ZAKŁAD BRACHYTERAPII
WIELKOPOLSKIE CENTRUM ONKOLOGII

Rola brachyterapii w leczeniu wznów nowotworów języka i dna jamy ustnej

The role of brachytherapy in recurrent tumours of the tongue and fundus of the oral cavity

Janusz Skowronek, MD, PhD, Ass. Prof.
Brachytherapy Department, Greater Poland Cancer Centre, Poznań
11.06.2010

Int. J. Radiation Oncology Biol. Phys., Vol. 50, No. 5, pp. 1190–1198, 2001

0360-3016/01/$–see front matter

PII S0360-3016(01)01567-X

CLINICAL INVESTIGATION **Head and Neck**

THE AMERICAN BRACHYTHERAPY SOCIETY RECOMMENDATIONS FOR HIGH-DOSE-RATE BRACHYTHERAPY FOR HEAD-AND-NECK CARCINOMA

SUBIR NAG, M.D.,* ELMER R. CANO, M.D.,† D. JEFFREY DEMANES, M.D.,‡
AJMEL A. PUTHAWALA, M.D.,§ AND BHADRASAIN VIKRAM, M.D.,‖ FOR THE AMERICAN BRACHYTHERAPY SOCIETY

- Brachytherapy is potentially useful in the treatment of head and neck cancers, because most **tumor sites**, such as the lip, tongue, floor of mouth, tonsil, pharynx, nasopharynx, sinuses, and neck, **are accessible for the placement** of afterloading applicators and catheters.
- Brachytherapy has the advantage of delivering a **higher radiation dose** to tumor while **sparing surrounding normal tissue** from radiation.
- Furthermore, the overall **treatment duration is shorter**, and the **dose distribution** conforms to tumor shape.
- Brachytherapy is used as "**monotherapy**" for the treatment of small primary tumors or recurrent disease after external beam radiation therapy (EBRT).
- However, brachytherapy is most commonly administered **in conjunction with moderate doses of EBRT.**

Table 1. Brachytherapy as sole treatment for oral cavity cancers

Author (ref)	EBRT	Fx Size (Gy)	# fx	Equiv. dose* (Gy)	# Pts.	L.C.
Dixit *et al.* (8)	0	3	20	65	3	–
Lau *et al.* (11)	0	6.5	7	63	27	53%
Inoue *et al.* (10)	0	6	10	80	14	100%
Donath *et al.* (9)	0	4.5–5	10	54–63	13	90%
Leung *et al.* (12)	0	5.5–6	10	71–80	13	100%

Abbreviations: Fx = fractions; equiv. = equivalent; Pts. = patients; L.C. = local control. EBRT = external beam radiation therapy.
* Equivalent dose for tumor effects as if given at 2 Gy/day using the linear quadratic model with an α/β ratio of 10 (25). See appendix.

Table 2. HDR brachytherapy as boost to EBRT for oral cavity cancers

Author (ref)	EBRT dose (Gy)	HDR dose/fx (Gy)	# fx	Equiv. dose* (Gy)	# Pts	L.C.	Survival
Yu *et al.* (13)	50	2.7	6	67	12	79%	45%
Dixit *et al.* (8)	40–48	3	7	63–71	18	80%	

Abbreviations: Fx = fractions; Equiv. = equivalent; Pt. = patients; L.C. = local control; HDR = high dose rate; EBRT = external beam radiotherapy.
* Equivalent dose for tumor effects as if given at 2 Gy/day using the linear quadratic model with an α/β ratio of 10 (25). See appendix.

Table 3 HDR protocols under investigation

	EBRT dose (Gy)	HDR for T1, T2 tumors	HDR for T3, T4 tumors	Lymph nodes
Puthawala†	50Gy	4 or 6 × 4 Gy	7 or 9 × 4 Gy	Implanted
Cano†	56Gy	–	6 × 4 Gy	Implanted
Nag†	50Gy	4 or 5 × 4 Gy	–	Operated
Vikram†	50Gy	10 × 3 Gy	–	Operated
Demanes*†	50–60 Gy*	6 × 3.8 Gy	6 × 3.8 Gy	Implanted

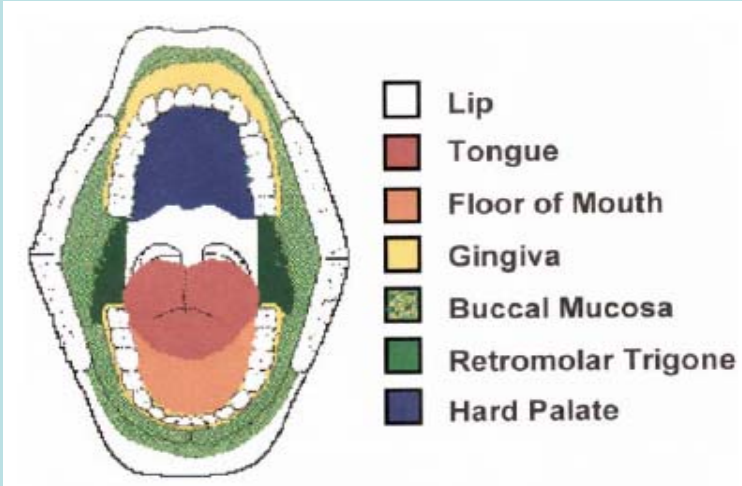
Abbreviations: HDR = high dose rate; EBRT = external beam radiation therapy.
* EBRT dose varies according to stage: T1, T2: 50 Gy; T3, 55 Gy; and T4, 60 Gy.
† Personal communication, 2000.

ABS Recommendations

- The ABS strongly emphasizes the **importance of using brachytherapy adequately** whenever feasible in the management of previously untreated head-and-neck cancers to minimize the need for treating recurrences at the primary site.

- The **extent of disease** should be carefully studied with CT, MRI, or PET scan as necessary.

- **Complication risks** are increased in patients with:
  - previous surgery,
  - skin or mucosal ulceration,
  - deep soft tissue necrosis,
  - bone exposure,
  - severe fibrosis.



- Under these circumstances **caution is advised**.
- Meticulous implant **technique** and adequate **doses** are necessary.
- Generally larger margins are required for recurrent tumors, especially if additional EBRT is not applied.

Doses

- Because of the **paucity of published data – lack of specific recommendations** for the indications for HDR brachytherapy in recurrent head and neck tumors.

- However, in view of the normal **tissue tolerance**, it is advisable to keep the **dose per fraction relatively small.**

In Europe - PDR is used more often, pulse fraction doses of 0,6 - 0,8 Gy given hourly, 20-25 pulses up to total dose of 15 - 20 Gy in **palliative** treatment.
In **definitive treatment** the fractionation is repeated till total dose of 40 - 50 Gy.

- In **previously irradiated** head-and-neck cancer patients, HDR brachytherapy should preferably be performed in the context of a controlled **clinical trial**.

ABS recommendations -recurrent HAN tumors

- Brachytherapy may play an **important role in the treatment of recurrent head-and-neck cancer.** The majority of these patients have previously received moderate to high doses of **EBRT with or without surgery** or chemotherapy.

- The **risks of additional therapy are high**, and additional radiation therapy must be **carefully planned** and implemented.

- Consideration must be given to the **previous radiation to normal tissues** (doses and fields), when the radiation was administered, the **extent of the recurrent disease,** and the **condition of the tissues.**

    - **Reirradiation with EBRT alone is not frequently used because of expected high morbidity.**

- **LDR** brachytherapy doses of 50 to 60 Gy have for **several decades** been used for the treatment of patients with recurrent head-and-neck cancer, with 30–70% salvage rate and 30–40% complication rates.

- There are **few published reports** of **HDR** in this clinical setting, to evaluate its efficacy and safety.

