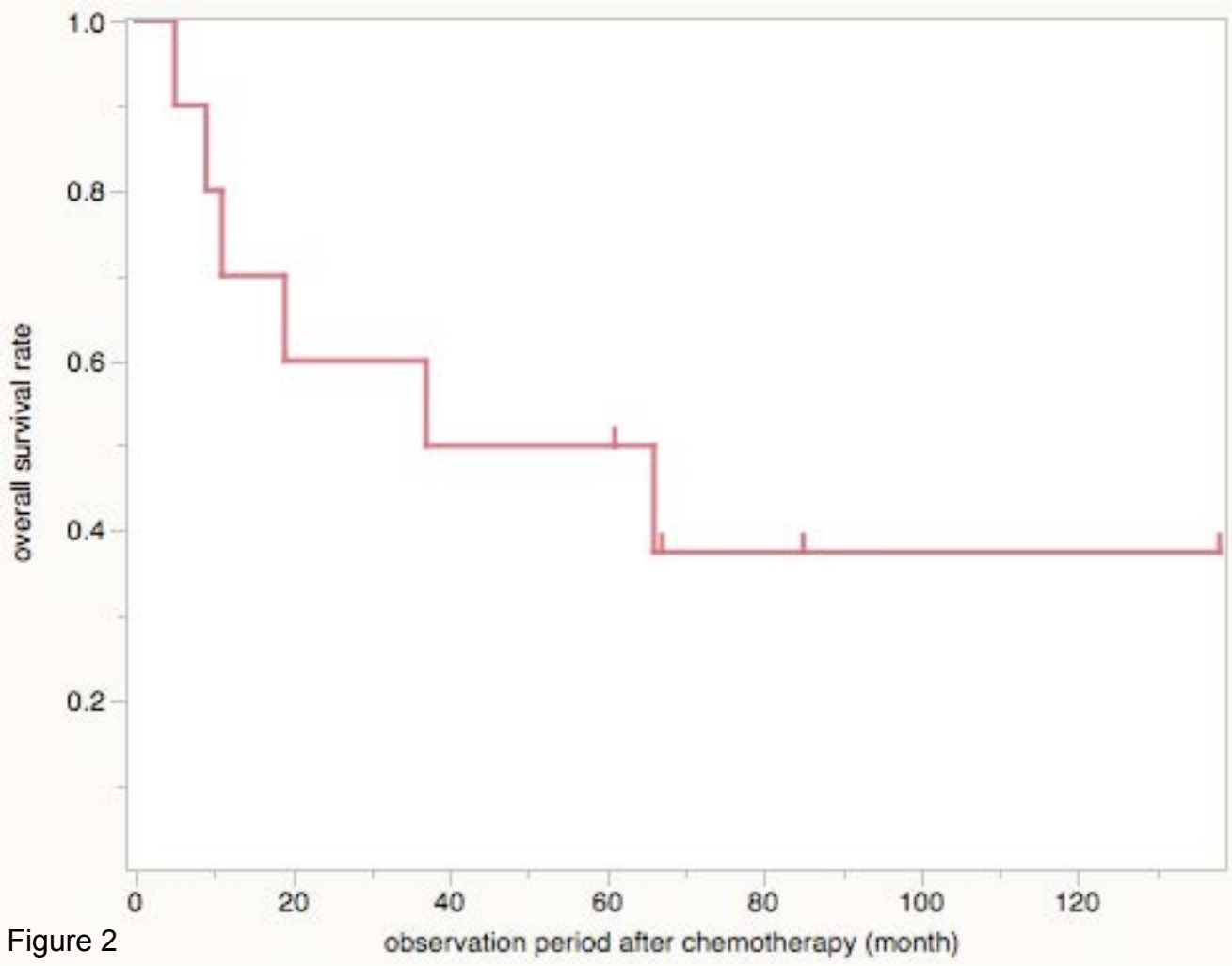

1.0
0.8
0.6
0.4
0.2
overall survival rate
