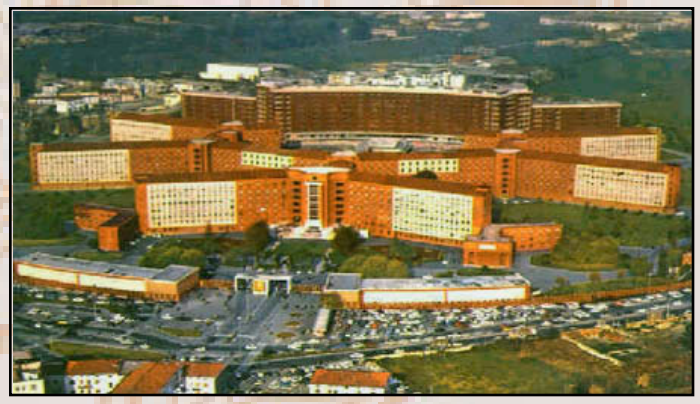
Biology and technology contribution to clinical advancement: the case of oropharyngeal cancer

Brescia – May 8th, 2009

SURGERY FOR THE TREATMENT OF OROPHARYNGEAL CARCINOMA: STATE OF ART

Piero Nicolai



Department of Otorhinolaryngology
University of Brescia

TNM Classification of Malignant Tumours
International Union Against Cancer (UICC) (6th Edition, 2002)
OROPHARYNX

T3: Tumor more than 4 cm in greatest dimension

T4a: Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible

T4b: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base; or encases carotid artery

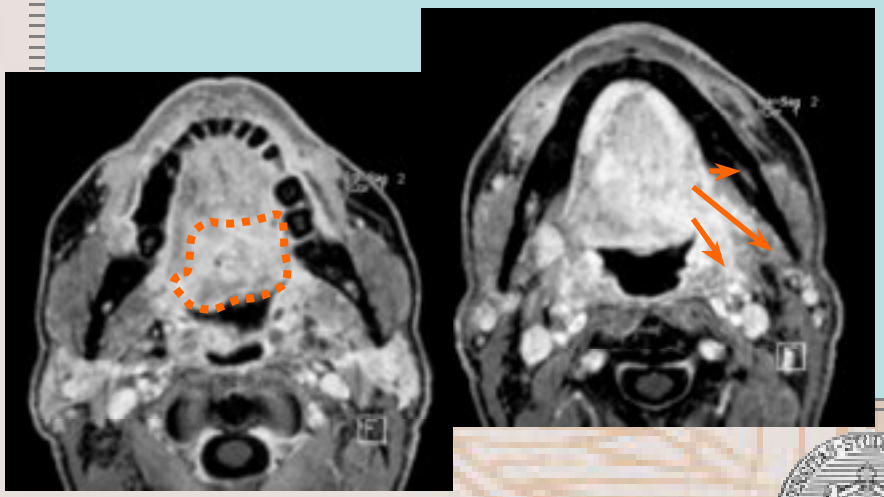
unresectable (or uncurable?)

OROPHARYNGEAL CARCINOMA

PRE-TREATMENT EVALUATION

Clinical examination: duration of symptoms
referred otalgia
tongue mobility
trismus
infiltrating vs exophytic lesion
comorbidities (!)

Radiologic examination (MR/CT): soft tissue extension
Functional imaging (PET/CT) mandibular involvement
pterygoid muscles and plates
styloid muscles
hypoglossal nerve(s)
lingual arterie(s)
nasopharynx
"N" status (+US)



OROPHARYNGEAL CARCINOMA

MANDIBULAR INVOLVEMENT

	OPG*	CT#	SPET°	SPECT*	MRI^
SENSITIVITY	50%	96%	95%	95%	93%
SPECIFICITY	94%	87%	48%	72%	93%
PPV	91%	89%	65%	79%	88%
NPV	63%	95%	93%	93%	96%

* : Imola et al., Laryngoscope 2001
\# : Mukherji et al., AJR 2001
° : Zieron et al., Head Neck 2001
^ : Bolzoni et al., Arch Otolaryngol Head Neck Surg 2004

OROPHARYNGEAL CARCINOMA

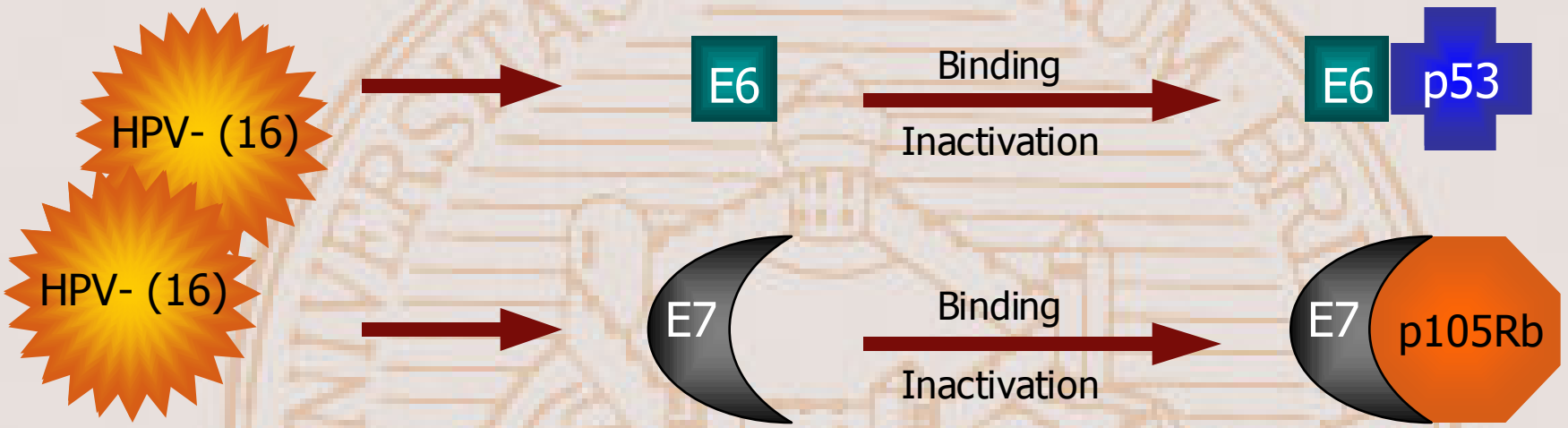
CRITERIA FOR PRIMARY TREATMENT SELECTION

- Surgery
- Concomitant CHT-RT

Resectable vs "unresectable" lesions
Loss of function (total glossectomy, total laryngectomy)
Exophytic vs infiltrating lesions
Presence of massive necrosis
Mandibular involvement
Retropharyngeal mets
Comorbidities
Induction chemotherapy (?)
Biological markers (?)