Radiotherapy and Oncology 91 (2009) 150–156

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

GEC-ESTRO recommendations

GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas

Jean-Jacques Mazeron [a,*], Jean-Michel Ardiet [b], Christine Haie-Méder [c], György Kovács [d], Peter Levendag [e], Didier Peiffert [f], Alfredo Polo [g], Angels Rovirosa [h], Vratislav Strnad [i]

[a] Department of Radiation Oncology, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
[b] Department of Radiation Oncology, Hôpital Lyon-Sud, Pierre Bénite, France
[c] Department of Brachytherapy, Institut Gustave Roussy, Villejuif, France
[d] Interdisciplinary Brachytherapy Unit, University of Lubeck, Luebeck, Germany
[e] Department of Radiation Oncology, Erasmus Medical Center-Daniel den Hoed Cancer Center, Rotterdam, The Netherlands
[f] Department of Radiation Oncology, Centre Alexis Vautrin, Nancy, France
[g] Department of Radiation Oncology, Hospital Ramón y Cajal, Madrid, Spain
[h] Radiation Oncology Department, Hospital Clínic of Barcelona, Spain
[i] Department of Radiation Oncology, University Erlangen-Nuremberg, Erlangen, Germany

Table 5. Trials of recurrent head and neck tumor reirradiation

Author (ref)	# of Pts.	Brachy	EBRT	Results
Syed *et al.* (28)	29	^{192}Ir (50–70 Gy)	No	18–36 m Local ctrl 63%
Par *et al.* (31)	35	^{125}I (83 Gy)	No	5-yr DFS 41% 5-yr NED 29%
Vikram *et al.* (29)	21	^{125}I (60–80 Gy)	No	High relapse rate
Wang and Schulz *et al.* (32)	35	(Ra Pack) 30–60 Gy	No	5-yr DFS 25.7% 5-yr surv with disease 8.5%
Stevens *et al.* (26)	85	^{192}Ir (4 Pts.) 50 Gy	Yes (82 Pts.)	Act 5-yr surv 17% Local ctrl 27%
Zelefsky *et al.* (30)	100	^{192}Ir 40.2 Gy in 33 pts; ^{125}I 171 Gy in 84 pts	No	Overall act surv 12 m 44% Overall act surv 24 m 20%
Krull *et al.* (67)	19	^{192}Ir (10–30 Gy)	No	24 m local ctrl 34% 12 m surv 29% 24 m surv 24%
Nag *et al.* (21)	7	IOHDR 15 Gy	No	Local ctrl: 57% Median disease-free surv = 9 mo.
Emami *et al.* (27)	87	^{192}Ir*	No	Local ctrl: 37% at 2 yrs
Donath *et al.* (9)	12	HDR 3 Gy × 8	No	25% disease-free at 2–16 m
DeCrevoisier *et al.* (33)	169	No	Yes (65 Gy)	2-yr overall surv 21% 5-yr overall surv 12%
Leung *et al.* (34)	91	24–45 Gy HDR only (8 pts.); 14.8 Gy HDR with EBRT (42 pts.)	Yes (83 Pts.)	5-yr actuarial overall survival = 30% 5-yr disease-specific survival = 33% 5-yr local failure-free survival = 38%

Patients did not receive concomitant chemotherapy.

* The brachytherapy dose not given; the total cumulative dose, including previous irradiation doses, was limited to 100 Gy.

Abbreviations: Pts = patients; EBRT = external beam radiation therapy; HDR = high dose rate; IOHDR = intraoperative high dose rate brachytherapy; m = month; yr = year; surv = survival; DFS = disease-free survival; NED = no evidence of disease; ctrl = control; act = actuarial.

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Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 5, pp. 1444–1450, 2005

0360-3016/05/$–see front matter

doi:10.1016/j.ijrobp.2004.12.078

SALVAGE HIGH-DOSE-RATE (HDR) BRACHYTHERAPY FOR RECURRENT HEAD-AND-NECK CANCER

JAROSLAW T. HEPEL, M.D.,* A. M. NISAR SYED, M.D., F.R.C.S., F.A.C.R.,†
AJMEL PUTHAWALA, M.D., F.A.C.R.,† ANIL SHARMA, PH.D.,† AND PAUL FRANKEL, PH.D.‡

*Department of Internal Medicine, University of California at Irvine, Orange, CA; †Department of Radiation Oncology, Long Beach Memorial Medical Center, Long Beach, CA; and ‡Department of Biostatistics, City of Hope Medical Center, Duarte, CA

Table 7. Summary of published studies on HDR brachytherapy for recurrent head and neck cancer

Study	Number of patients	Radiation technique and dose	Results
Leung *et al.* (25)	91 (NPC)	a) 24–45 Gy HDR only (8 patients) b) 14.8 Gy HDR with EBRT (42 patients) c) EBRT only (41 patients)	5-year overall survival = 30% 5-year disease-specific survival = 33% 5-year local failure-free survival = 38%
Donath *et al.* (26)	16	24 Gy	19% disease-free survival at 2 to 16 months
Friedrich *et al.* (27)	38	10–30 Gy, 10 Gy/fx weekly	1-year local control = 47% 1-year overall survival = 49%
Present study	30	34 Gy, 300–400 cGy/fx, 2 fxs/day	2-year local control = 67% 2-year disease-specific survival = 45% 2-year overall survival = 37% Late complications = 16%

Abbreviations: EBRT = external-beam radiation therapy; fx = fractions; HDR = high-dose radiation; NPC = nasopharyngeal carcinoma.

Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 2, pp. 354–362, 2001

0360-3016/01/$–see front matter

PII S0360-3016(01)01637-6

CLINICAL INVESTIGATION **Head and Neck**

INTERSTITIAL LOW-DOSE-RATE BRACHYTHERAPY AS A SALVAGE TREATMENT FOR RECURRENT HEAD-AND-NECK CANCERS: LONG-TERM RESULTS

AJMEL PUTHAWALA, M.D., FACR,*† A. M. NISAR SYED, M.D., FRCS (LON & EDIN),*† SHERIEF GAMIE, M.D.,* YI-JEN CHEN, M.D., PH.D.,*† ADINA LONDRC, M.D.,* AND VAUGHN NIXON, M.D.‡

Departments of *Radiation Oncology and ‡Head and Neck Surgery, Memorial Cancer Institute, Long Beach Memorial Medical Center, Long Beach, CA; †Department of Radiation Oncology, University of California, Irvine Medical Center, Orange, CA

Table 6. Trials of recurrent head-and-neck tumor reirradiation

Study	Number of patients	Interstitial brachytherapy	External beam radiation	Intraoperative radiotherapy	Results
Wang, 1987[7]	35	Yes (Ra Pack) 30–60 Gy	No	No	5-yr DFS 25.7%; 5-yr survival with disease 8.5%
Syed *et al.*, 1977[6]	29	Yes (Ir^{192}) 50–70 Gy	No	No	18–36 months local control 63%
Peiffert *et al.*, 1994[12]	73	Ir^{192} (60 Gy)	No	No	Local control 78%; 5-yr overall survival 30%
Vikram *et al.*, 1995[13]	21	No	No	Yes I^{125} or Ir^{192} 40–80 Gy	Local control 81% at 2 yr with DFS of 55%
Emami *et al.*, 1996[22]	87	Yes Ir^{192} (total ≤100 Gy)	No	No	Local control 37% at 2 yr
Stevens *et al.*, 1994[23]	85	Yes (4 pts) 50 Gy	Yes (82 pts)	No	5-yr actuarial survival 17%; local control 27%
De Crevoisier *et al.*, 1998[24]	169	No	Yes (65 Gy)	No	2-yr overall survival 21%; 5-yr overall survival 12%
Rate *et al.*, 1991[28]	47	No	No	Yes (e) 20 Gy	2-yr actuarial survival 54.9%; 2-yr local control 61.5%
Nag *et al.*, 1998[29]	38	No	No	Yes (e^-) 15–20 Gy	Local control 41% at 6 mo; 1 yr 19%; 2 yr 13%
Park *et al.*, 1991[30]	35	No	No	Yes I^{125} (83 Gy)	5-yr DFS 41%; 5-yr NED 29%
Zelefsky *et al.*, 1998[31]	100	Yes (33 pts) Ir^{192} 40.2 Gy	No	Yes (84 pts) I^{125} 171 Gy	Overall actuarial survival 12 mo 44%; overall actuarial survival 24 mo 20%
Present series	220	LDR Ir^{192}	No	No	Local control 77%; 5-yr DFS 33%

Abbreviations: DFS = disease-free survival; e = electron beam RT; I^{125} = Iodine^{125}; Ir^{192} = Iridium^{192}; LDR = low dose rate; NED = no evidence of disease; pts = patients.

Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 2, pp. 354–362, 2001

0360-3016/01/$–see front matter

PII S0360-3016(01)01637-6

CLINICAL INVESTIGATION — Head and Neck

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Departments of *Radiation Oncology and ‡Head and Neck Surgery, Memorial Cancer Institute, Long Beach Memorial Medical Center, Long Beach, CA; †Department of Radiation Oncology, University of California, Irvine Medical Center, Orange, CA

Table 2. Patient characteristics

Median age	56 years (range 16–88)
Sex	
Male	136
Female	84
Median time interval between prior treatment and recurrence	2.3 years (range 2 months–14 years)
Prior surgery	114 (52%)
Prior radiation	
External only	180 (82%)
External and brachytherapy	40 (18%)
Median dose	5717 cGy (range 39–74 Gy)
LDR brachytherapy reirradiation dose (median)	53 Gy (range 46–60 Gy)
Concurrent chemotherapy	88 (40%)
Interstitial hyperthermia	133 (60%)

Table 1. Sites of recurrent head-and-neck cancers

Sites	Number of patients
Lip	2
Buccal mucosa	2
Floor of mouth	11
Anterior tongue	9
Hard palate	2
Soft palate	19
Retromolar trigone	2
Tonsillar region	20
Base of tongue	45
Nasopharynx	22
Larynx/pharynx	13
Hypopharynx	8
Neck only	65*
Total	220

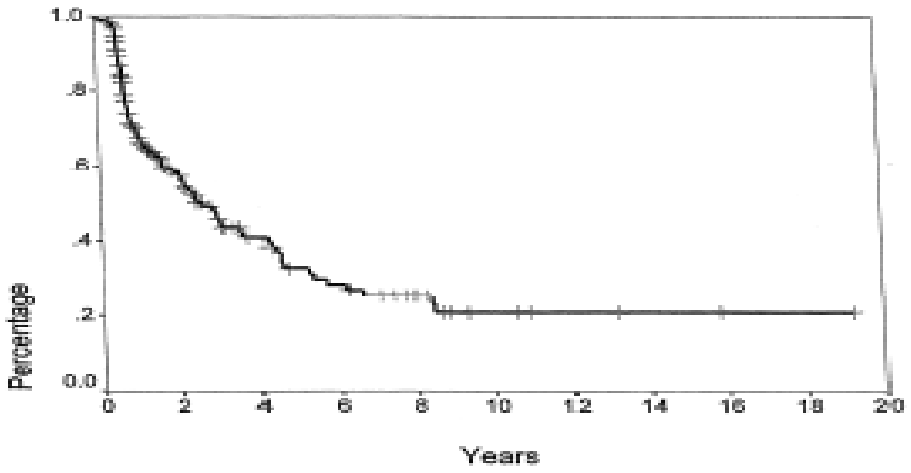


Fig. 2. Disease-free survival (Kaplan–Meier curves) for entire group.

Greater Poland Cancer Centre experience

- Retrospective analysis of repeated HDR and PDR brachytherapy.
- Analysis of CR, PR, NR, PD in 1, 3, 6 i 12 months after brachytherapy.
- Analysis of chosen prognostic factors, e.g. tumour locations and primary treatment.

Material

- **64 patients** (median age 59,7 years),
  35 (54,7%) - **HDR**
  29 (45,3%) - **PDR**
- January 1999 – January 2006,
- 54 (84,4%) – men, 10 (15,6%) - female

Primary treatment:

- 48 (75%) - surgery + EBRT
  13 (20,3%) - EBRT
  3 (4,7%) - surgery

Primary treatment

	HDR	PDR	total
Surgery + EBRT	24	24	48
EBRT	11	2	13
Surgery	-	3	3
After EBRT		61 (95,3%)	
median TD [Gy]	59,3	61,5	60,25
$T_{śr}$ to recurrence [months]	17,8	12,5	15,6

Clinical locations of primary tumour

Larynx, hypopharynx	25
Tongue, fundus of oral cavity	19
Oropharynx	11
Salivary glands	3
Epipharynx	2
CUP	2
Nose	1
Lip	1
razem	64

Clinical locations of primary tumour

	HDR	PDR
Larynx, hypopharynx	8	17
Tongue, fundus of oral cavity	14	5
Oropharynx	7	4
Salivary glands	1	2
Epipharynx	2	-
CUP	2	-
Nose	1	-
Lip	-	1

Histopathology

Squmaous cell carcinoma	57
Adenocarcinoma	1
Others	6

HDR brachytherapy

TD_{max} [Gy]	20 – 48
$TD_{śr}$ [Gy]	29,2
D_{fr} [Gy]	4 – 6
Number of fractions	5 – 6

Sole brachytherapy	30
BT + EBRT + Chtch	1
Surgery + BT	4

PDR brachytherapy

TD_{max} [Gy]	20 – 50
$TD_{śr}$ [Gy]	26,8
D_{fr} [Gy]	19,2 – 25,0

Number of fractions	**1 x**	20 Gy	18
		25 Gy	1
	2 x	19,2 Gy	1
		20 Gy	7
		25 Gy	2

PDR brachytherapy

Most frequently – 1 fractions
20 Gy in 25 pulses po 0,8 Gy co 1 godz.

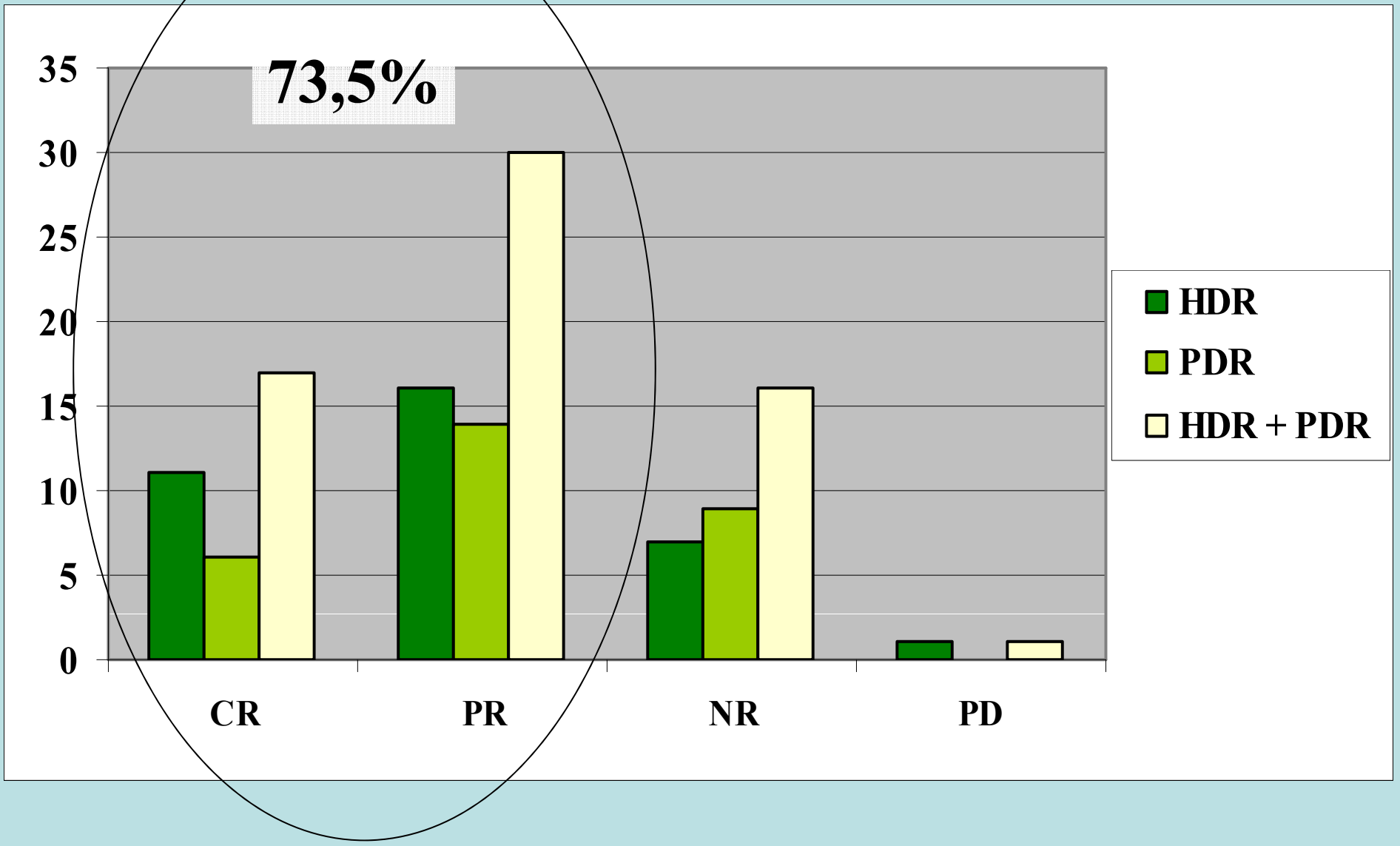
Sole brachytherapy	28
BT + EBRT + Chtch	1

Heterogeneity of tumour locations and other factors – statistical analysis was not possible.

