Procédures cliniques en radio-oncologie: Tumeurs de la sphère ORL

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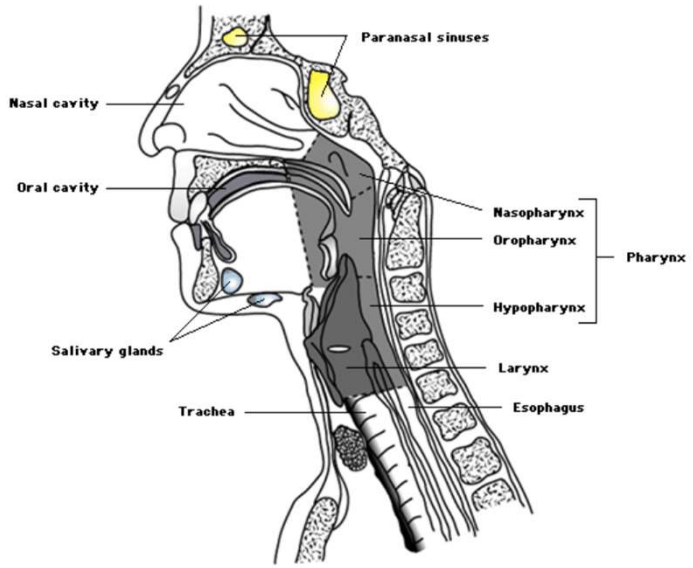
Les cancers ORL

- Classiquement, carcinomes épidermoïdes des muqueuses de la cavité buccale ou du pharynx
- Inclut également des tumeurs plus rares des:
  - Glandes salivaires
  - Sinus
  - Carcinomes épidermoïdes cutanées de la tête et du cou
  - Cas particulier = lymphomes, traité comme les autres lymphomes

Cancers ORL – classification

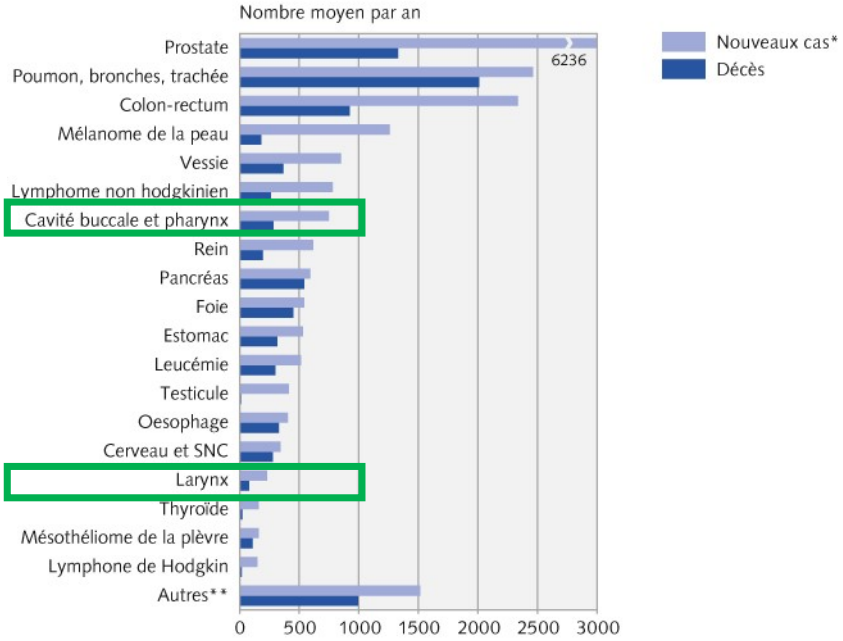
- Nasopharynx
- Oropharynx
- Cavité buccale
- Hypopharynx
- Larynx



Stadification et stratégies différentes selon la localisation

Incidence en Suisse

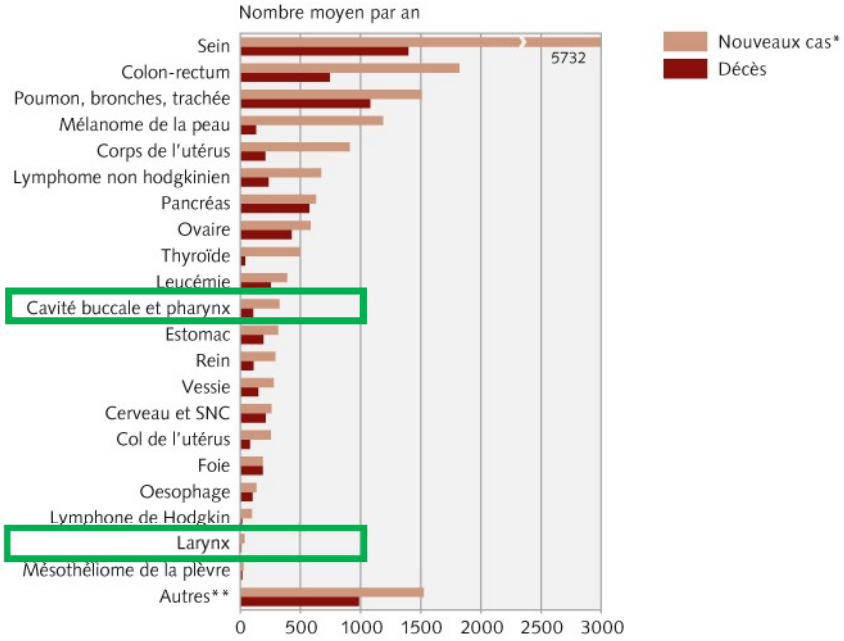
Nouveaux cas et décès chez les hommes selon la localisation cancéreuse, 2008–2012



