DEPARTMENT OF OTOLARYNGOLOGY HEAD NECK SURGERY
UNIVERSITY OF PAVIA
IRCCS POLICLINICO SAN MATTEO FOUNDATION – PAVIA
Chairman: Prof. Benazzo

Elettrochemioterapia

ASPETTI TECNICI

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A. Occhini, M. Benazzo

ECT: definition

Local treatment derived from the combination of two effects:

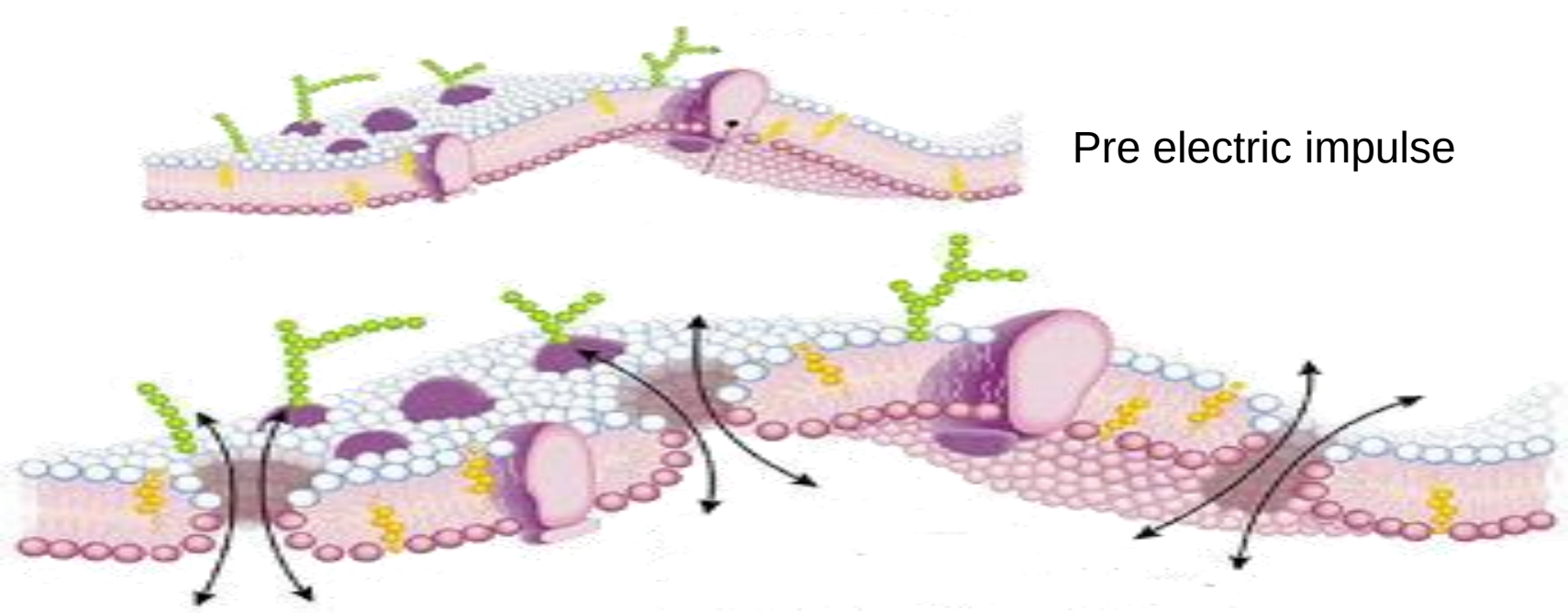
Administration of reduced drug doses
Electroporation of cell membranes

ECT is a local therapeutic approach to the treatment of tumors which are independent of histology

ECT: physical principle

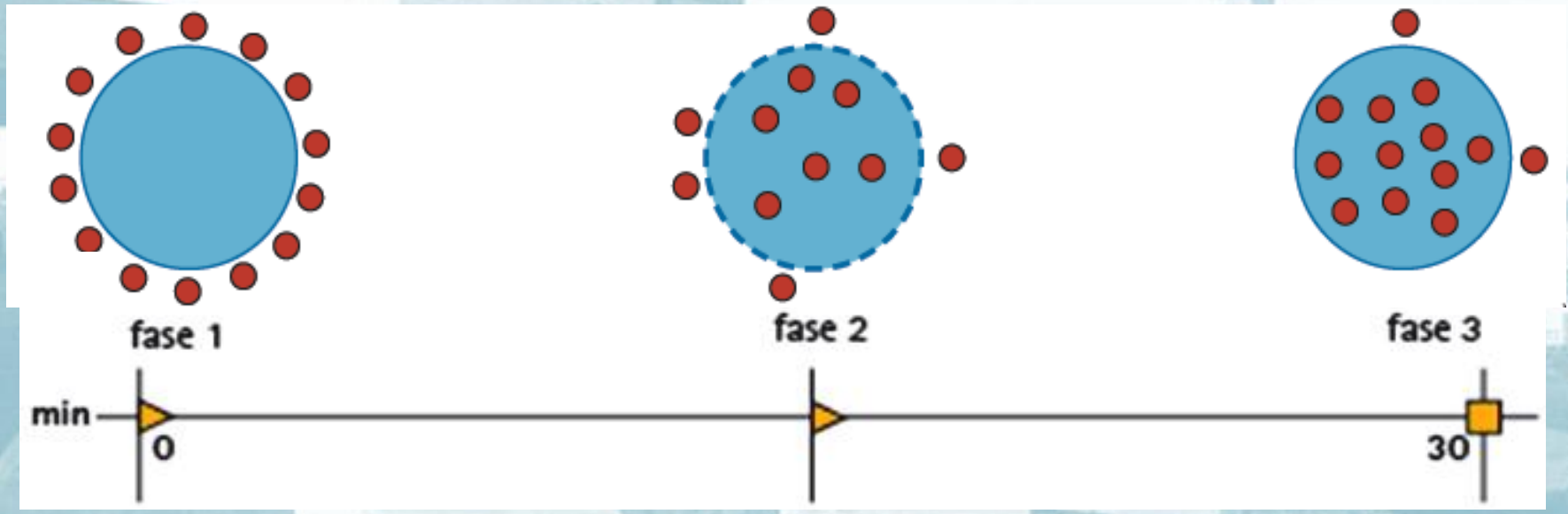
Electroporation is a physical phenomenon which enhances, thanks to electric impulses, cell membrane permeability.