Results

After 4 weeks	HDR	PDR	Total
CR	11 (31,4%)	6 (20,7%)	**47 73,5%**
PR	16 (45,7%)	14 (48,3%)	
NR	7 (20%)	9 (31%)	16 (25%)
PD	1 (2,95%)	-	1 (1,5%)

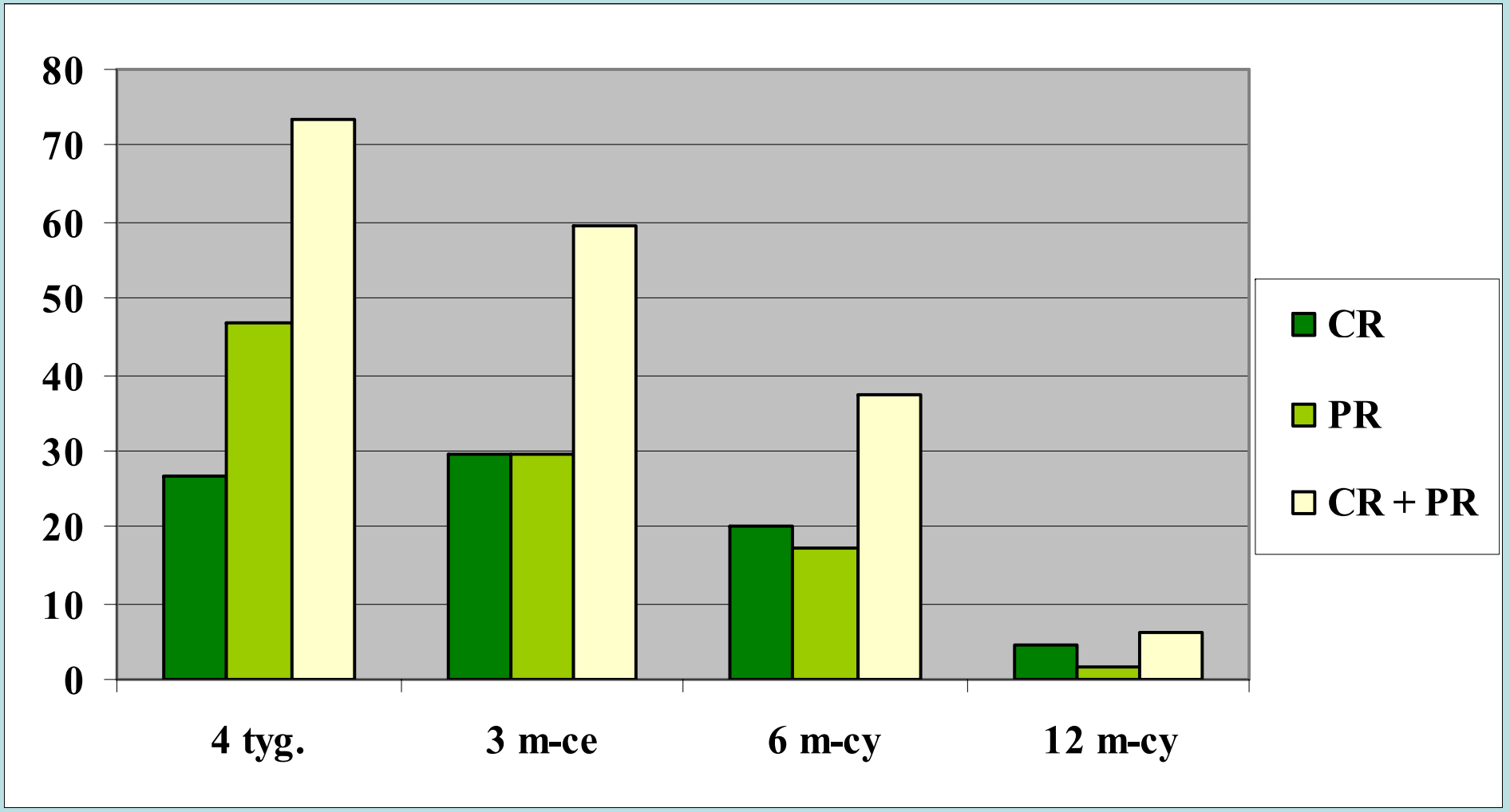
Results



Results

CR + PR	HDR	PDR	Total
after 3 months	25 (71,4%)	13 (44,8%)	38 (59,4%)
after 6 months	15 (42,8%)	9 (31%)	24 (37,5%)
after 12 months	4 (11,4%)	-	4 (6,25%)

Results



Results

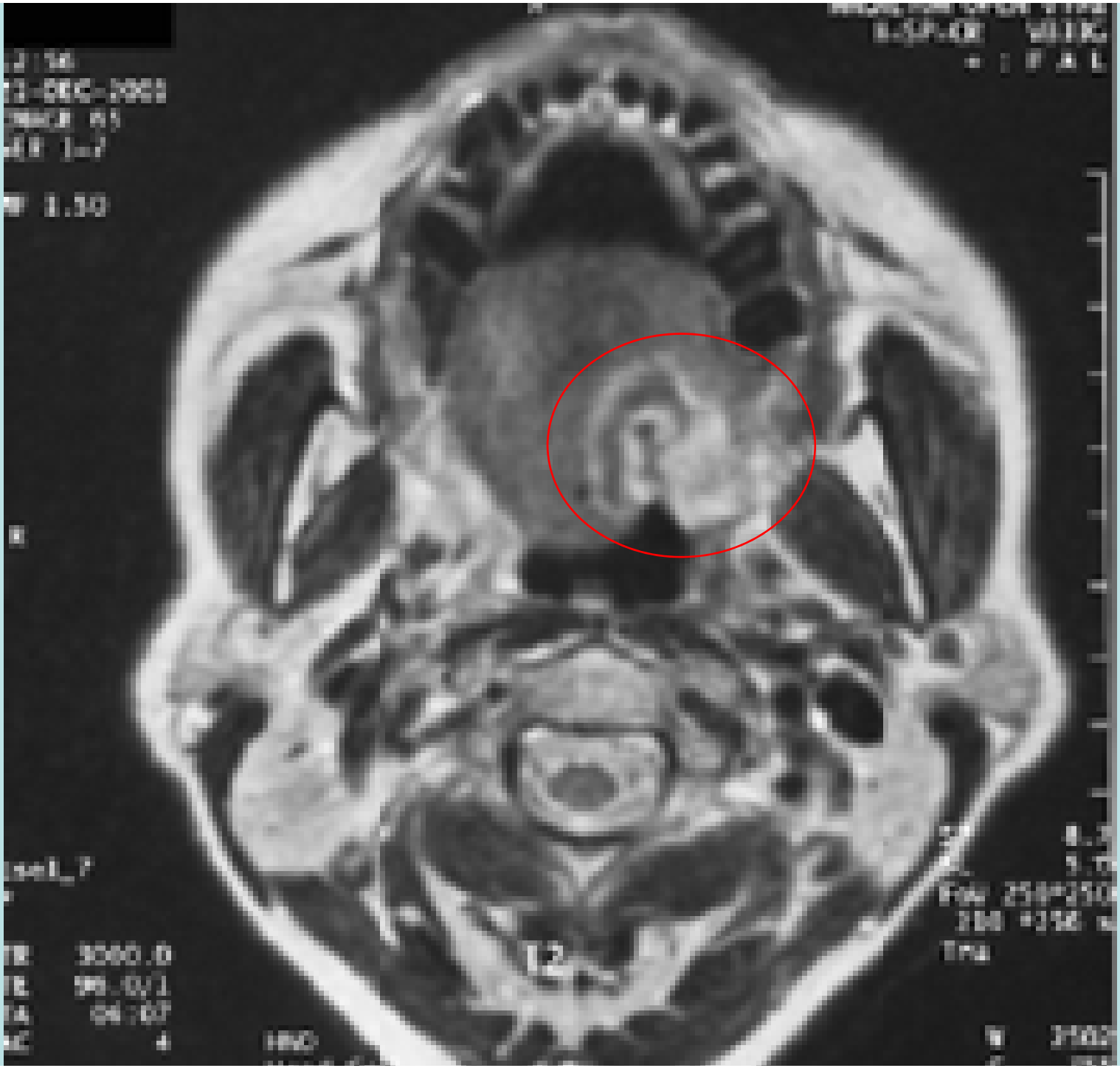
Complications after 4 weeks	HDR	PDR	Total
necrosis / fistula	5 (14,3%)	8 (27,6%)	13 (20,3%)

Conclusions

HDR or PDR brachytherapy can be treatment of choice in patients previously irradiated with external beam radiotherapy, treated surgically or with both modalities.

It appears to be that, in some cases, both HDR and PDR brachytherapy can prolong **overall survival time.**

A comparative and prospective investigation on larger group of patients is needed.