OROPHARYNGEAL CARCINOMA

p53 - p105Rb: interaction with HPV



- HPV (16) infection more frequent in NSND (p=0.003)
- HPV infection more frequent in laryngeal and oropharyngeal cancer (p=0.02)
- Overexpression and no mutations of p53 in NSND

Fouret et al, Arch Otolaryngol Head Neck Sur1997;123:513-516

OROPHARYNGEAL CARCINOMA

Role of HPV 16

- HPV positive status affects OS (p=0.002), incidence of tumor relapse (p=0.03), and second tumors (p=0.01)

Licitra et al, J Clin Oncol 2006

- Assessment of HPV, p53, p16, and EGFR status may be crucial in order to obtain more tailored and beneficial treatments for orophayngeal cancer

Perrone et al, Clin Cancer Res 2006

OROPHARYNGEAL CARCINOMA

HPV, EGFR

- 64% of cases positive for HPV
- Always younger patients
- HPV titer was significantly associated to a better response to induction CHT, better OS, better DSS
- Intensity of EGFR expression significantly correlated with poor response to induction CHT and poor OS
- EGFR expression inversely correlated to HPV titer
- All non-smokers were HPV +
- High EGFR/HPV- patients had the worse prognosis

Kumar et al, Int J Radiat Oncol Biol Phys 2007

OROPHARYNGEAL CARCINOMA

Role of HPV 16

- HPV presence was associated with:
  - Younger age (p=0.016)
  - Nonsmoking status (p=0.037)
  - A greater proportion of men (p=0.08)
  - Better response to induction chemotherapy (p=0.003)
  - Better response to CHT-RT (p=0.005)
  - Better OS (p=0.007) and DSS (p=0.008)

Worden et al, J Clin Oncol 2008

OROPHARYNGEAL CARCINOMA

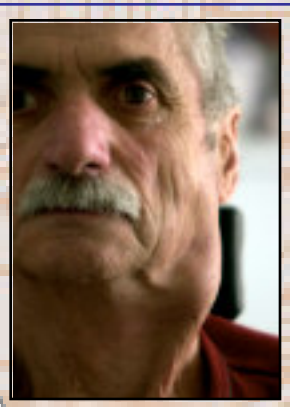
FACTORS AFFECTING TREATMENT RESPONSE AND DFS

- T- status
- N- status
- Stage
- Subsite of primary

T1-T4 lesions: 2-yr recurrence rate	
N0	50% (11/13 pure regional)
N1	59%
N2	65%
N3	82%
Total	**62%**