* Nouveaux cas estimés sur la base des données des registres des tumeurs
** Nouveaux cas sans les cancers non mélaniques de la peau

Source: Le cancer en Suisse, rapport 2015, graphique G 3.1

Nouveaux cas et décès chez les femmes selon la localisation cancéreuse, 2008–2012



* Nouveaux cas estimés sur la base des données des registres des tumeurs
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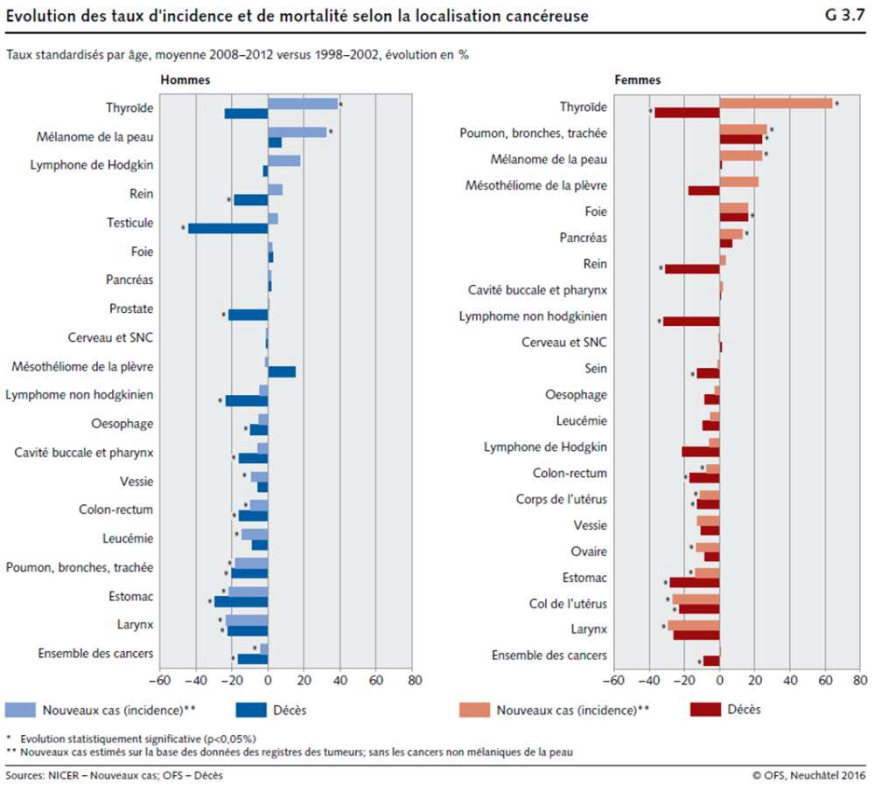
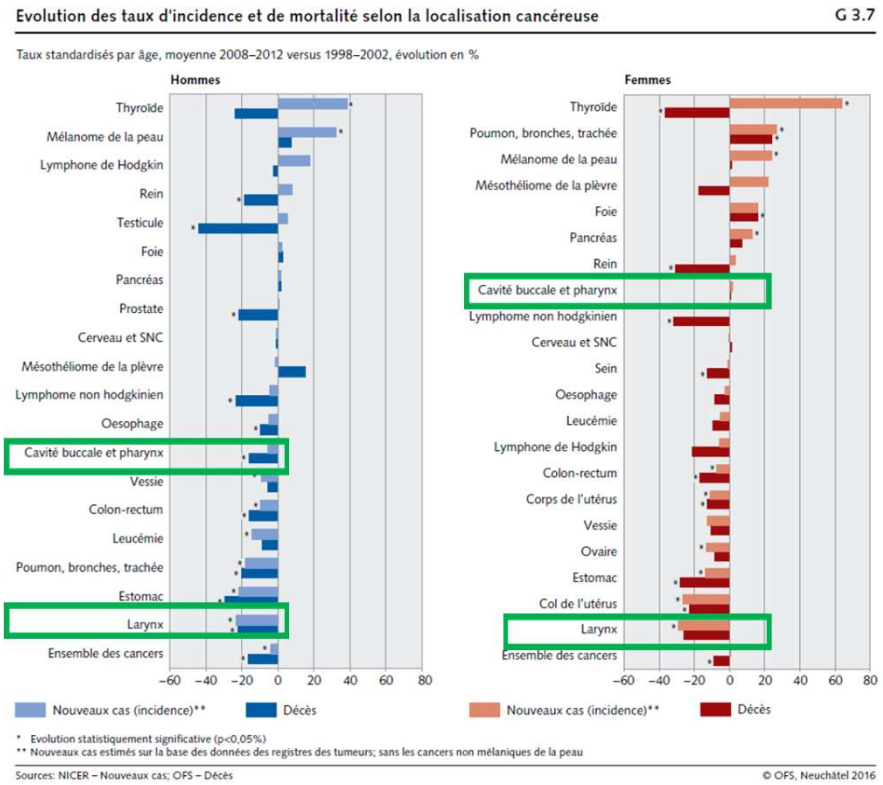
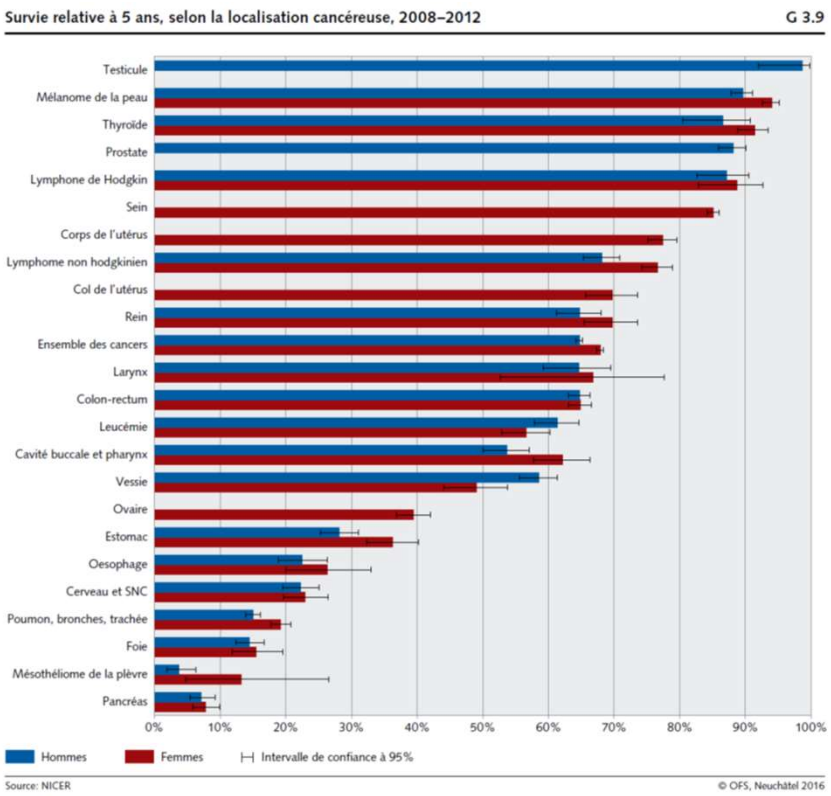
Tendances en Suisse