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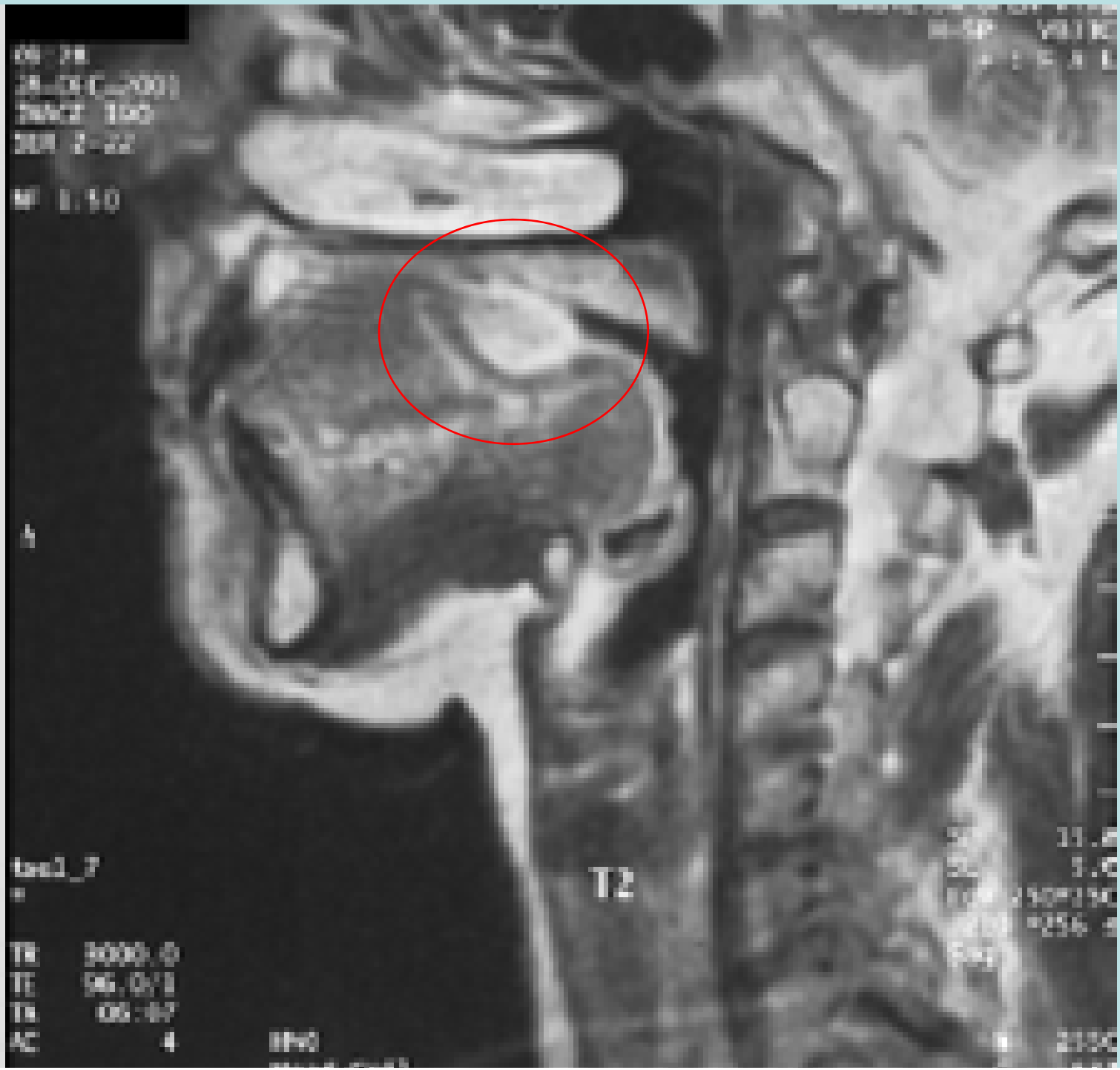
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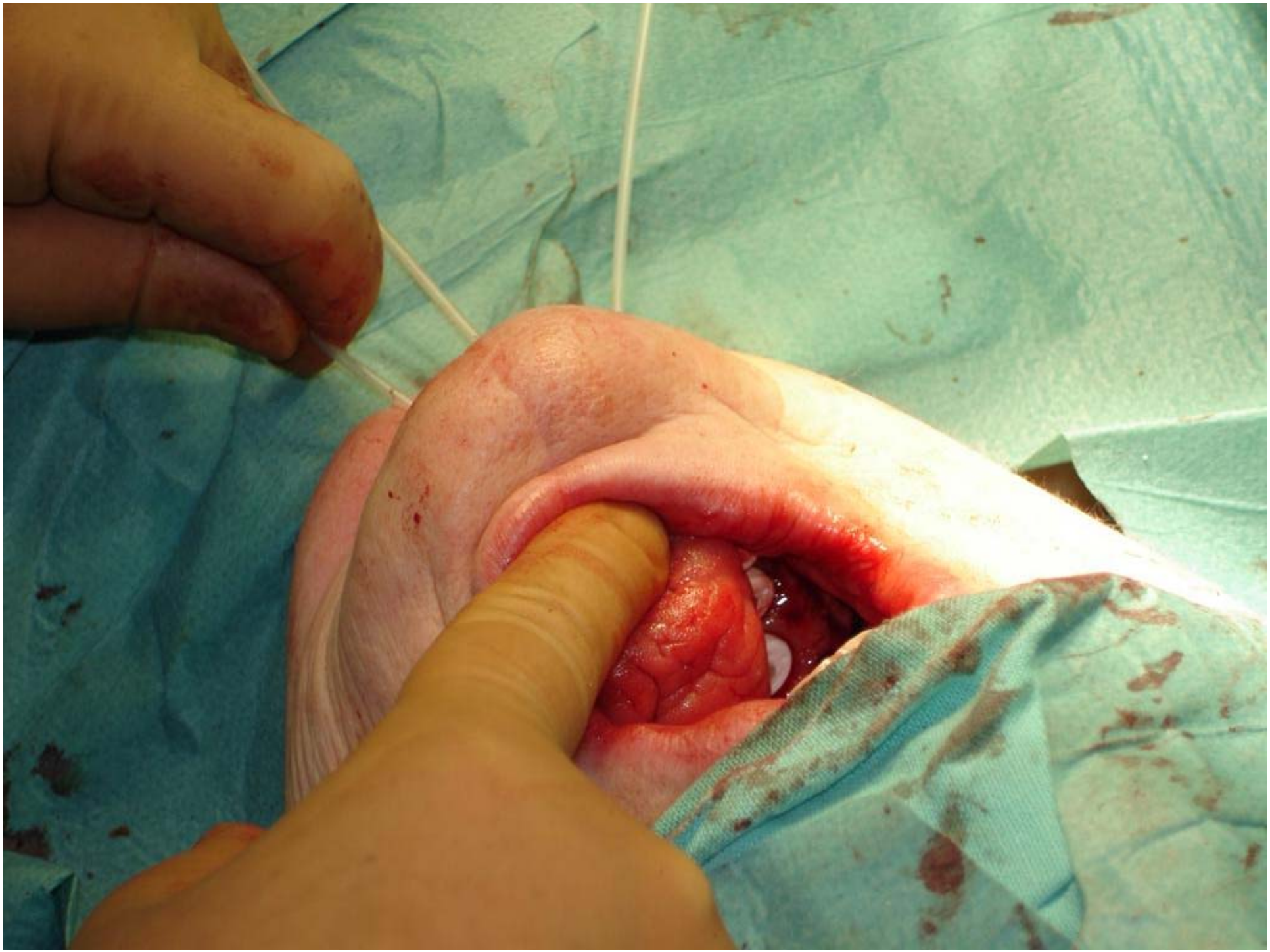