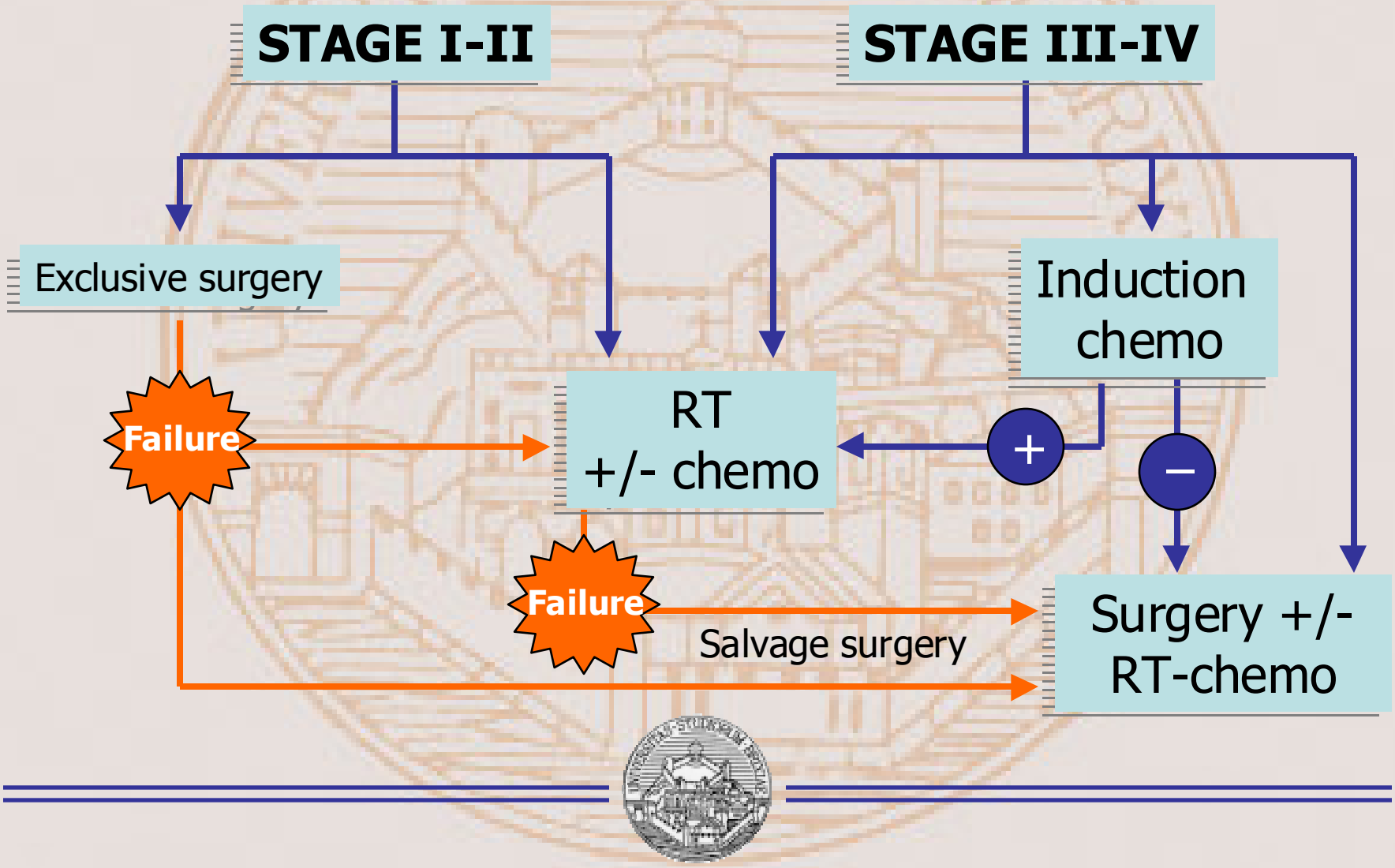
Sundaram et al. Laryngoscope 2005

5-yr DFS for stage IV base of tongue SCC	
Riley et al., 1983	14% (BOT)
Levy et al., 1991	0% (BOT)
Weber et al., 1993	0% (BOT)
Hinerman, et al., 1994	35% (only T4 BOT)
Sundaram, et al., 2005	66% (T3) 28% (T4) *All subsites



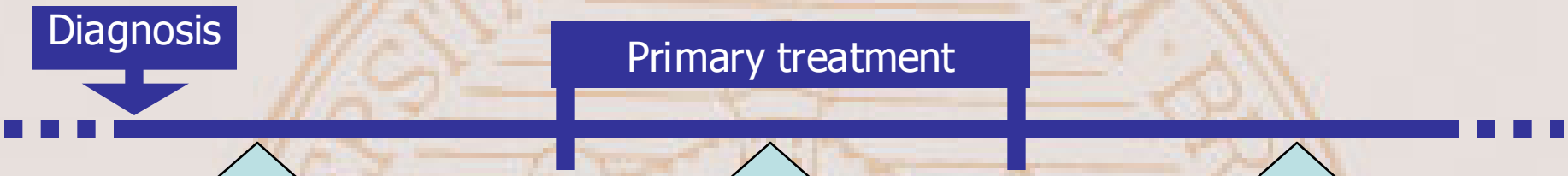
OROPHARYNGEAL CARCINOMA

CHOICE OF TREATMENT



OROPHARYNGEAL CARCINOMA

CHEMOTHERAPY



Neo-adjuvant CHT

Several meta-analyses demonstrated its inefficacy in improving 5-yr survival. However, it could predict the response to RT in organ preservation protocols.

Browman et al, Head Neck 2001
Worden et al, ASCO 2005

Concomitant CHT

It can be associated with different RT regimens:

- Conventional RT
- Hyperfractionated RT
- Accelerated RT
- Continuous RT
- Split RT

Adjuvant CHT

It does not seem to modify survival by itself; however, in association with RT is able to improve local-regional control, DFS, and to delay distant metastases (with higher toxicity)

Cooper et al. N Engl J Med 2004

Bernier et al. N Engl J Med 2004

OROPHARYNGEAL CARCINOMA

INDUCTION OR NEO-ADJUVANT CHEMOTHERAPY

Continuous infusion (day 1 - 4): Cisplatin 25 mg/m^2 + 5-FU 750 mg/m^2
3-hour infusion (day 2): paclitaxel 135-175 mg/m^2

I cycle
85-100% dosage

Response=0
↑ Toxicity

STOP CHT

Response=0
↓ Toxicity

II +/- III cycle

Surgery + RT

Response>0
↓ Toxicity

Response>0
↑ Toxicity

CDDP→carboplatin
Dose reduction
New schedule

Concomitant CHT-RT

OROPHARYNGEAL CARCINOMA

SALVAGE SURGERY

Efficacy correlated with:

- Recurrence stage (p=0.0005)
- Recurrent site (p=0.06; worse for oroph and neck)
- Not at all with time to presalvage recurrence (p=NS)

Goodwin, Laryngoscope 2000

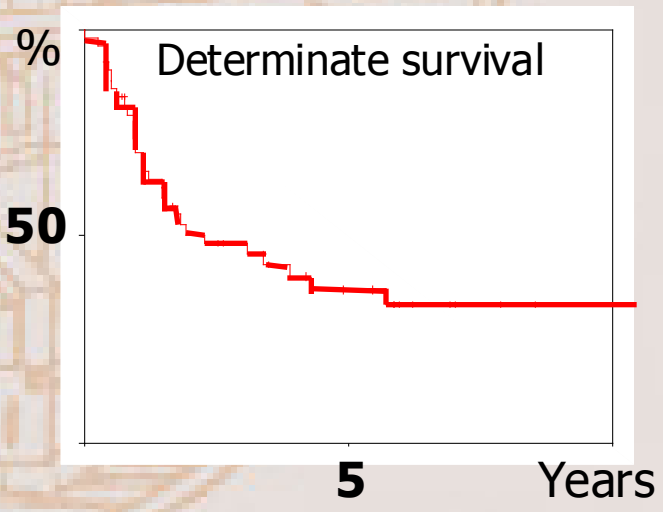
PERSONAL SERIES
JANUARY 1994 - DECEMBER 2003

STAGE III/IV OROPHARYNGEAL CANCER

N° pts: **50**
Mean age: **56.2** (range, 36-71)
Male/female ratio: **44/6**
Histology: **49** SCC, 1 MEC
Previous treatment: **21 pts** (42%)

SURVIVALS (Kaplan-Meier method)

Overall survival (5-yr): **32.2%** ± 7.2
Determinate survival (5-yr): **36.9%** ± 7.5