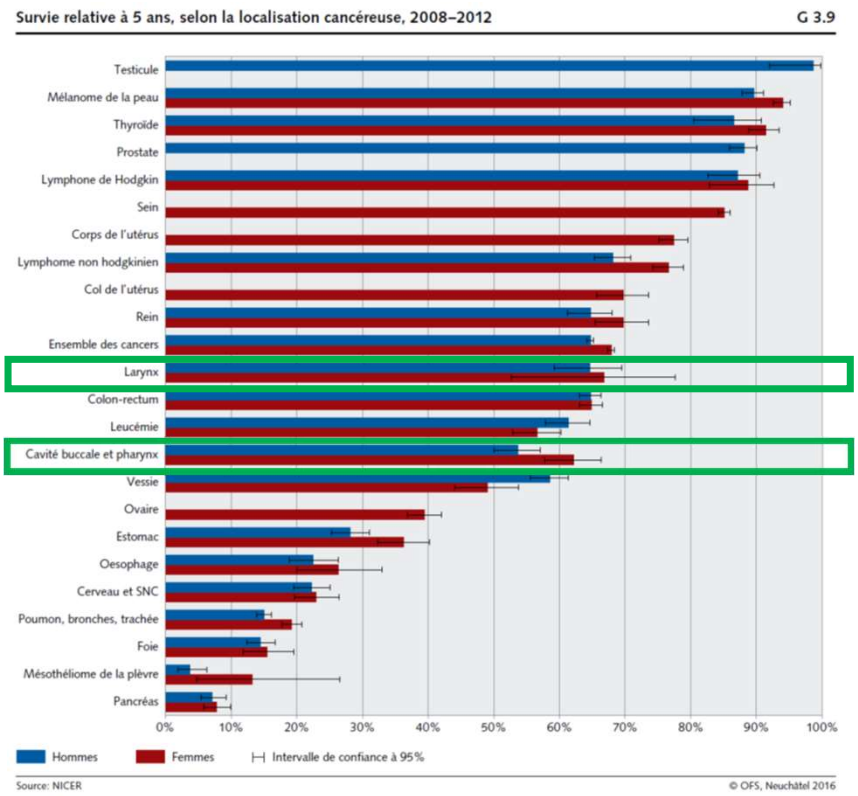
Tendances en Suisse



Pronostic


Survie relative à 5 ans, selon la localisation cancéreuse, 2008–2012
G 3.9
Testicule
Mélanome de la peau
Thyroïde
Prostate
Lymphone de Hodgkin
Sein
Corps de l'utérus
Lymphome non hodgkinien
Col de l'utérus
Rein
Ensemble des cancers
Larynx
Colon-rectum
Leucémie
Cavité buccale et pharynx
Vessie
Ovaire
Estomac
Oesophage
Cerveau et SNC
Poumon, bronches, trachée
Foie
Mésothéliome de la plèvre
Pancréas
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Hommes
Femmes
Intervalle de confiance à 95%
Source: NICER
© OFS, Neuchâtel 2016

Pronostic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Ensemble des cancers
Larynx
Colon-rectum
Leucémie
Cavité buccale et pharynx
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Poumon, bronches, trachée