This phenomenon allows drugs to enter the cytoplasm and increases their antitumor activity



Bleomycin

ECT: physical principle



The drug surrounds the cell but can not penetrate.

Cell membrane gets less waterproof and the drug can access the cell.

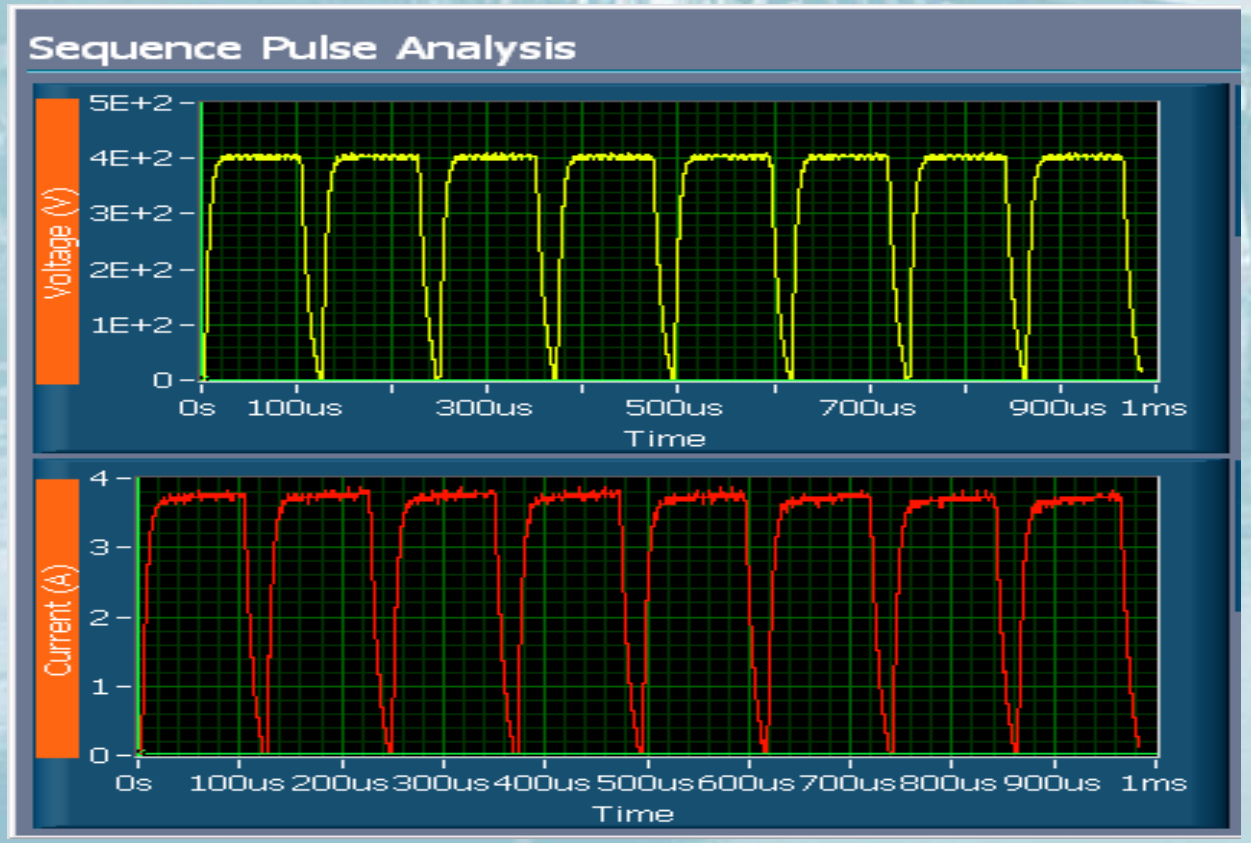
Pores closure

The drug remains inside the cell

Bleomycin's toxicity increases up to 10 times through cell membranes electroporation in vivo

ECT: Cliniporator

Treatment dosimetry given by the measure of real time electric current takes into the tumoral tissue