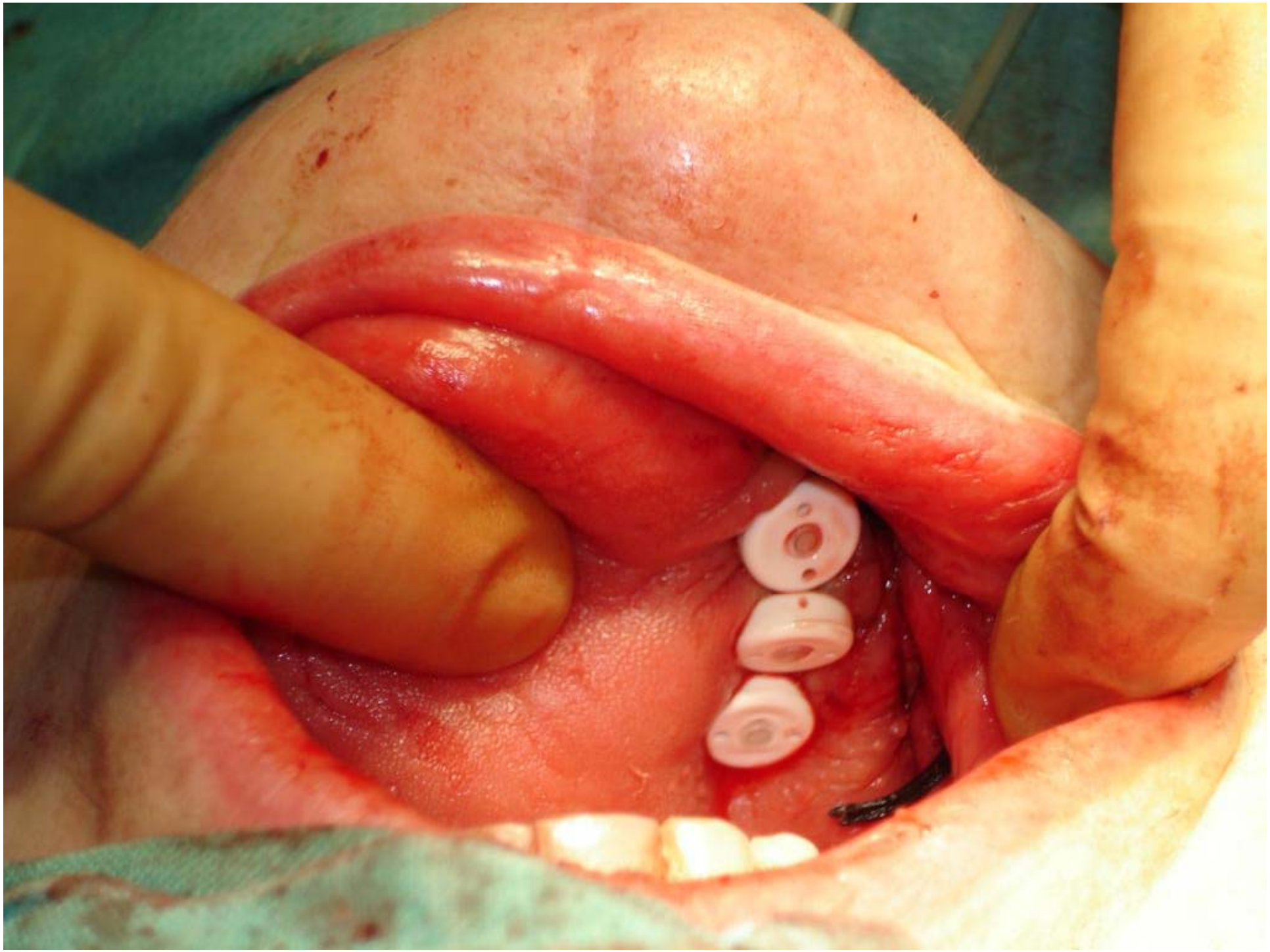

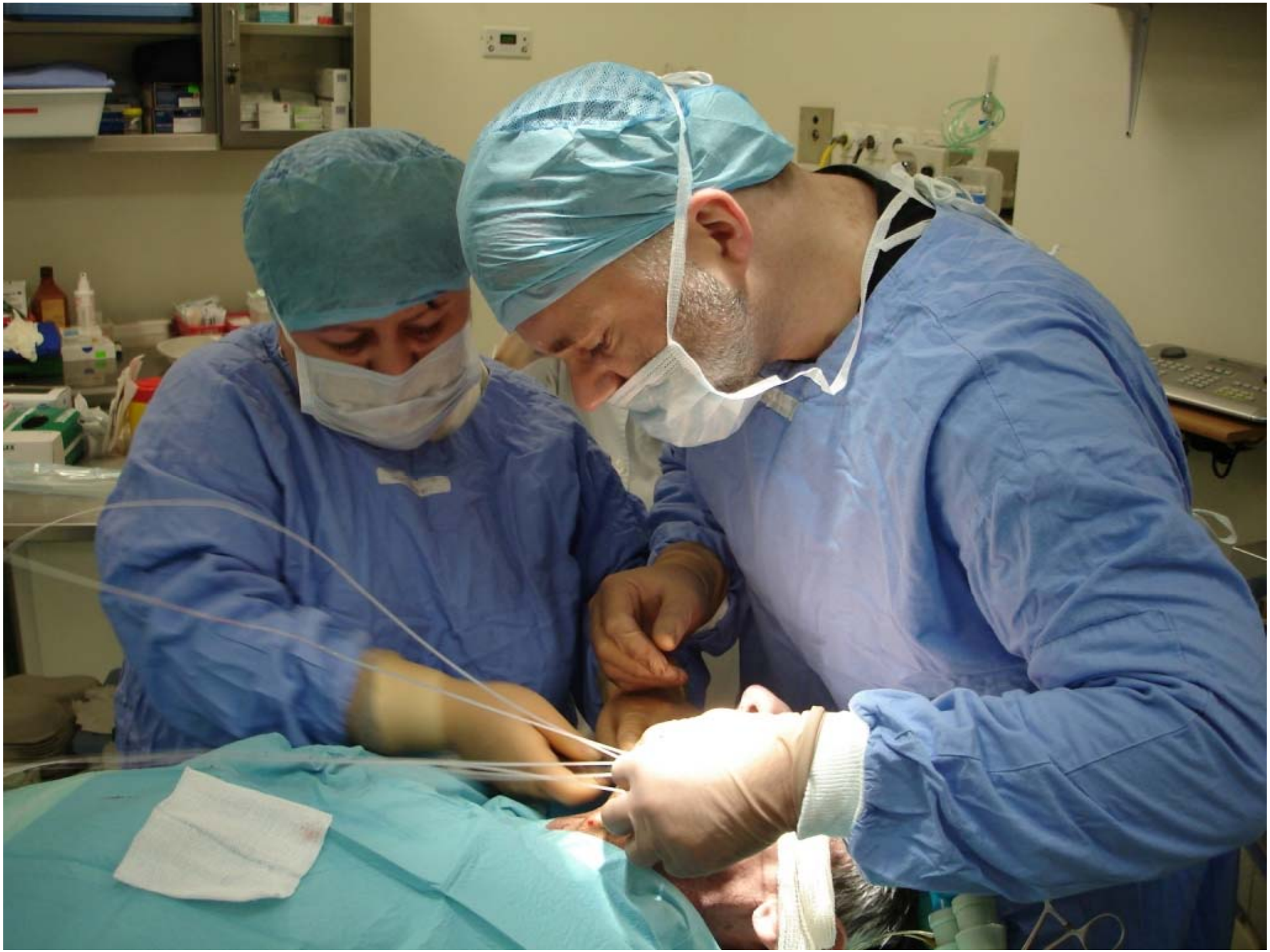

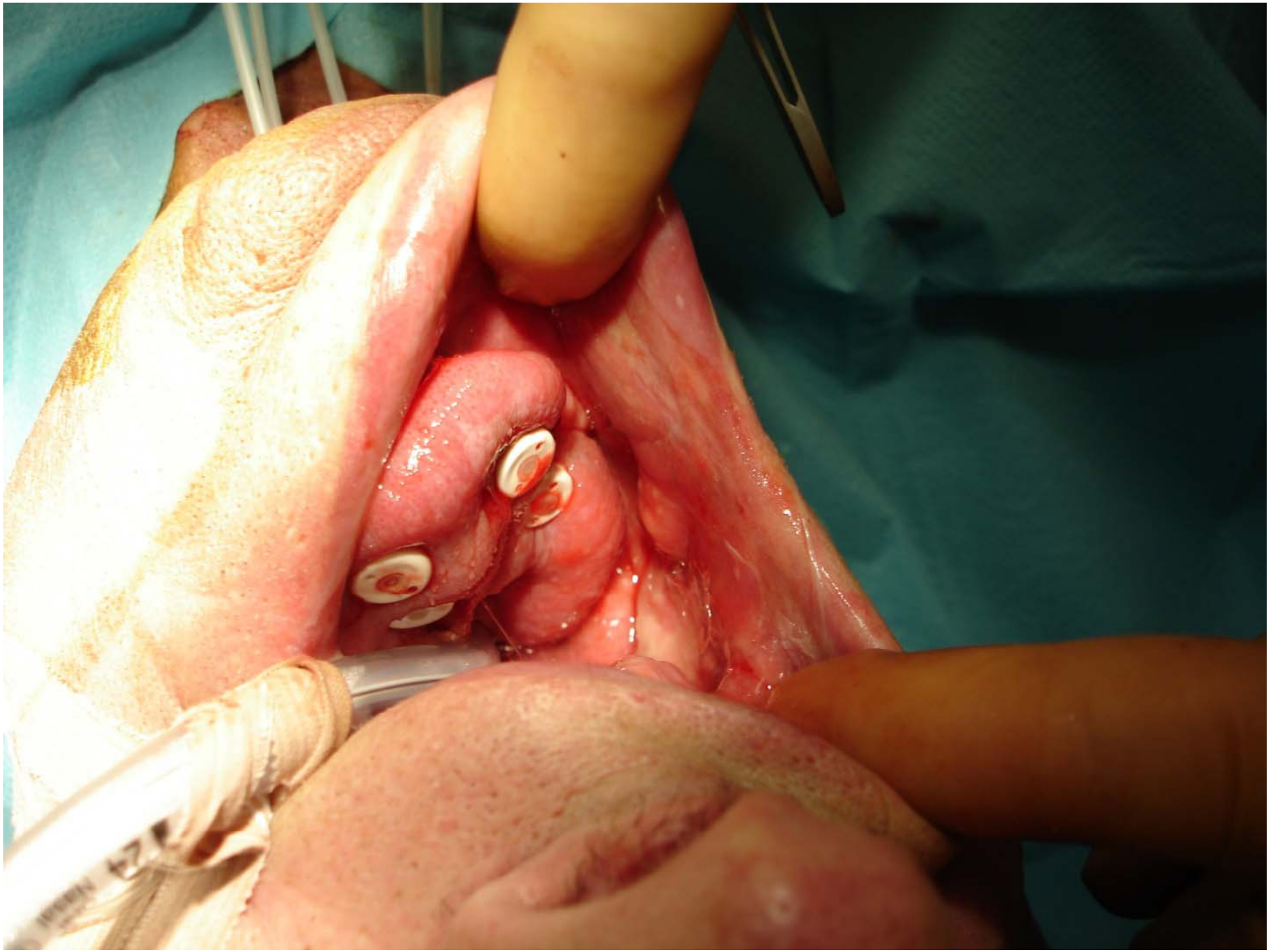