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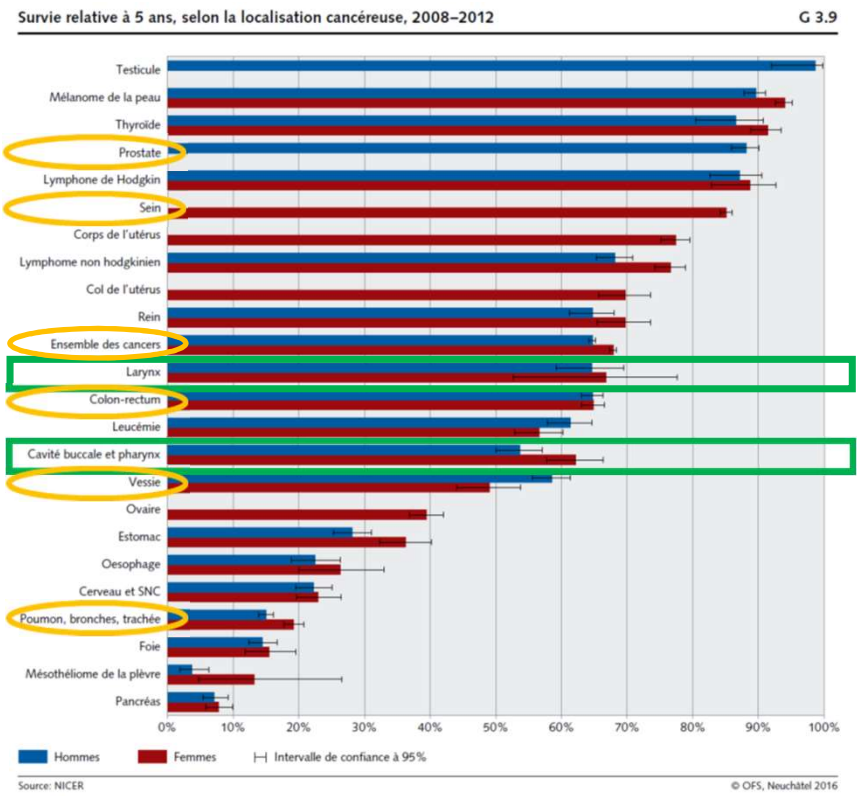
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Thyroïde
Prostate
Lymphone de Hodgkin
Sein
Corps de l'utérus
Lymphome non hodgkinien
Col de l'utérus
Rein
Ensemble des cancers
Larynx
Colon-rectum
Leucémie
Cavité buccale et pharynx
Vessie
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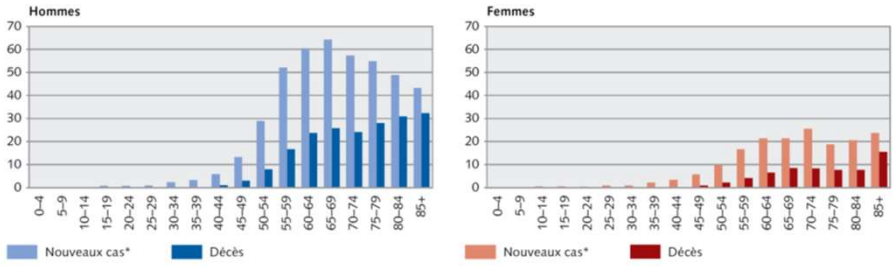
Cavité buccale et pharynx

Cancer de la cavité buccale et du pharynx selon l'âge, 2008–2012 G 4.1.1

Taux spécifique par âge, pour 100'000 habitants

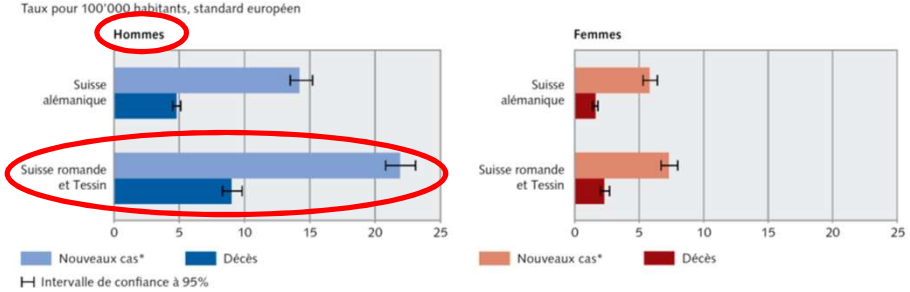


* Nouveaux cas estimés sur la base des données des registres des tumeurs

Sources: NICER – Nouveaux cas; OFS – Décès

Cancer de la cavité buccale et du pharynx: comparaison régionale, 2008–2012 G 4.1.2