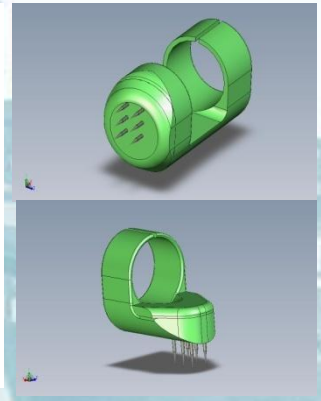


ECT: Electrodes

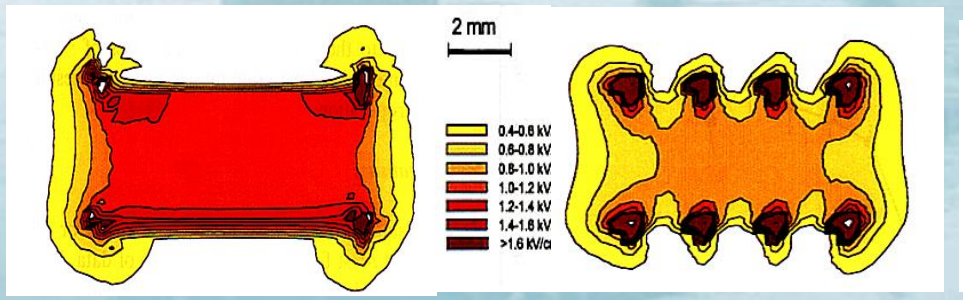
Plate

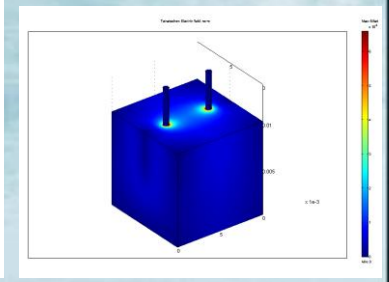
Linear

Hexagonal



Finger





ECT: ESOPE study

ESOPE (2003-2005)

(European Standard Operating Procedures of ECT)

Safety and efficacy evaluation

Define Standard Operating Procedures for clinical activity

ECT: ESOPE study

NON RANDOMIZED PROSPECTIC MULTICENTRIC STUDY

AIM:

- Evaluate and confirm ECT efficay and safety with bleomycin & cisplatinum for skin cancers (any histology)
- Define Standard Operating Procedures for clinical activity (SOP)

ECT: ESOPE study

Standard operating procedures

- anaesthesia
- drug administration modality
- pulsed erogation
- follow-up
- clinical indications

PARTNERS ESOPE

- Institut Gustave-Roussy, Parigi - France
- Cork Cancer Center, Cork - Ireland
- Institute of Oncology, Lubiana - Slovenia
- Herlev Hospital, Copenhagen - Denmark
- IGEA, Carpi - Italy

ECT: ESOPE study

Operative procedures

Anaesthesia

GENERAL high numbers of lesions, big dimensions

LOCAL few lesions, small dimensions, patient non suitable for general anaesthesia

Drug's infusion

BLEOMYCIN Intratumoural – Intravenous

CYSPLATIN Intratumoural

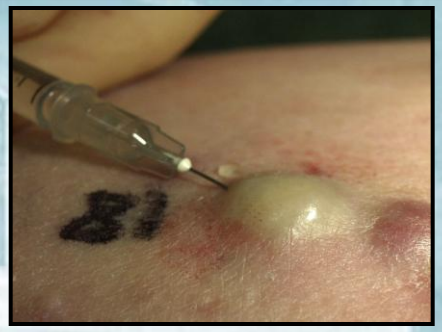
Electric pulses erogation

Three models of electrodes: lamina, linear needles and hexagonal needles

Pulses erogation frequencies: 1Hz and 5kHz

ECT: ESOPE study “drug administration”

INTRATUMORAL			
Volume $ab^2\pi/6$	$D < 0.5\ cm^3$	$0.5\ cm^3 < D < 1\ cm^3$	$D > 1\ cm^3$
BLM - 1000IU/ml	$1ml/cm^3$ (> 0,1ml)	$0.5ml/cm^3$	$0,25\ ml/cm^3$
CDDP - 2mg/ml	$1ml\ (2\ mg)/cm^3$	$0.5ml\ (1\ mg)/cm^3$	$0,25\ ml\ (0.5mg)/cm^3$



INTRAVENOUS

Bleomycin Standard Dose: 15000 IU/m^2

Electric pulses are applied 8 min after drug administration in order to allow capillary diffusion

Time window for electric pulses application is 20-30 min

Standard operating procedures in H&N

- Patient selection
- Nodule selection
- Route of administration
- Treatment modality
- Anaesthesia
- Post-op. analgesia
- Evaluation of tumor response
- Data collection

Standard operating procedures in H&N

Patient selection

Check	Absolute contraindications	Relative contraindication
Cardiac arrythmias, pace maker	Thorax application < 7 cm	Head Neck application (> 30 cm from heart)
Pulmonary function (fibrosis)	i.v. bleomycin	< 30% O_2 delivery i.t. bleomycin
Haematology (PLT < 70000/mm^3, INR>1,5)		Verify type of electrodes
Renal function (Creatinine< 150µmol/l)		Adequate idratation
Difficulties with local/general anaesthesia	yes	
Allergy to bleomycin	yes	
Cumulative dose of bleomycin	>240000 IU/m^2	

Standard operating procedures in H&N

- Patient selection
- Nodule selection
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Standard operating procedures in H&N

Nodule selection

RECIST criteria

Measurement of tumor lesions
Longest diameter in the plane of measurement must be recorded with a **minimum size** of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

10 mm caliper measurement by clinical examination

Measurement of lymph nodes
≥ 15 mm in **short** axis by CT scan

Eisenhauer EA, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) Eur J Cancer 2009;45:228-47

Standard operating procedures in H&N

- Patient selection
- Nodule selection
- Route of administration
- Treatment modality
- Anaesthesia
- Post-op. analgesia
- Evaluation of tumor response
- Data collection