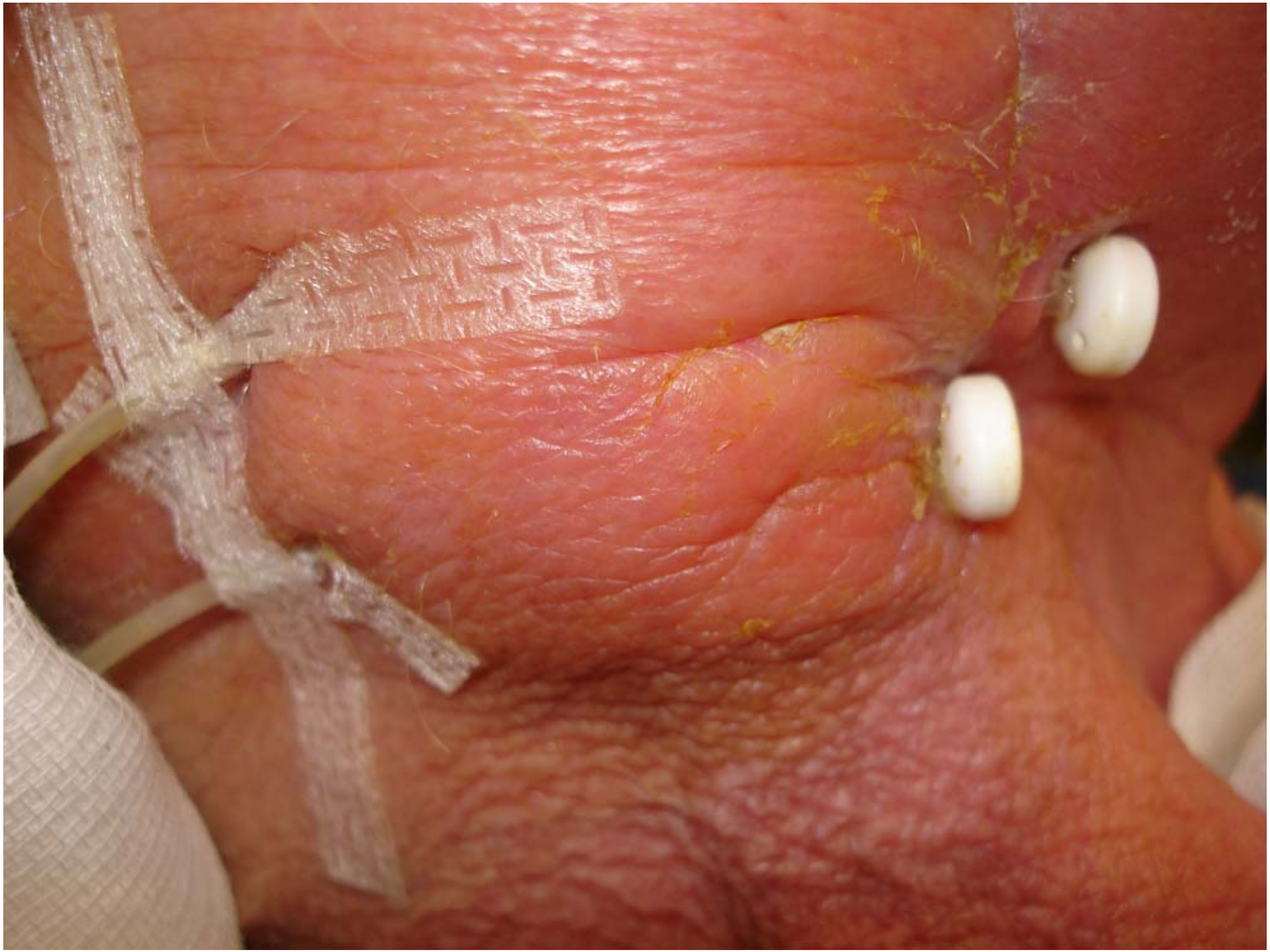

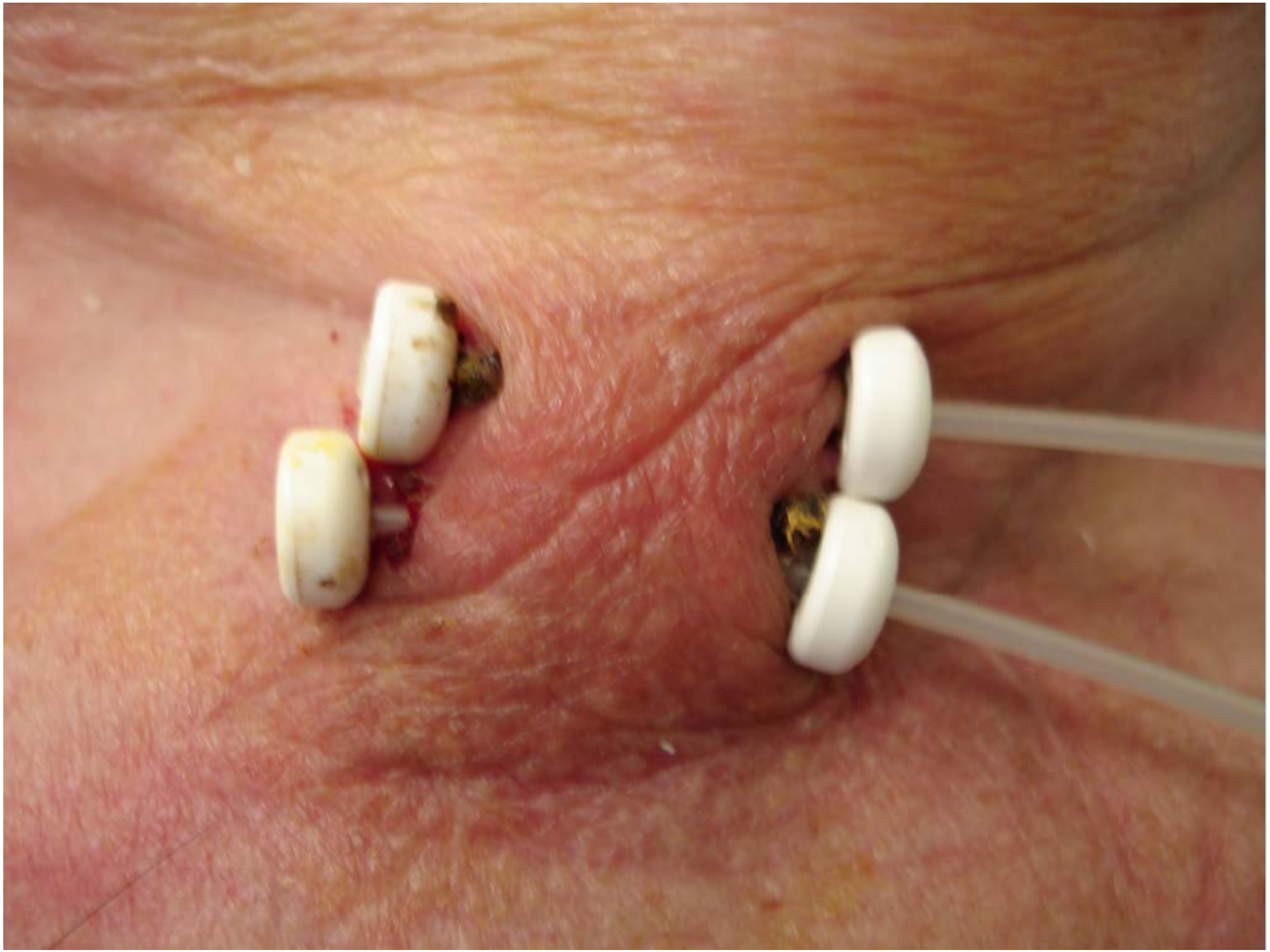

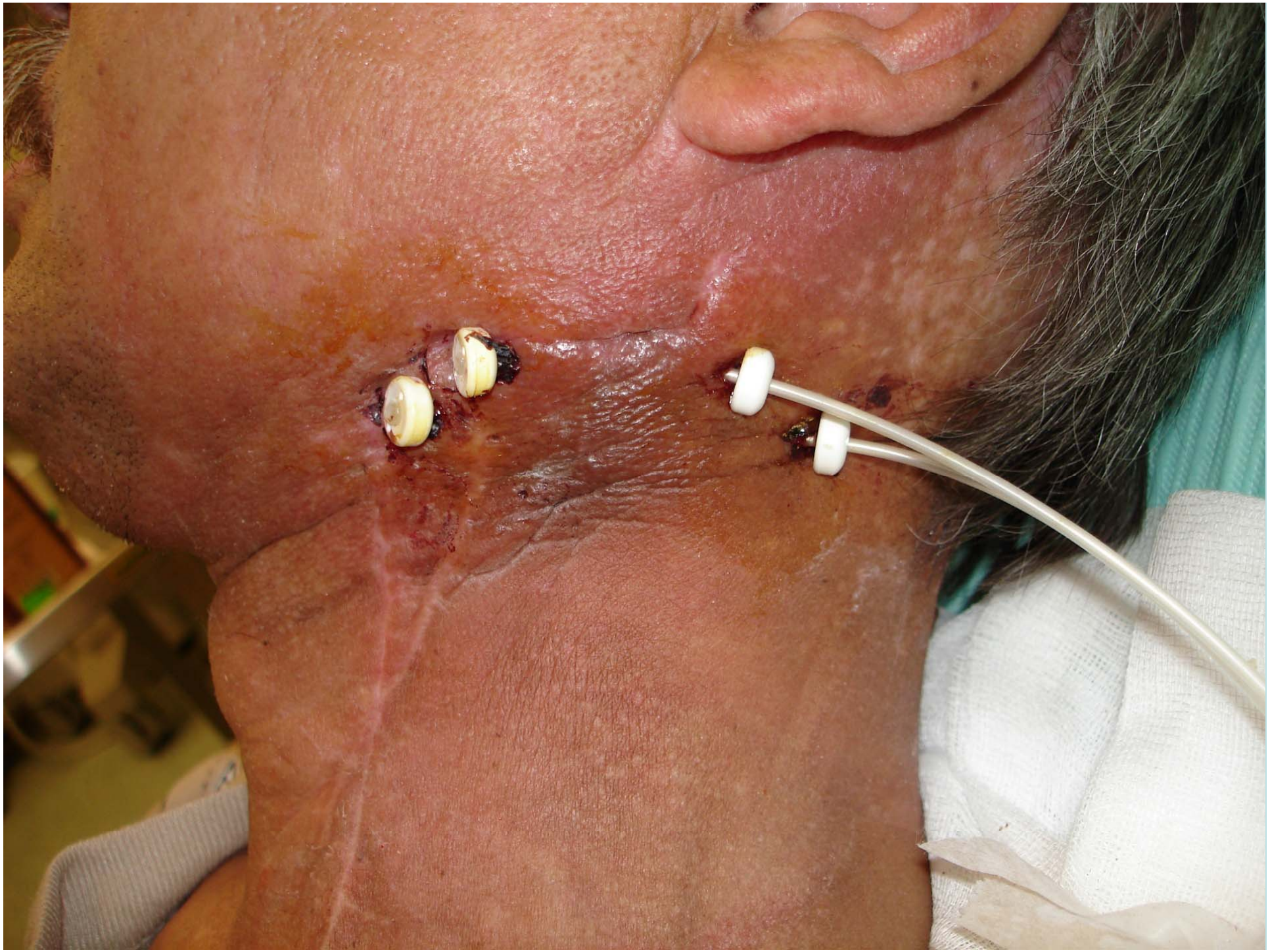