Taux pour 100'000 habitants, standard européen



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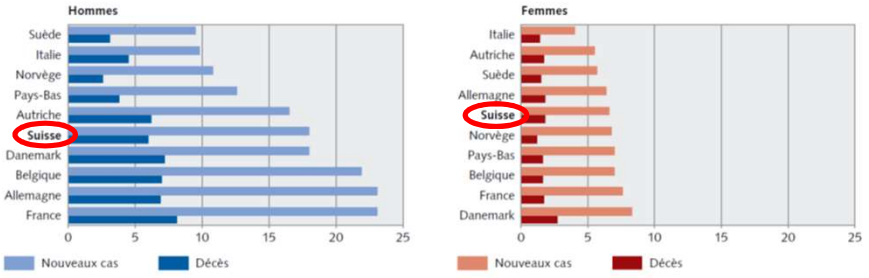
Cavité buccale et pharynx

Cancer de la cavité buccale et du pharynx: comparaison internationale, 2012 G 4.1.3

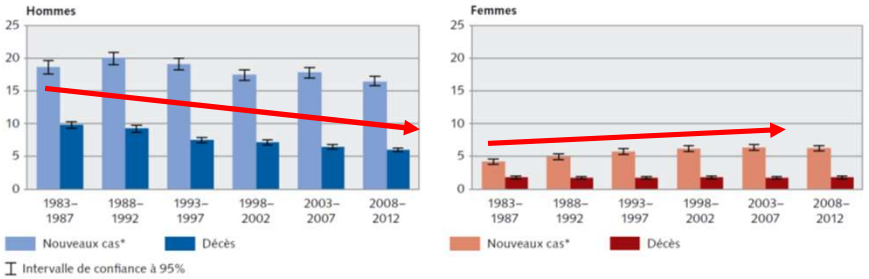
Taux pour 100'000 habitants, standard européen



Source: Ferlay J. et al. (2013). Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012

Cancer de la cavité buccale et du pharynx: évolution temporelle G 4.1.4

Taux pour 100'000 habitants, standard européen



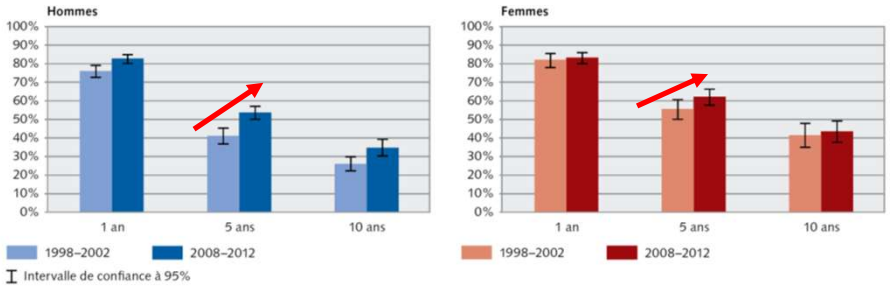
Intervalle de confiance à 95%

* Nouveaux cas estimés sur la base des données des registres des tumeurs

Sources: NICER – Nouveaux cas; OFS – Décès

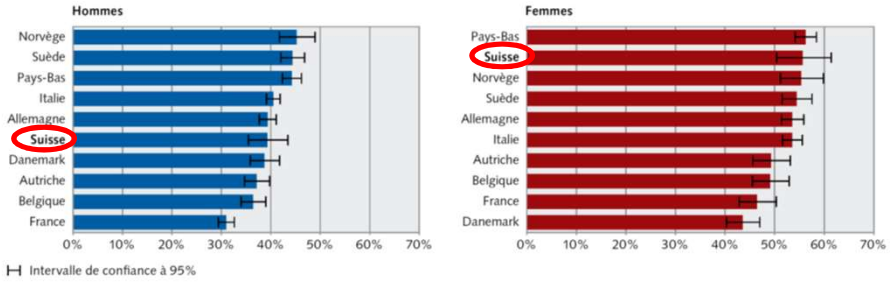
Cavité buccale et pharynx

Cancer de la cavité buccale et du pharynx: survie relative à 1, 5 et 10 ans G 4.1.5