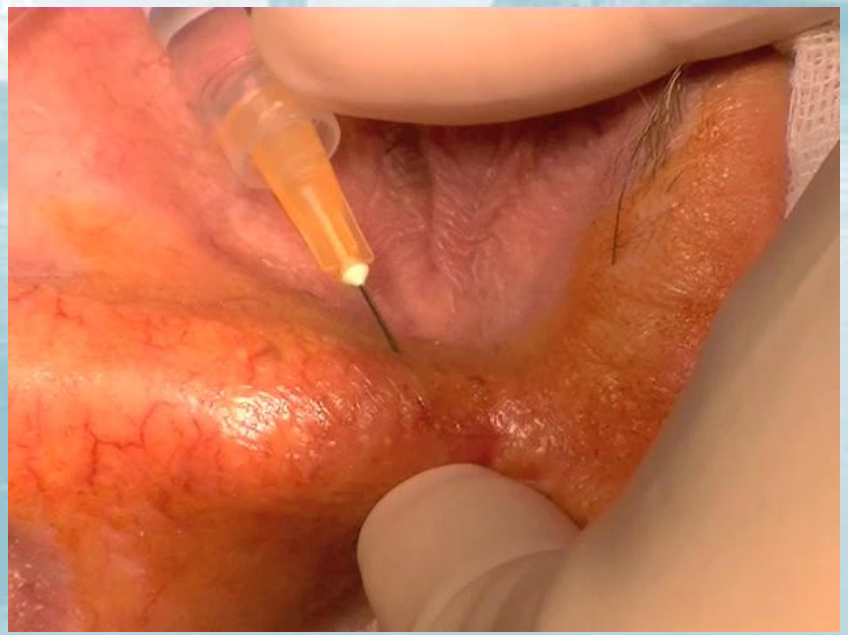
Standard operating procedures for HN

Route of administration

INTRATUMORAL			
Volume $ab^2\pi/6$	$D < 0.5\ cm^3$	$0.5\ cm^3 < D < 1\ cm^3$	$D > 1\ cm^3$
BLM (concentration 1000 IU/ml)	1ml (1000 IU)/cm^3 of tumor	0.5 ml (500 IU)/cm^3 of tumor	0,25 ml (250 IU)/cm^3 of tumor

Electroporation

immediately after injection



Standard operating procedures for HN

Route of administration

INTRAVENOUS

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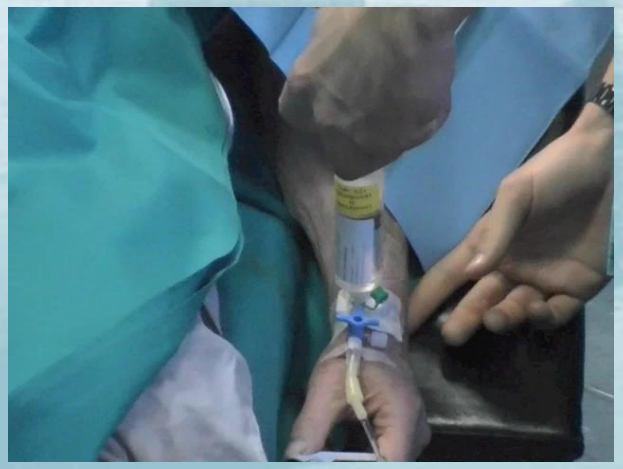
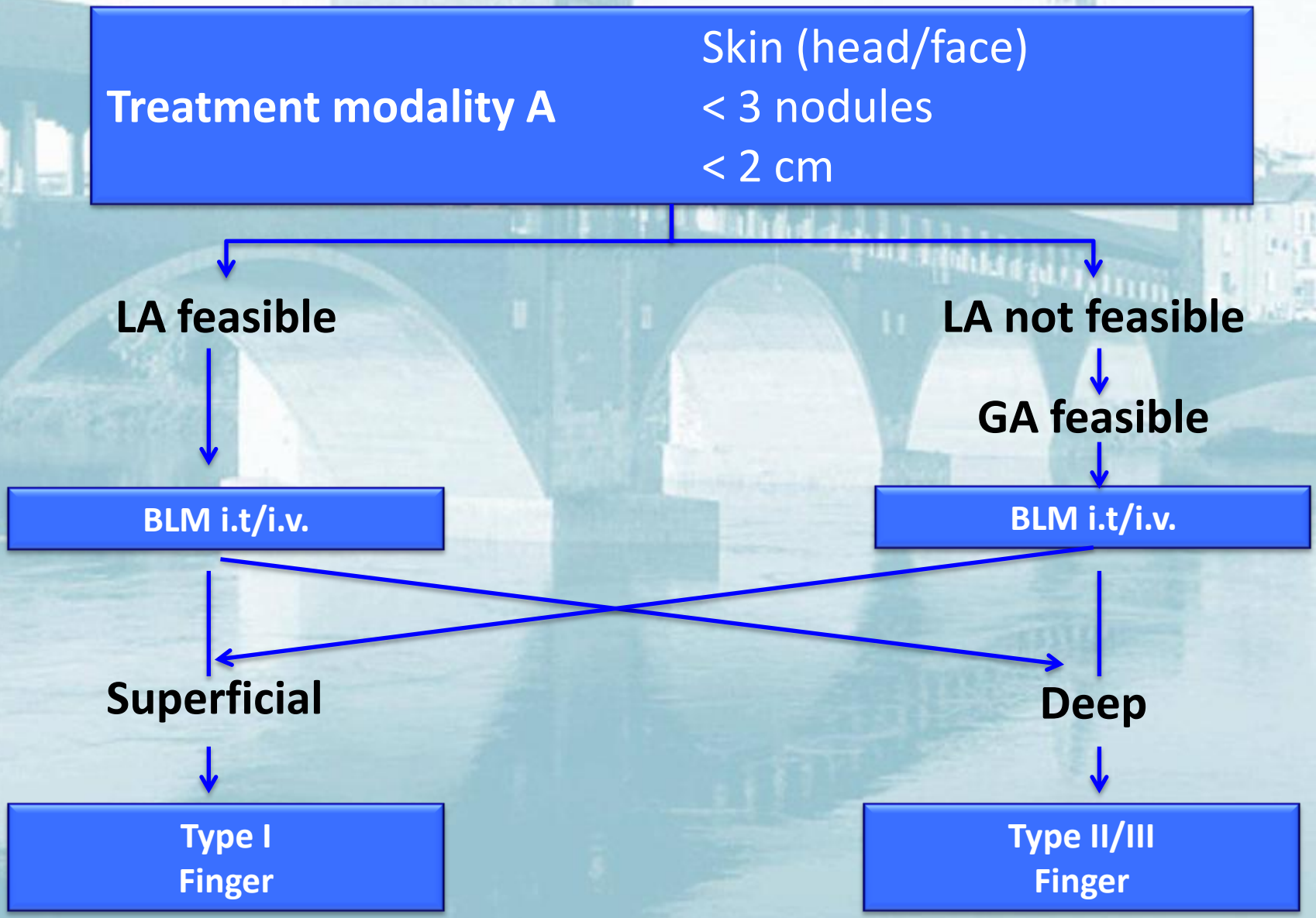