0
20
40
60
80
100
120
observation period after chemotherapy (month)

Figure 2

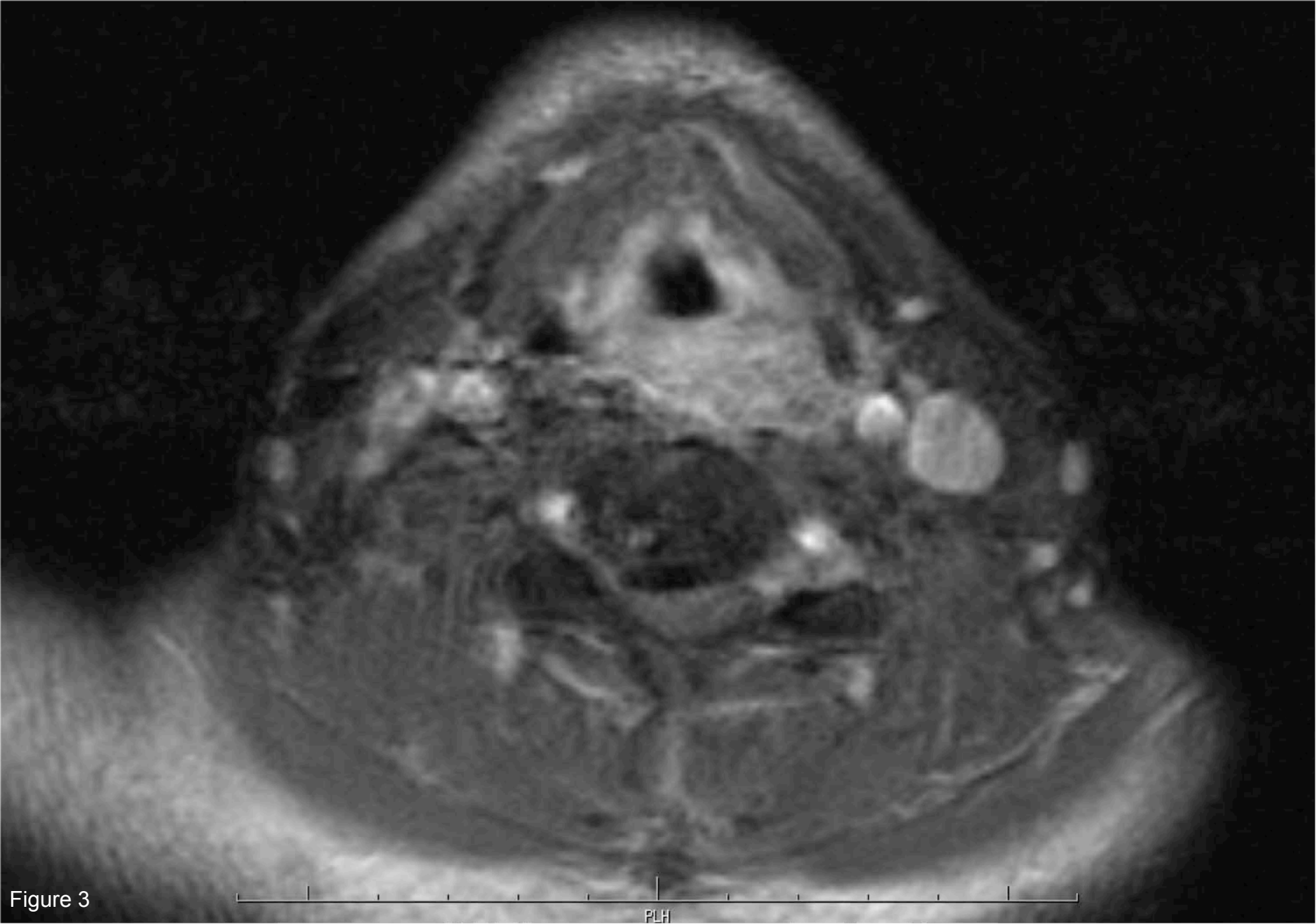
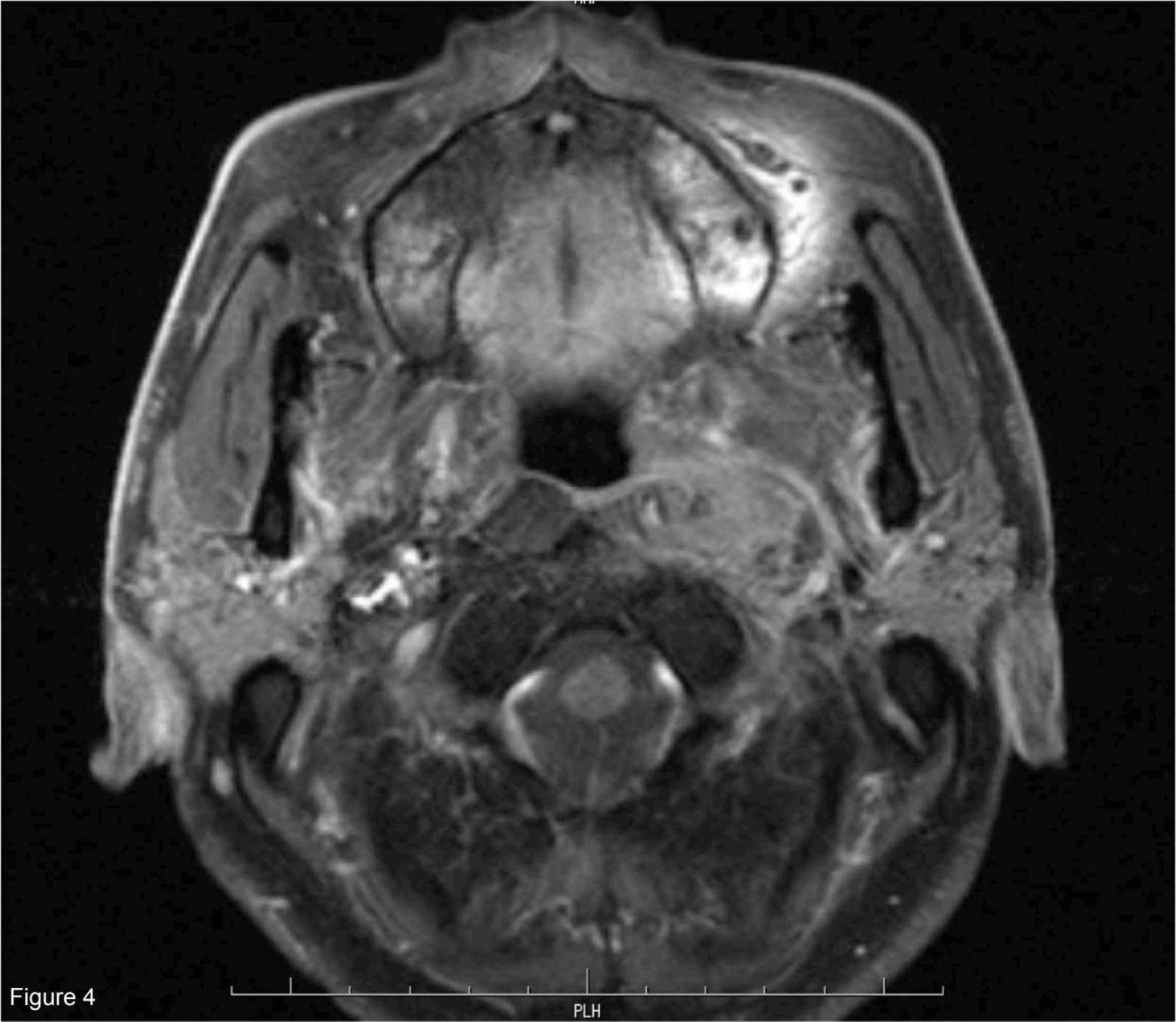