Source: NICER

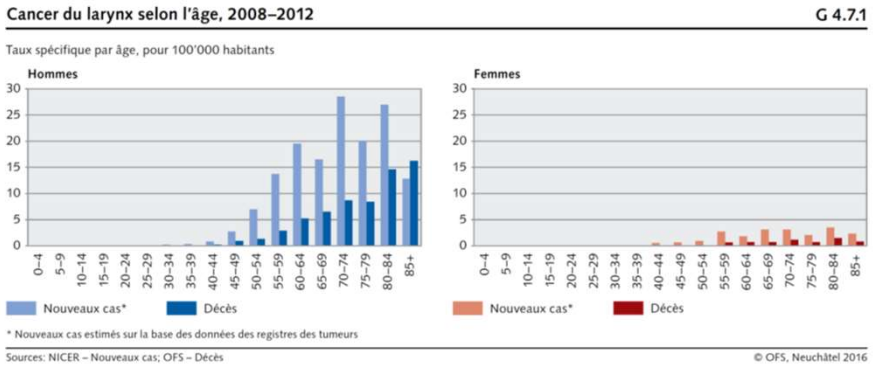
Cancer de la cavité buccale et du pharynx*: comparaison internationale de la survie relative à 5 ans, 2000–2007 G 4.1.6



* Dans la base de données Eurocare-5, regroupe les codes C01–C06, C09–C14 de la CIM-O-3
Les données pour l'Allemagne, la Belgique, la France, l'Italie et la Suisse sont estimées sur la base de données régionales, la couverture du pays étant incomplète.

Source: EUROCARE-5 Database – Survival Analysis 2000–2007

Larynx


Cancer du larynx selon l'âge, 2008–2012
G 4.7.1
Taux spécifique par âge, pour 100'000 habitants
Hommes
Femmes
30
25
20
15
10
5
0
0–4
5–9
10–14
15–19
20–24
25–29
30–34
35–39
40–44
45–49
50–54
55–59
60–64
65–69
70–74
75–79
80–84
85+
Nouveaux cas*
Décès
* Nouveaux cas estimés sur la base des données des registres des tumeurs
Sources: NICER – Nouveaux cas; OFS – Décès
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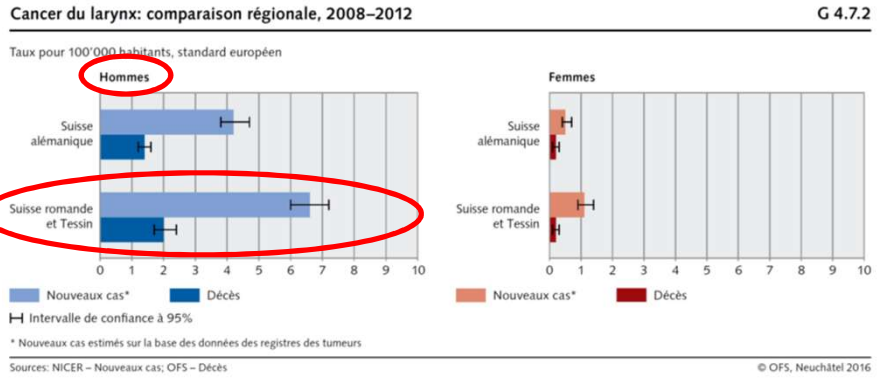
Cancer du larynx: comparaison régionale, 2008–2012
G 4.7.2
Taux pour 100'000 habitants, standard européen
Hommes
Femmes
Suisse alémanique
Suisse romande et Tessin
0
1
2
3
4
5
6
7
8
9
10
Nouveaux cas*
Décès
Intervalle de confiance à 95%
* Nouveaux cas estimés sur la base des données des registres des tumeurs
Sources: NICER – Nouveaux cas; OFS – Décès
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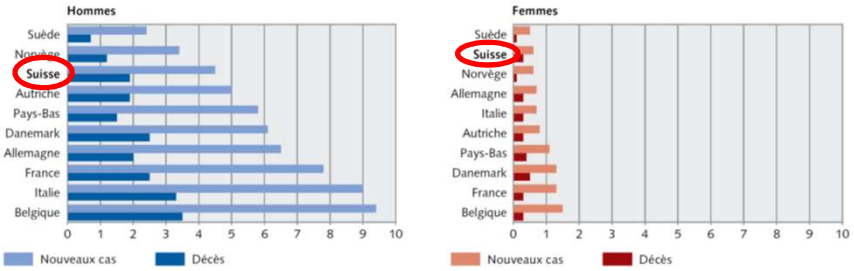
Larynx

Cancer du larynx: comparaison internationale, 2012 **G 4.7.3**

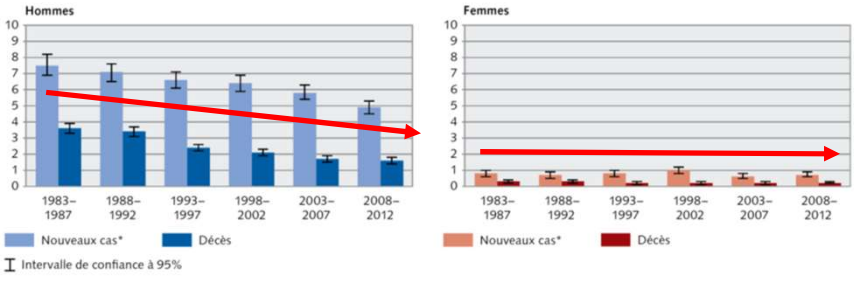
Taux pour 100'000 habitants, standard européen