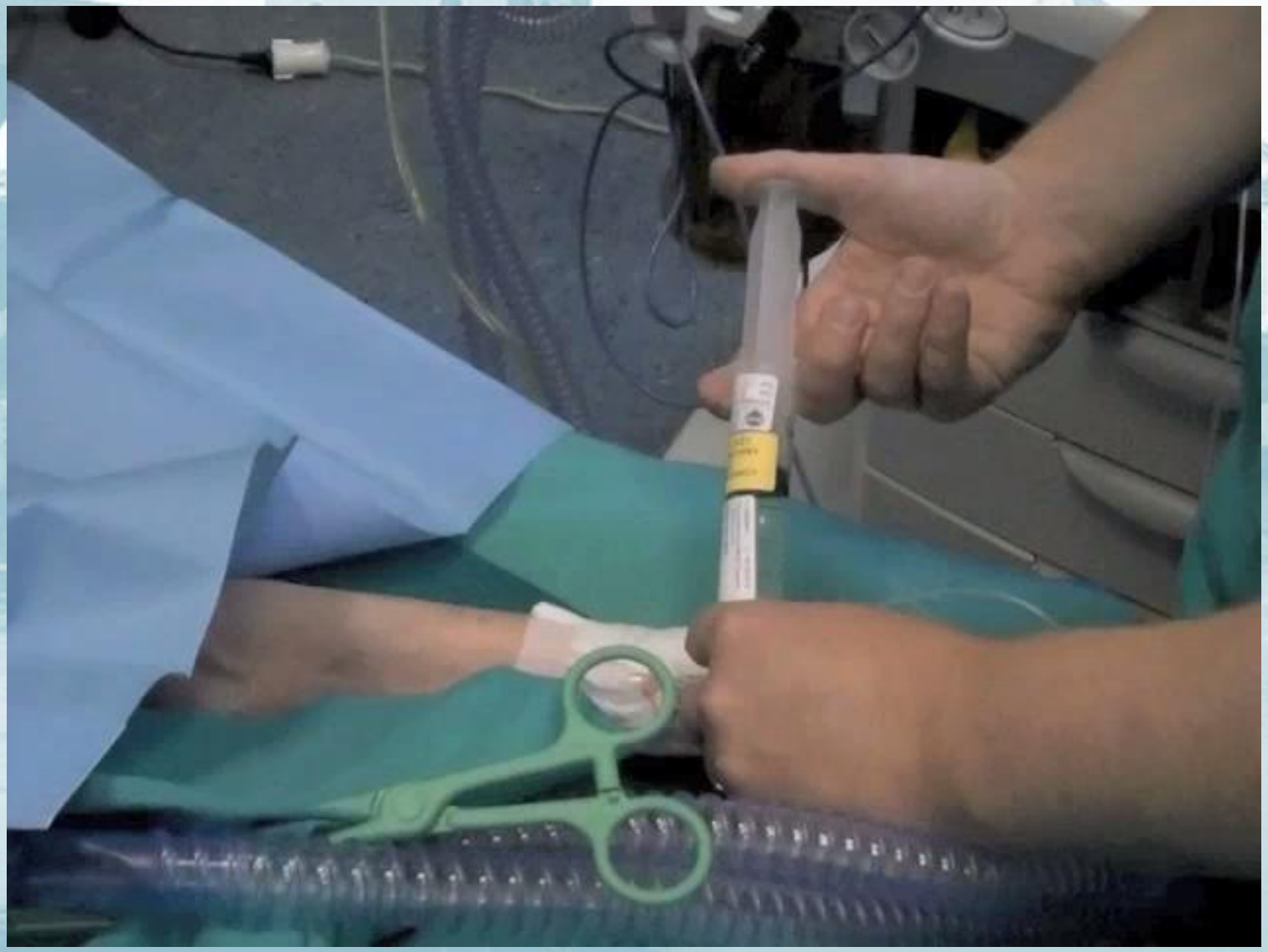
Standard operating procedures for HN

- Patient selection
- Nodule selection
- Route of administration
- Treatment modality
- Anaesthesia
- Post-op. analgesia
- Evaluation of tumor response
- Data collection