Figure 3



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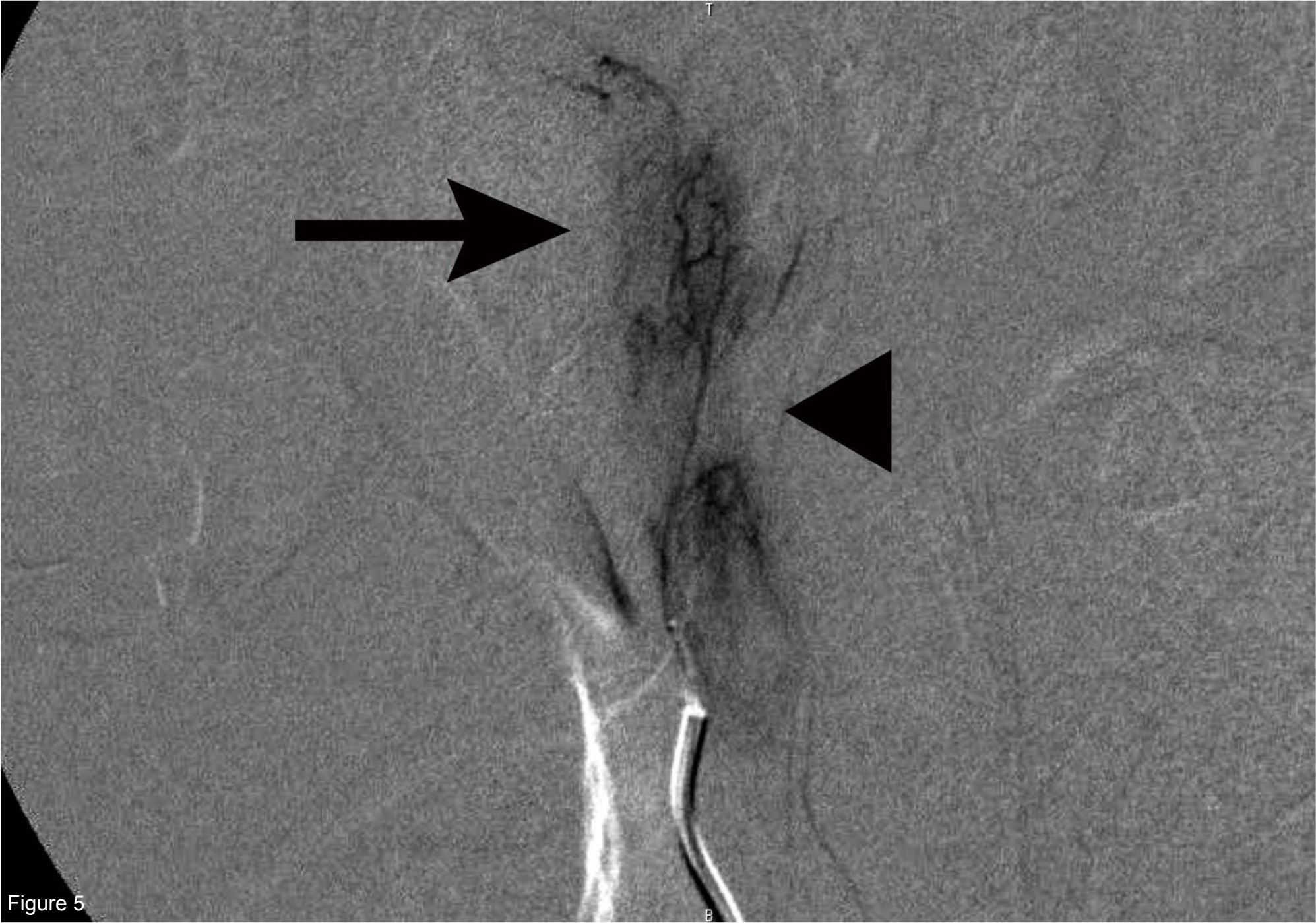

Figure 5

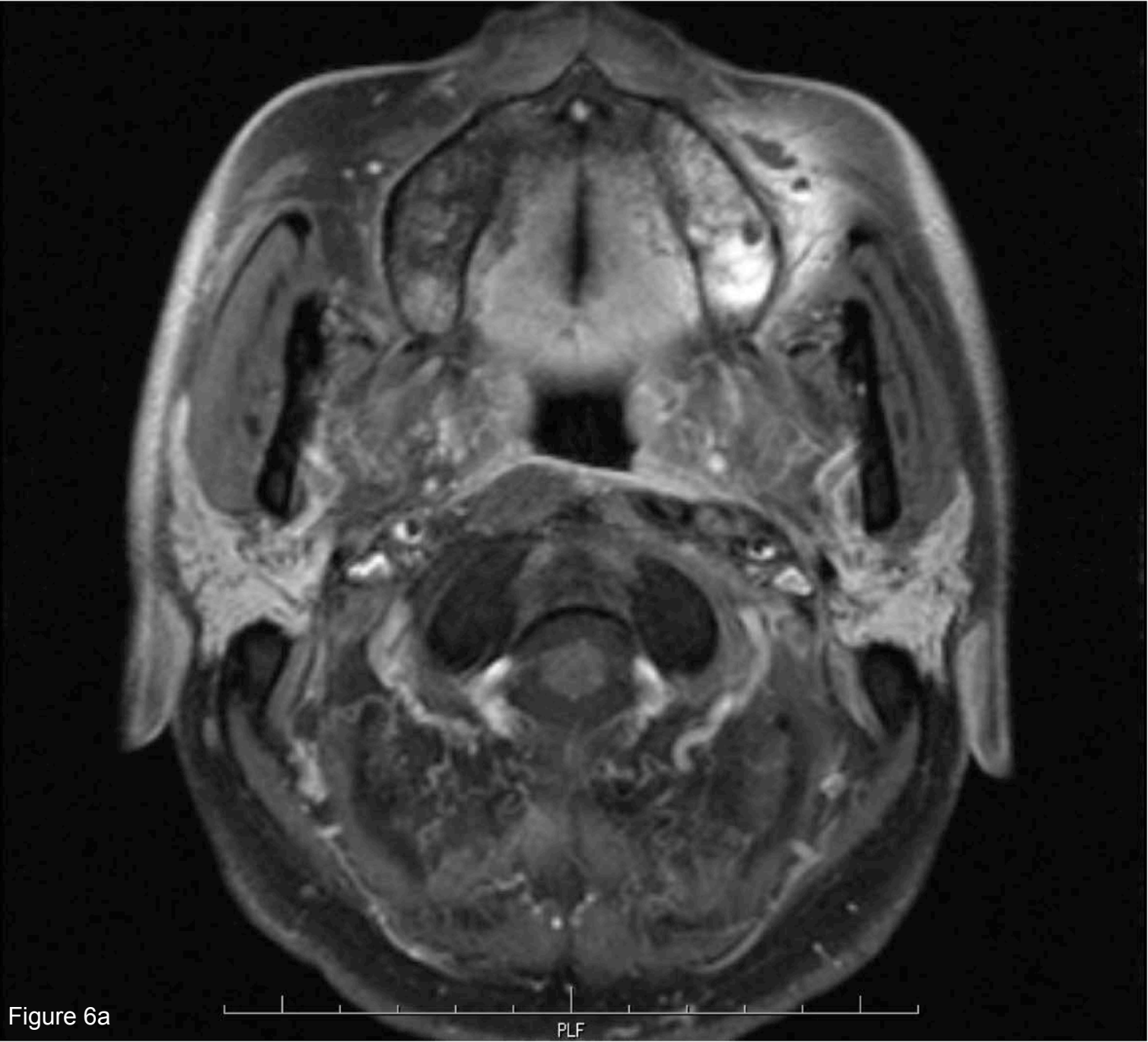