Source: Ferlay J. et al. (2013). Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012

Cancer du larynx: évolution temporelle **G 4.7.4**

Taux pour 100'000 habitants, standard européen



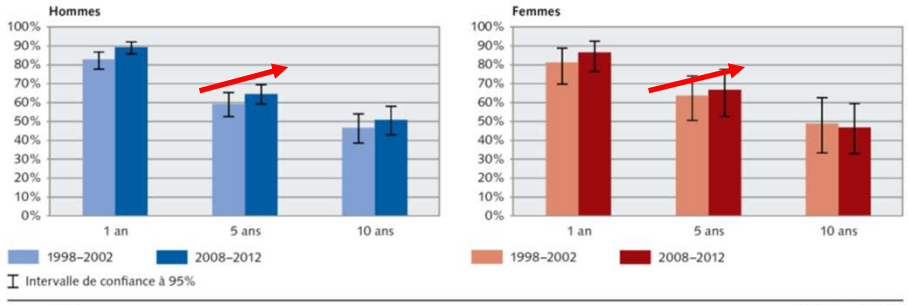
Intervalle de confiance à 95%

* Nouveaux cas estimés sur la base des données des registres des tumeurs

Sources: NICER – Nouveaux cas; OFS – Décès

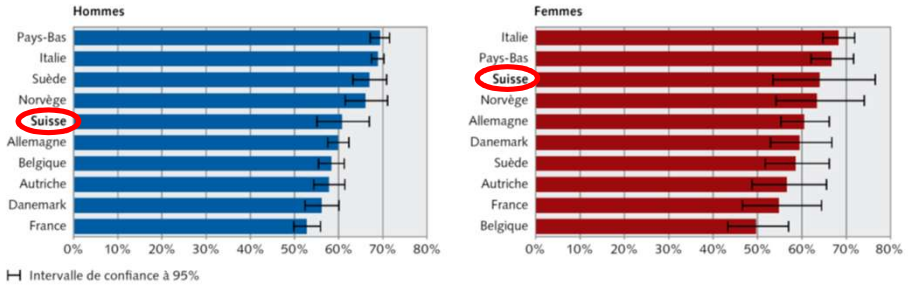
Larynx

Cancer du larynx: survie relative à 1, 5 et 10 ans G 4.7.5



Source: NICER

Cancer du larynx: comparaison internationale de la survie relative à 5 ans, 2000–2007 G 4.7.6



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Source: EUROCARE-5 Database – Survival Analysis 2000–2007

Résumé cancers ORL en Suisse

- Maladie touchant plus les hommes (bcp plus pour le ca du larynx), et plus la Suisse romande et le Tessin → cf facteurs de risque
- Incidence en diminution progressive ces dernières décennies, en tout cas pour les hommes → cf facteurs de risque
- Mortalité en régression ces dernières années → cf améliorations de la prise en charge et évolution facteurs de risque (notamment HPV)
- Pronostic plutôt bon en Suisse comparé à nos voisins (qualité de la prise en charge, détection plus précoce…?)

Facteurs de risque

- Classiquement (environ ¾ des cas actuellement):
  - Tabac (fumé ou mastiqué)
  - OH
- Autres majeurs (environ ¼ des cas, en progression):
  - EBV (Epstein-Barr virus) dans les cancers du nasopharynx
  - HPV (human papilloma virus) dans les cancers de l'oropharynx
- Plus rares:
    - Expositions professionnelles (sciure, formaldehyde)
    - Saumure, reflux, mauvaise hygiène buccale, etc…
- Pas de vraie rôle d'une prédisposition génétique