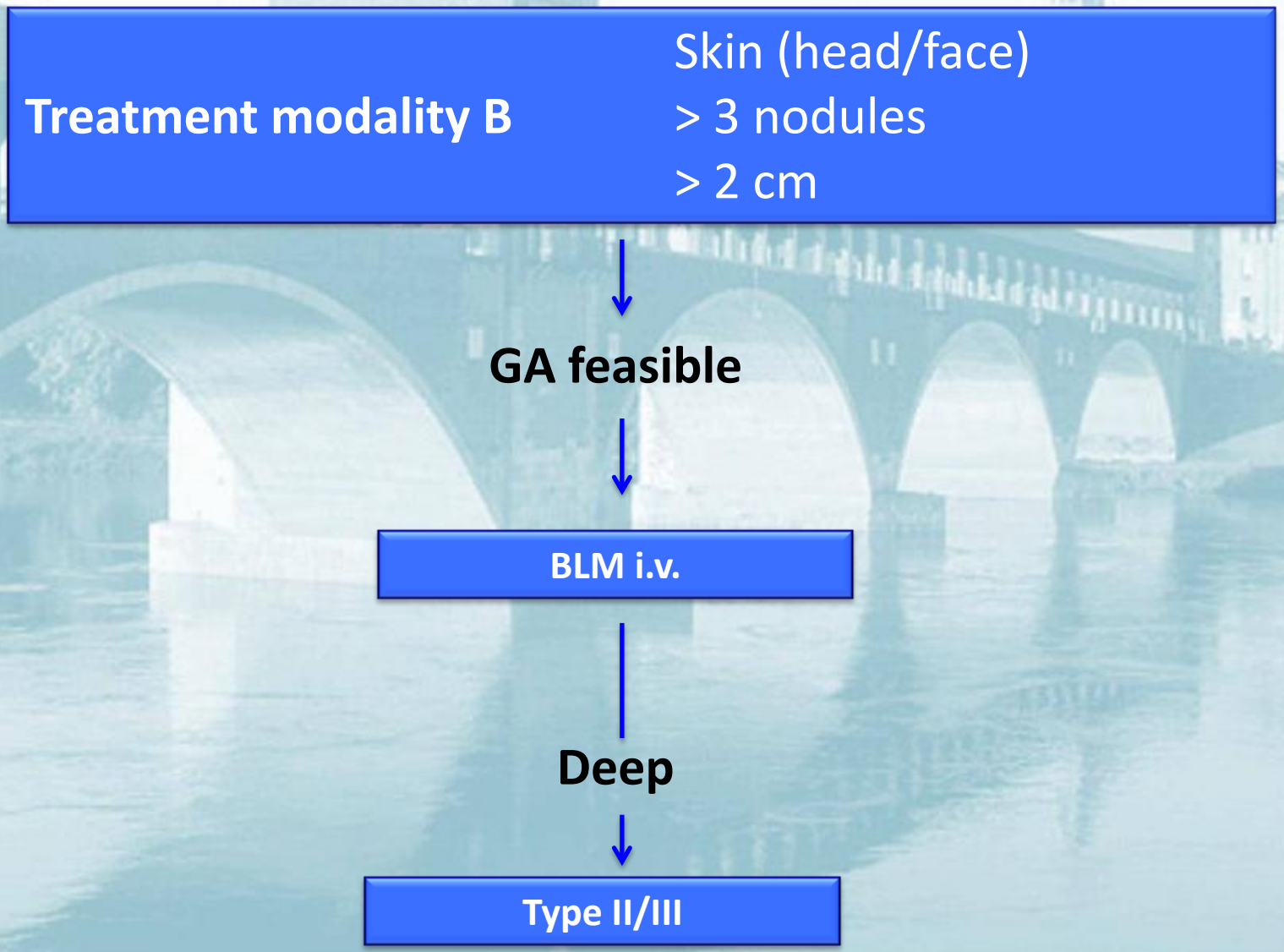
Standard operating procedures in H&N



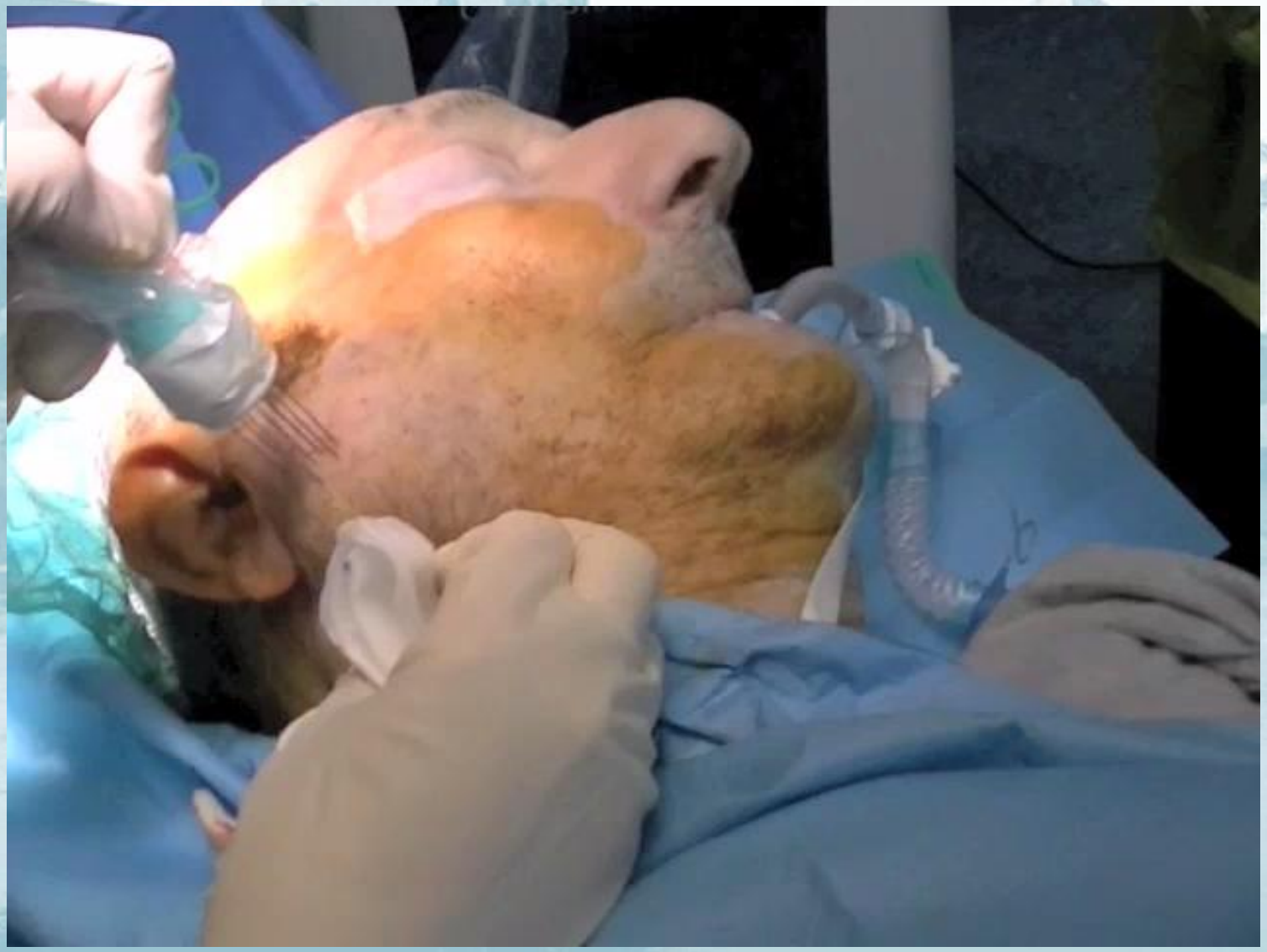
Standard operating procedures in H&N



Standard operating procedures in H&N



Standard operating procedures in H&N



Standard operating procedures in H&N

Treatment modality C

Skin (cheek,chin,neck)
Intraoral
Any number
Any size

↓

GA feasible

↓

BLM i.v.