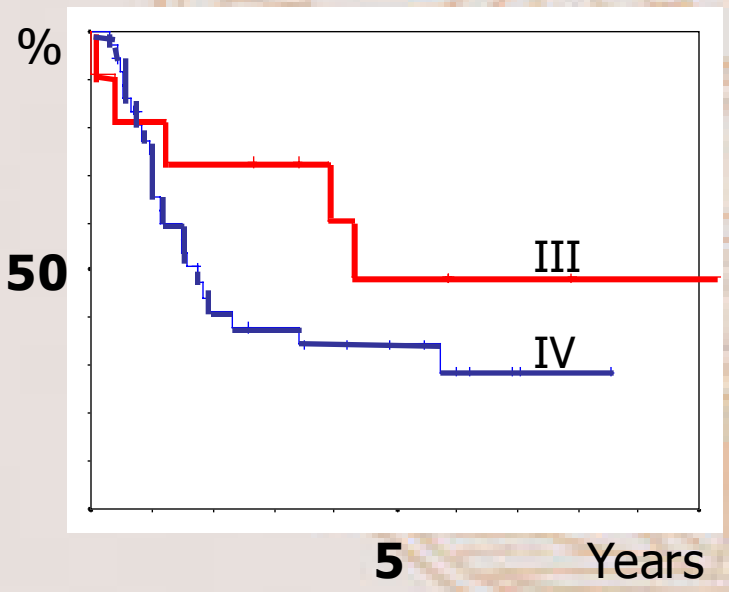


STATISTICAL ANALYSIS

UNIVARIATE (Log rank test)

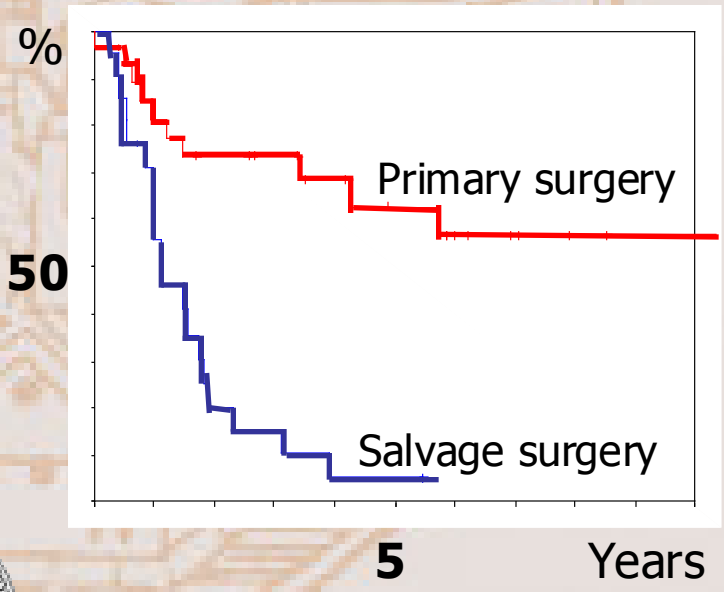
Stage: p=0.2

Stage III: 48.5% ± 16.6
Stage IV: 34.6% ± 8.4



Previous treatment: p=0.0001

Primary surgery: 62.9% ± 10.2
Salvage surgery: 5.1% ± 5.0

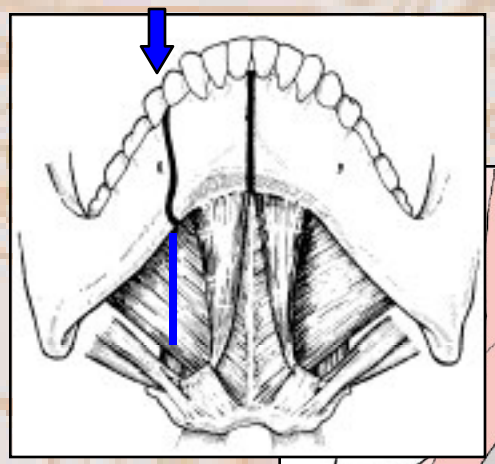


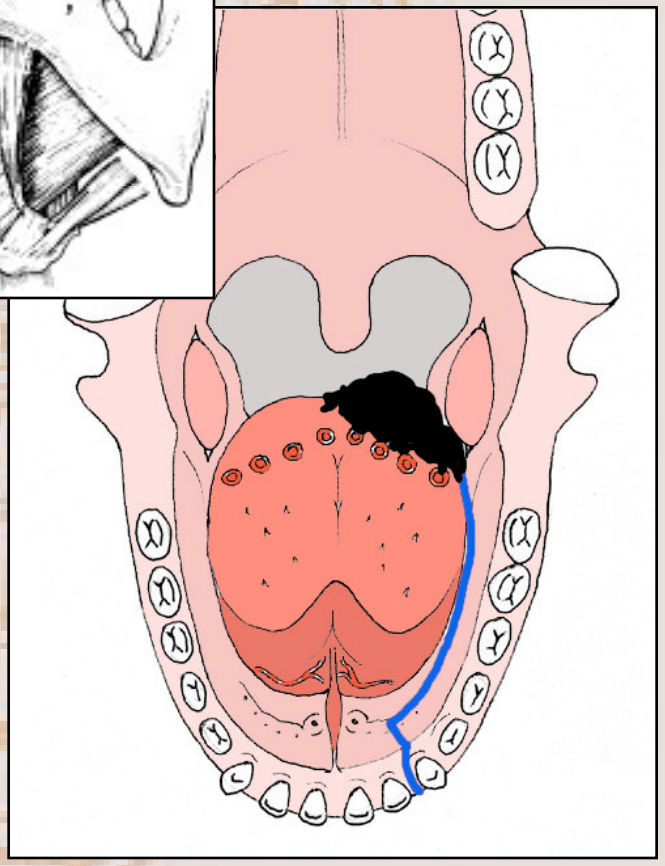
SURGICAL APPROACHES

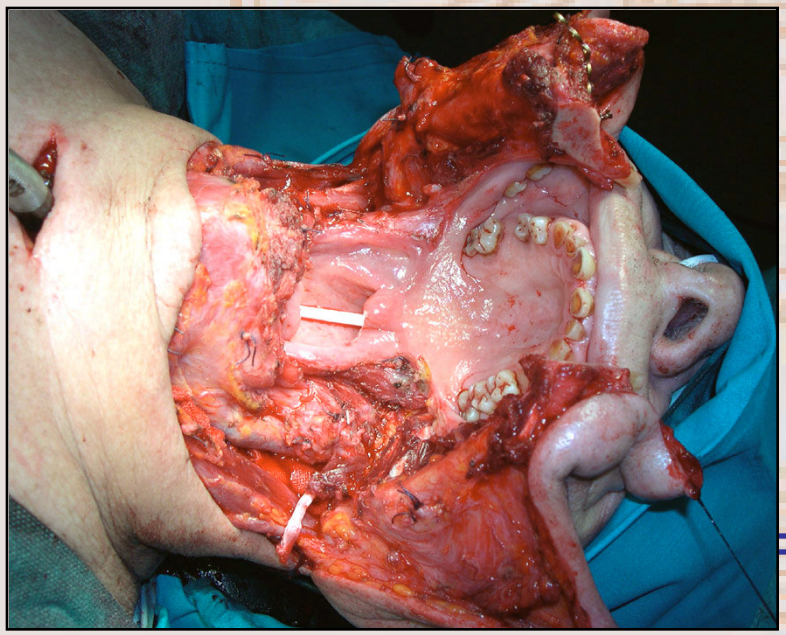
MANDIBULAR SWING

The mandible is splitted to improve exposure of the lesion and to better delineate surgical margins of resection