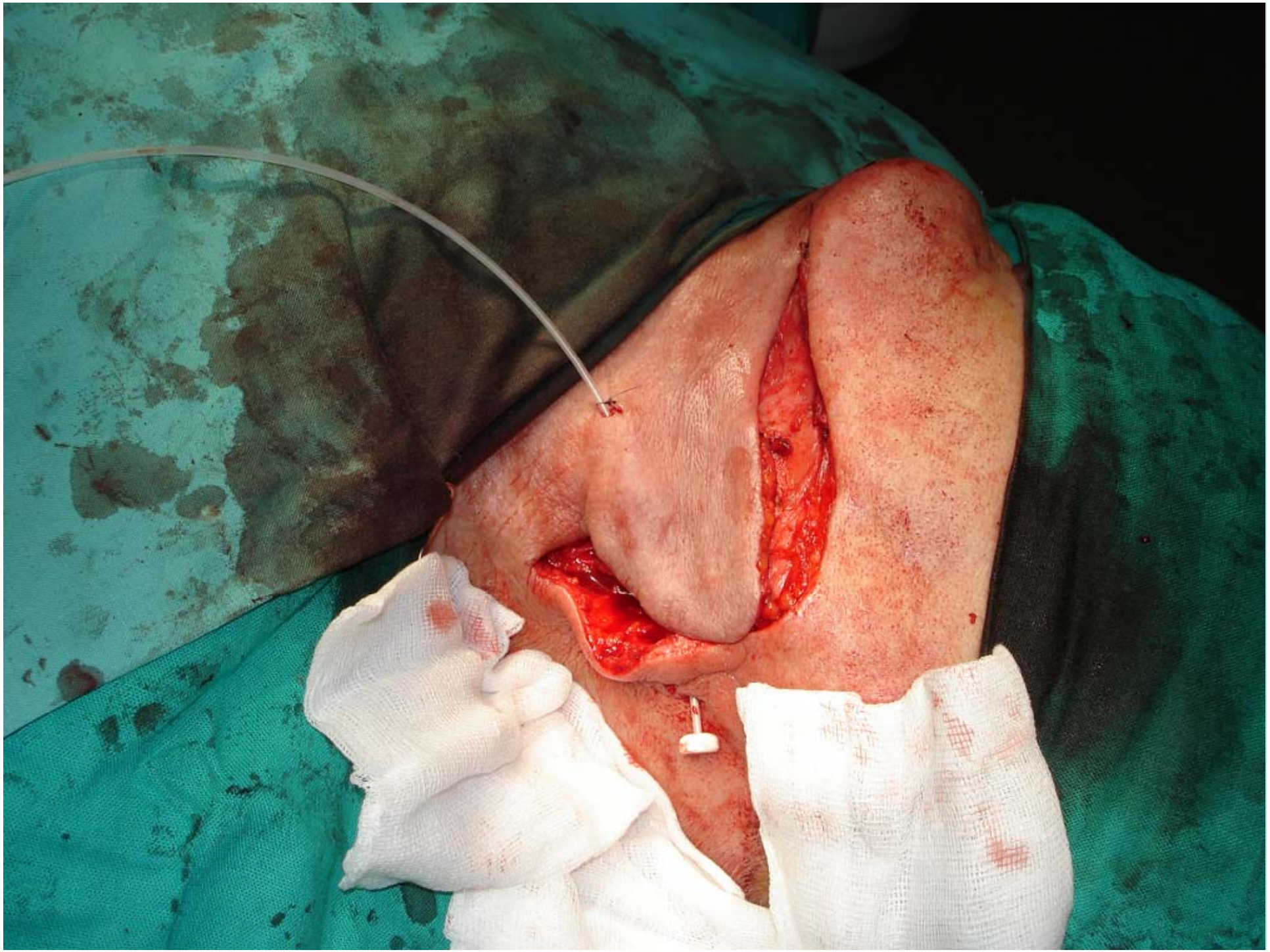


Surgery
Radiotherapy
Chemiotherapy
Immunotherapy
Gene therapy
Adjuvant therapy

Thank you