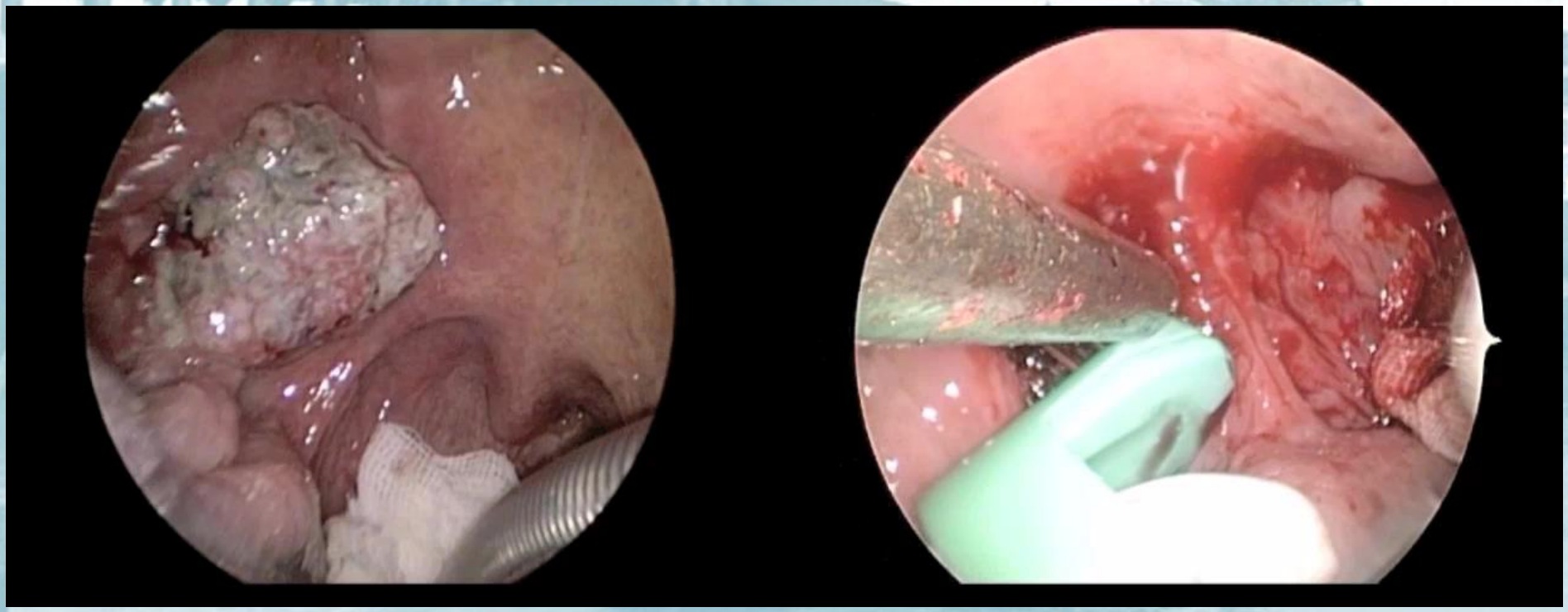
↓

Superficial/deep

↓

Type II/III
Finger

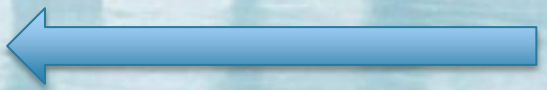
Standard operating procedures in H&N



Mucosal lesions

Standard operating procedures in H&N

- Patient selection
- Nodule selection
- Route of administration
- Treatment modality
- Anaesthesia
- Post-op. analgesia
- Evaluation of tumor response
- Data collection



Standard operating procedures in H&N

Local anaesthesia ± sedation

- Non-invasive monitoring (ECG, O_2-Saturation, NIBP)
- Midazolam 2 mg i.v.
- Remifentanil 0.03-0.06 γ/Kg/min
- O_2 2-4 l/min
- Local infiltration Lidocaine
  Mepivacaine+Adrenalin
  etc.

Standard operating procedures in H&N

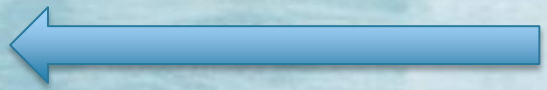
General anaesthesia

- Non-invasive monitoring (ECG, O_2-Saturation, NIBP)
- Remifentanil 0.1-0.2 γ/Kg/min
- Narcosis with Propofol 2-3 mg/Kg
- Curarisation Rocuronium 0.3-0.45 mg/Kg
- OTI (LMA) and AMV*
- Prosecution of narcosis Desflurane 4-6% ET

*Oro-tracheal intubation (laryngeal mask); Artificial mechanical ventilation

Standard operating procedures in H&N

- Patient selection
- Nodule selection
- Route of administration
- Treatment modality
- Anaesthesia
- Post-op. analgesia
- Evaluation of tumor response
- Data collection



Standard operating procedures in H&N

Post-operative analgesia

VAS

0 1 2 3 4 5 6 7 8 9 10

PROTOCOL A:	MILD PAIN	(**0-2**)
PROTOCOL B:	MODERATE PAIN	(**3-4**)
PROTOCOL C:	SEVERE PAIN	(**5-10**)

Standard operating procedures in H&N

PROTOCOL A: 24 hrs pain monitoring

Ketorolac / Ketoprofen
Paracetamol

- **i.o. (preferably)**
- **i.v.**

Every 8 hrs

I.O. gastric protection (protonic pump inhibitors)

IF VAS > 4 between two administrations: TRAMADOL

Guidelines of the IRCCS Policlinico S. Matteo Foundation

Standard operating procedures in H&N

PROTOCOL B: 24 hrs pain monitoring

intraoperative

Ketorolac 30 mg +
Tramadol 100 mg +
Ondansetron 4 mg

24 hrs elastomer infusion (rechargeable)

Ketorolac 60 mg +
Tramadol 200 mg

I.V. gastric protection (protonic pump inhibitors)

IF VAS > 4 : PARACETAMOL 1 g (i.v. bolus injection)

Guidelines of the IRCCS Policlinico S. Matteo Foundation

Standard operating procedures in H&N

PROTOCOL C: 30 hrs pain monitoring

intraoperative

Ketorolac 30 mg +
Morphine 10 mg +
Ondansetron 4 mg

30 hrs elastomer infusion (rechargeable)

Morphine 20-30 mg

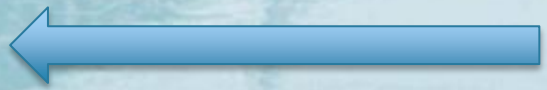
I.V. gastric protection (protonic pump inhibitors)

IF VAS > 4 : PARACETAMOL 1 g (i.v. bolus injection)

Guidelines of the IRCCS Policlinico S. Matteo Foundation

Standard operating procedures in H&N

- Patient selection
- Nodule selection
- Route of administration
- Treatment modality
- Anaesthesia
- Post-op. analgesia
- Evaluation of tumor response
- Data collection



Standard operating procedures in H&N

Evaluation of tumor response (2 months after ECT)

RECIST criteria

Complete response (CR): disappearance of all target lesions.
Any pathological lymph node must have reduction in short axis to <10 mm

Partial response (PR): at least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters

Progressive disease (PD): at least 20% increase in the sum of diameters of target lesions, or an absolute increase of the sum of diameters of at least 5 mm, or the appearance of new lesions

Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47

Standard operating procedures in H&N

- Patient selection
- Nodule selection
- Route of administration
- Treatment modality
- Anaesthesia
- Post-op. analgesia
- Evaluation of tumor response
- Data collection

Standard operating procedures in H&N

Data collection: according to the INSPECT database

- prestudy visit
- QoL questionnaires
- treatment chart
- follow up
- performance status and adverse event collection
- off study form

INSPECT (International Network for Sharing Practice in ECT) form, version 2.0

Save the date

1st World Congress on Electroporation

and Pulsed Electric Fields in Biology, Medicine and Food & Environmental Technologies

Portorož, Slovenia

6 to 10 September 2015

Grand Hotel Bernardin

Portorož