Advanced lesions with marginal involvement of the lateral wall not reaching the medial pterygoid muscle





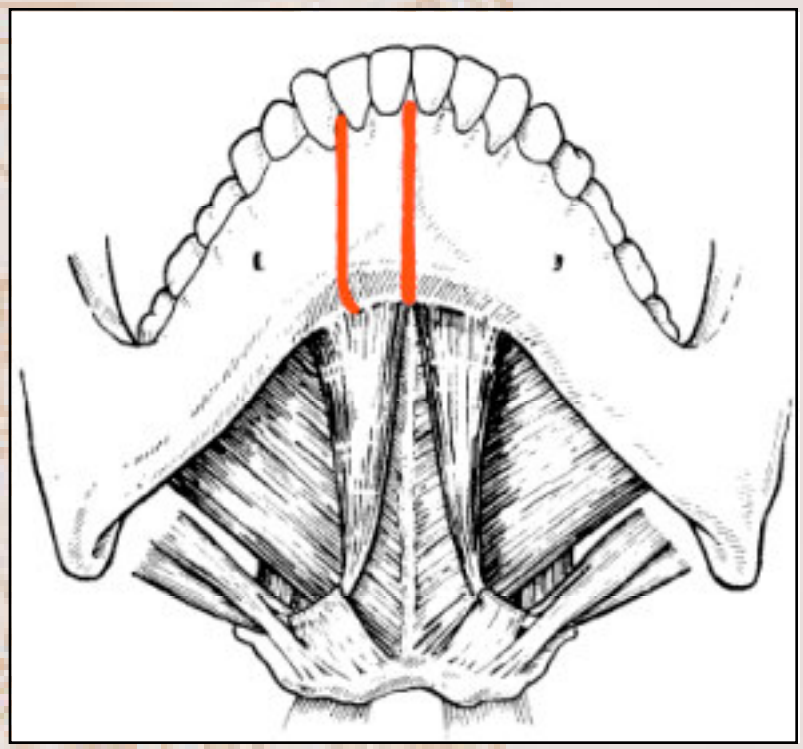


SURGICAL APPROACHES

MANDIBULAR SWING

The distance between the lateral incisor and the canine was 1-6.2 mm, while the distance between the two central incisors ranged from 0.5 to 4.7 mm ($p<0.05$).
Moreover, midline mandibulotomy requires detachment of multiple muscles (digastric, mylohyoid, geniohyoid, genioglossus) which may lead to masticatory and swallowing problems

Shohat et al, Int J Oral Maxillofac Surg 2005

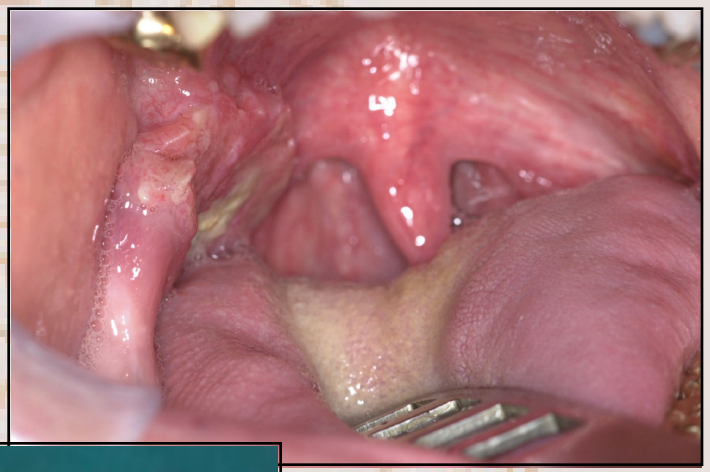


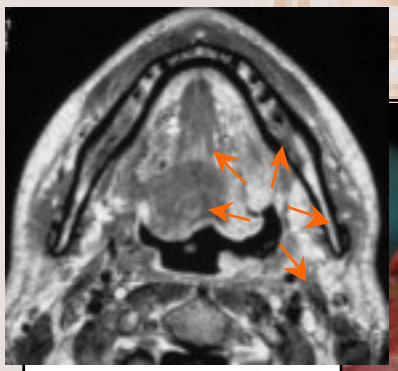
SURGICAL APPROACHES

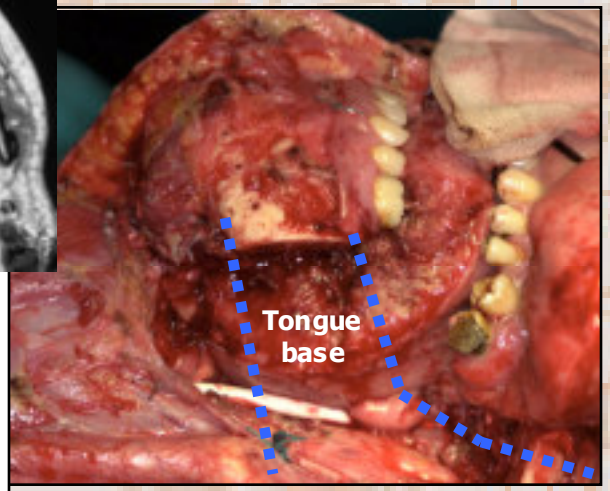
MANDIBULAR RESECTION

A part of the mandible is resected "en bloc" with the tumor when direct involvement is suspected, or because of its close proximity to the deep resection margin