Figure 6a

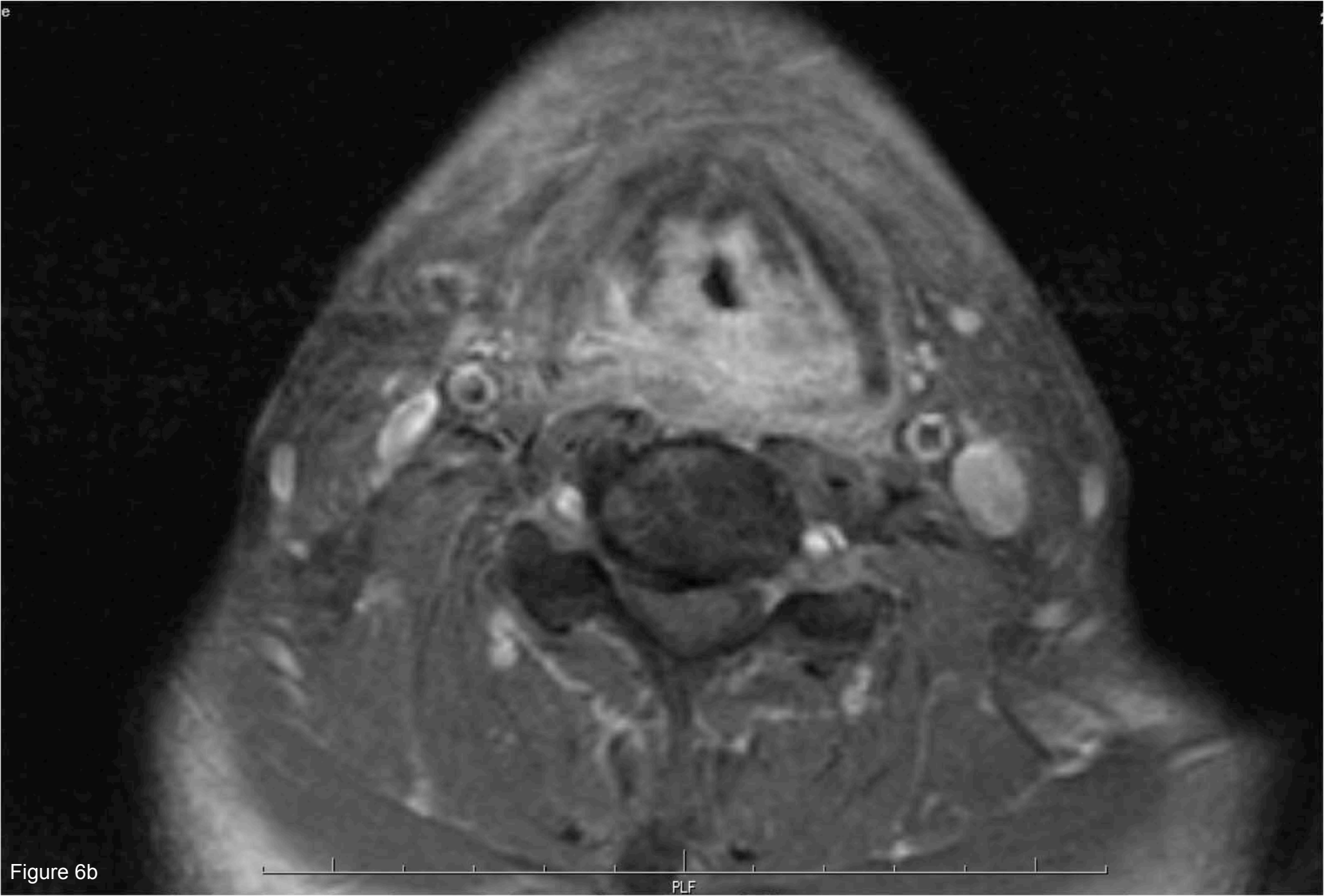

Figure 6b