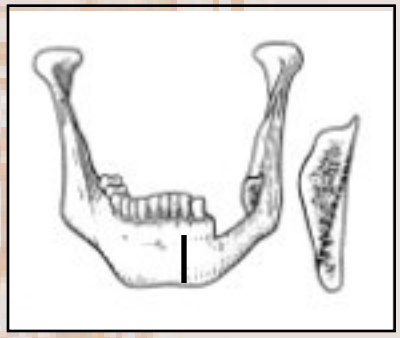
Advanced recurrent lesions of the lateral pharyngeal wall are mostly resected together with a part of the mandible







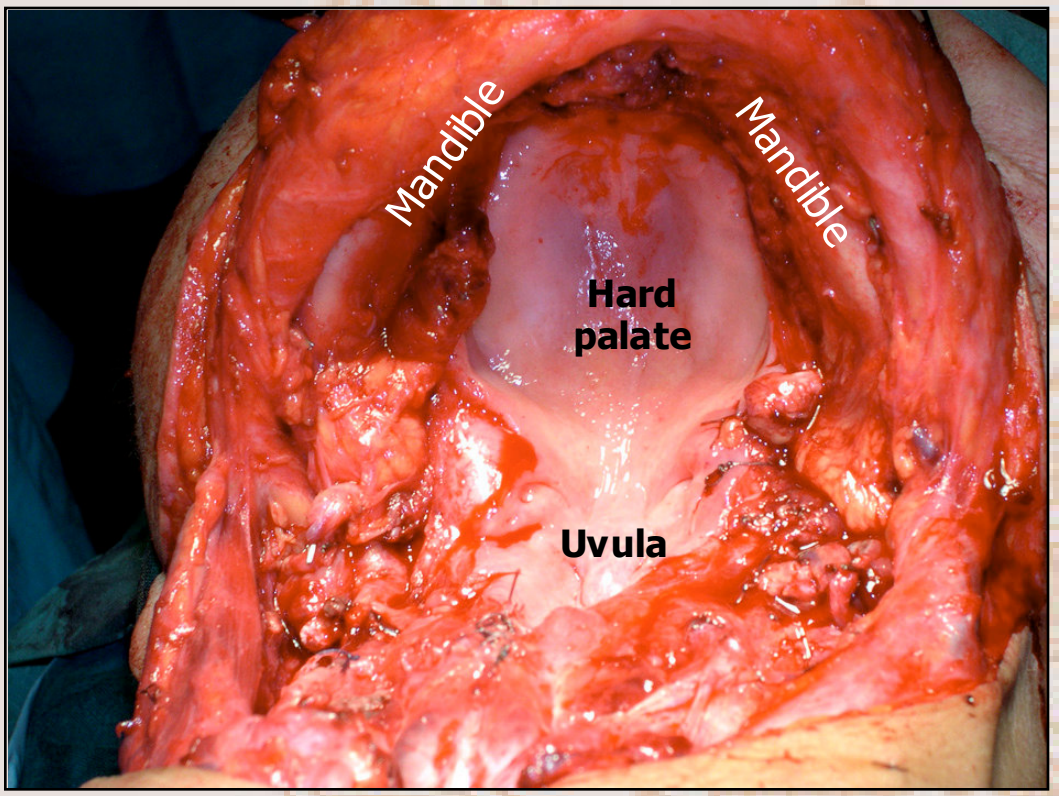
Segmental resection

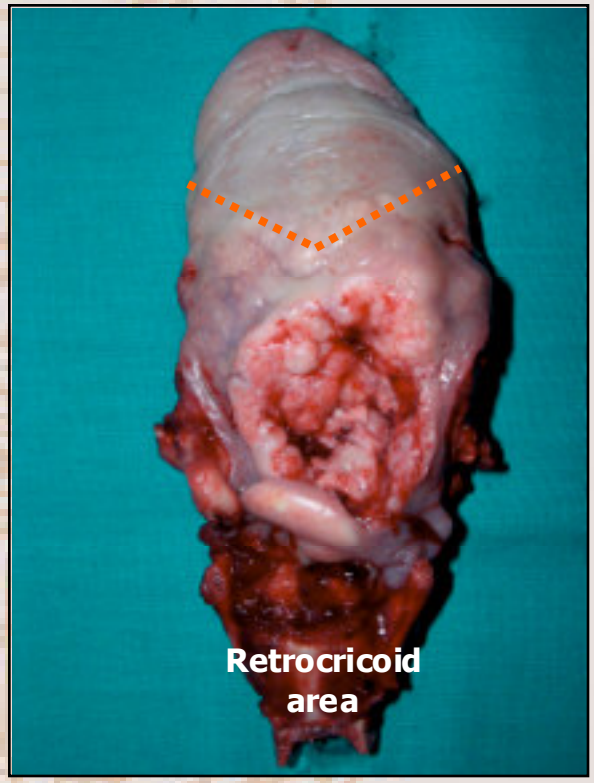


Marginal resection

SURGICAL APPROACHES

PULL-THROUGH





RECONSTRUCTIVE SURGERY

MAIN TARGETS AND OPTIONS

To allow resections otherwise not feasible
To optimize "residual" functions:
To improve "residual" quality of life

→ Velo-palatal competence
Effective swallowing
Mandibular continuity

PEDICLED FLAPS

Spoke wheel!

Pectoralis major
Upper trapezius
Lower trapezius
Latissimus dorsi

FREE FLAPS

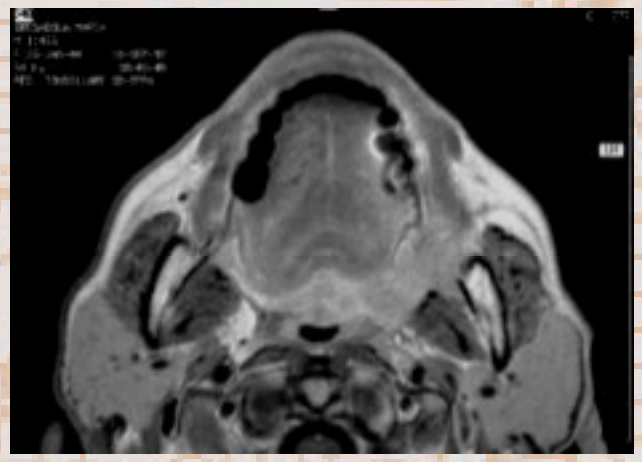
Forearm
Rectus abdominis (DIEP)
Anterolateral tight (ALT)
Lateral arm
Iliac crest
Fibula

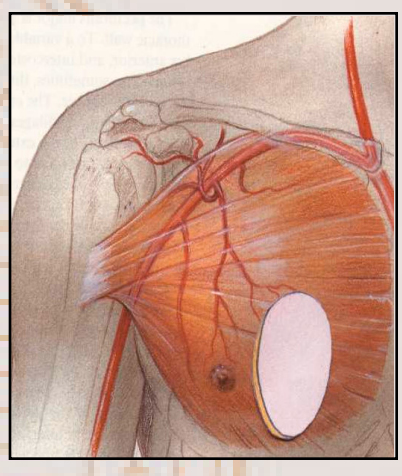
RECONSTRUCTIVE OPTIONS

PEDICLED FLAPS

When and why…

- Severe comorbidities
- Vascular diseases
- Diabetes (?)
- Salvage surgery (?)
- Free flap failure
- Personal confidence

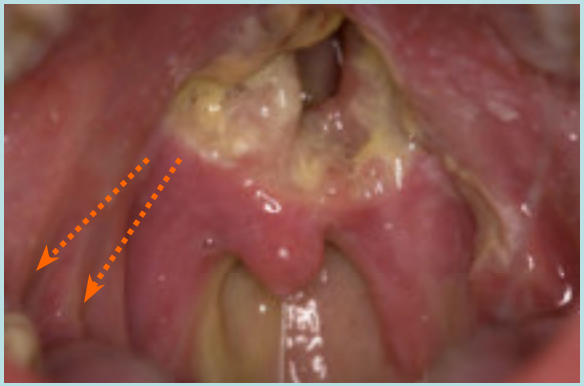




RECONSTRUCTIVE OPTIONS

FOREARM FREE FLAP (FFF)

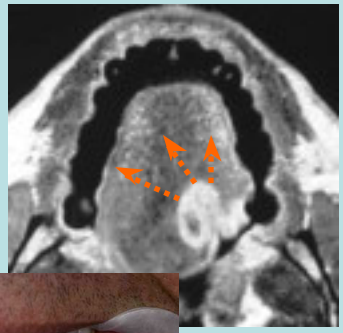
Soft palate



Combined with pharyngo-palatal synechia

Lateral wall

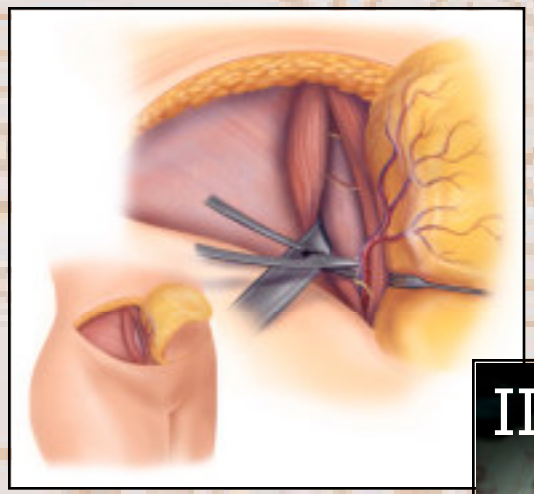
Base of tongue

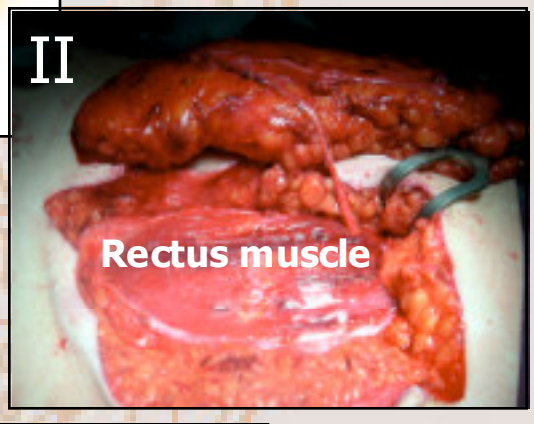


RECONSTRUCTIVE OPTIONS

RECTUS ABDOMINIS (DIEP)

- **PERFORATOR FLAP**
- This is not a new microsurgical technique but rather an improvement due to a refinement in the understanding of the anatomy
- It requires a more thorough dissection of the flap but no change in the microsurgical technique





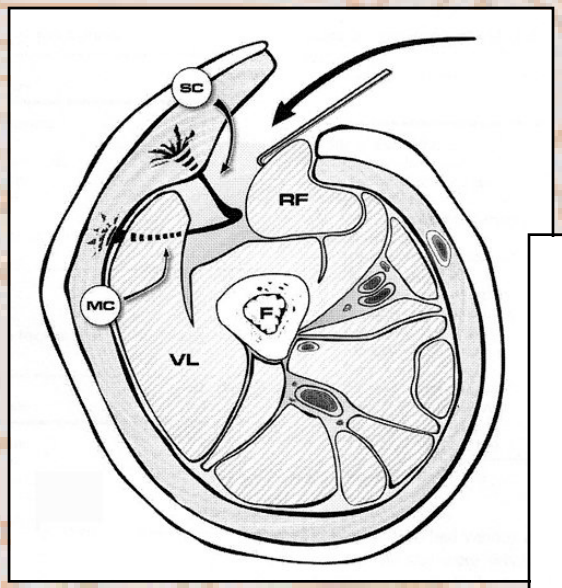
- Anatomic variability of perforators
- Difficulty of the operation
- Length of time
- Higher risk for total failure

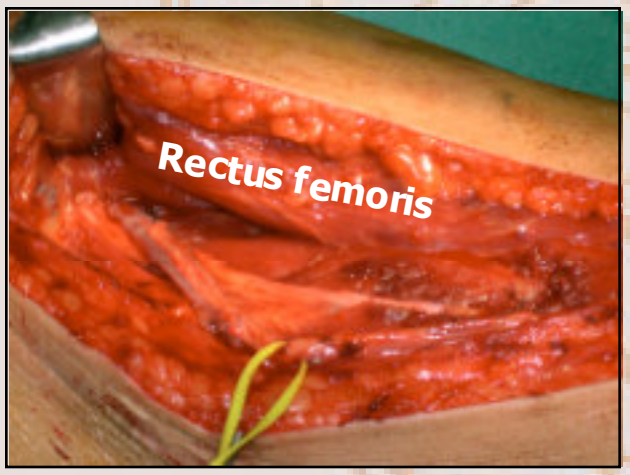
RECONSTRUCTIVE OPTIONS

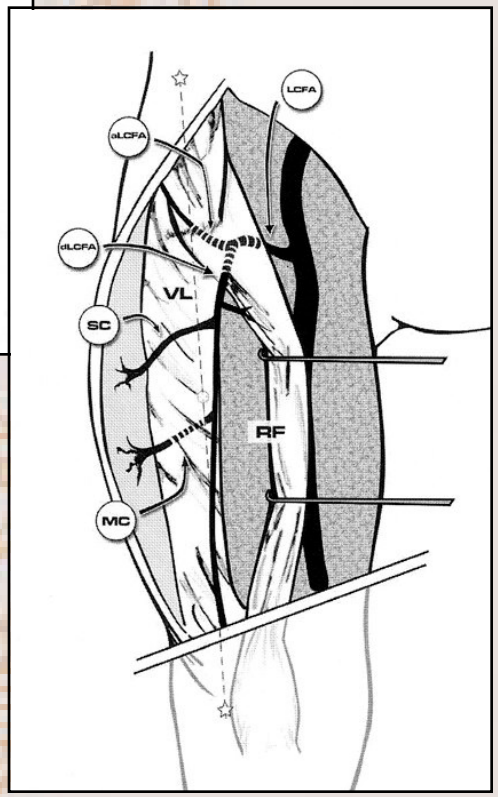
ANTERO-LATERAL TIGHT (ALT)

- Acceptance is limited by:

- Tedious dissection
- Length of time
- Perforators abnormalities





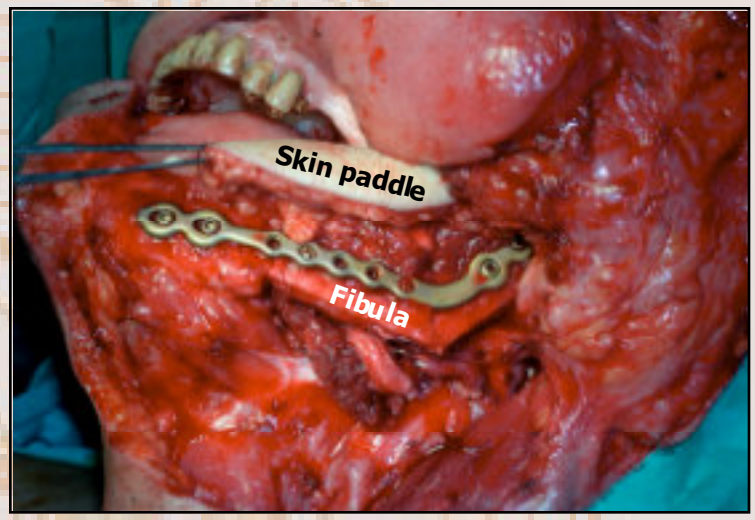


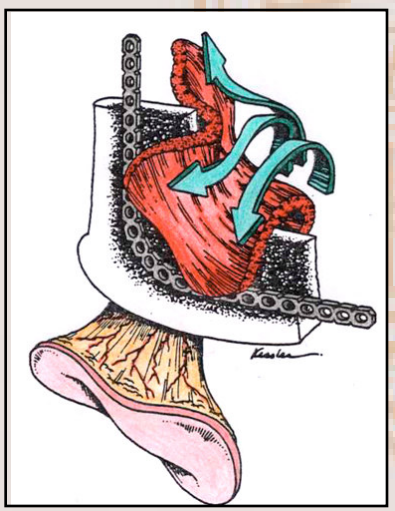
RECONSTRUCTIVE OPTIONS

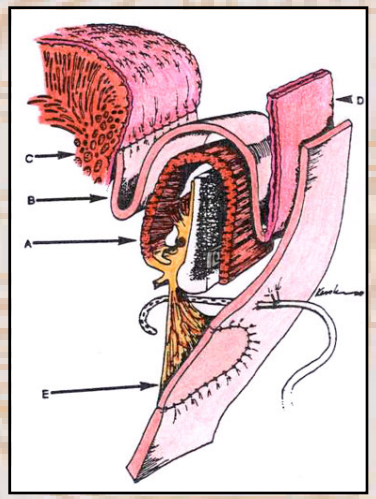
ILIAC CREST and FIBULA

Mandibular reconstruction represents a crucial issue in the following situations:

- Young dentate patients
- Good prognosis
- Able to financially support dental implants







20-40% of cutaneous plate exposure for anterior defects. For limited lateral defects, in case of plate exposure, recurrent disease has to be excluded

CONCLUSIONS

- T3-T4 lesions of the oropharynx often have a dismal prognosis
- Factors affecting treatment response and DFS are: high stage, with special reference to "N" status, and subsite of the primary (worse local-regional control for base of tongue)
- Patients treated for persistent or recurrent lesions have an extremely poor outcome (5-yr DSS: 5.1%; p=0.0001)

CONCLUSIONS

- Transmandibular approach with paramedian mandibulotomy is considered the gold-standard for oropharyngeal lesions in view of a favourable exposure and minimal morbidity
- Reconstructive options should be tailored according to patient's age, body habitus, comorbidities, and prognosis
- In general, free flaps lead to better functional outcomes, with the radial forearm being the ideal choice for lateral wall and soft palate defects, and DIEP and ALT for subtotal and total glossectomies

OPEN ISSUES

- Is there agreement on the imaging studies required to select the adequate treatment?
- Should biological markers (HPV 16, p53, EGFR) be routinely used for treatment selection?
- Is there a role for induction chemotherapy in treatment selection?
- Which is the role of EGFR inhibitors?
- Do we have information concerning how many patients can not complete a concomitant regimen of chemo-radiation because of acute toxicity?
- Are there enough data to compare residual quality of life of patients submitted to organ preservation protocols vs that of patients treated by surgery and post-op chemo-RT?