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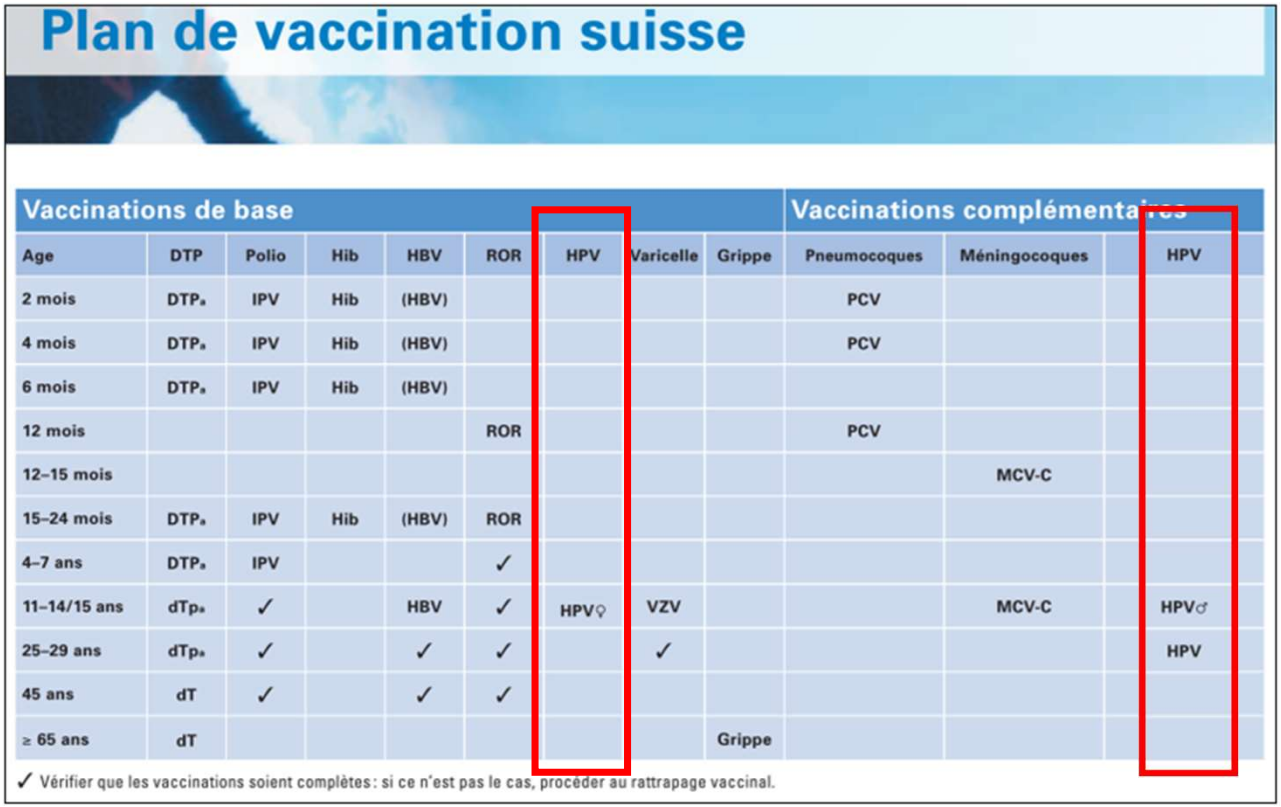
HPV - rappel

Plan de vaccination suisse

Vaccinations de base									Vaccinations complémentaires		
Age	DTP	Polio	Hib	HBV	ROR	HPV	Varicelle	Grippe	Pneumocoques	Méningocoques	HPV
2 mois	DTPa	IPV	Hib	(HBV)					PCV		
4 mois	DTPa	IPV	Hib	(HBV)					PCV		
6 mois	DTPa	IPV	Hib	(HBV)							
12 mois					ROR				PCV		
12–15 mois										MCV-C	
15–24 mois	DTPa	IPV	Hib	(HBV)	ROR						
4–7 ans	DTPa	IPV			✓						
11–14/15 ans	dTpa	✓		HBV	✓	HPV♀	VZV			MCV-C	HPV♂
25–29 ans	dTpa	✓		✓	✓		✓				HPV
45 ans	dT	✓		✓	✓						
≥ 65 ans	dT							Grippe			

✓ Vérifier que les vaccinations soient complètes : si ce n'est pas le cas, procéder au rattrapage vaccinal.

HPV - rappel



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12 mois					ROR				PCV			
12–15 mois										MCV-C		
15–24 mois	DTPa	IPV	Hib	(HBV)	ROR							
4–7 ans	DTPa	IPV			✓							
11–14/15 ans	dTpa	✓		HBV	✓	HPV♀	VZV			MCV-C		HPV♂
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HPV - rappel

Maladies transmissibles

Vaccination contre les HPV : recommandation de vaccination complémentaire pour les garçons et jeunes hommes âgés de 11 à 26 ans

Depuis 2007, la vaccination contre les papillomavirus humains (HPV) est recommandée en Suisse pour toutes les filles et les jeunes femmes à titre de vaccination de base afin de prévenir le développement du cancer du col de l'utérus et d'autres maladies provoquées par les HPV. Sur la base des dernières connaissances scientifiques, l'OFSP et la CFV recommandent aujourd'hui d'étendre la vaccination aux garçons et aux jeunes hommes âgés de 11 à 26 ans, de préférence entre 11 et 14 ans, avant le début de l'activité sexuelle. Cette vaccination est recommandée à titre de vaccination complémentaire pour la prévention des cancers et des verrues génitales associés aux HPV.

ment de la néoplasie [5;9–12]. Plus de 80 % des cancers de l'anus sont causés spécifiquement par les HPV de types 16 et 18, dont les antigènes sont contenus dans les vaccins [9;12;13]. Le tableau 1 ci-dessous montre quels pourcentages de ces cancers sont associés aux HPV16 /18.

Le poids total des tumeurs associées aux HPV chez les hommes et les femmes est estimé à environ 5 % de l'ensemble des cancers dans le monde, celui qui pèse sur les femmes étant toutefois le plus important [12]. Certaines données font état d'une augmentation de l'incidence des tumeurs induites par les HPV chez les deux sexes [14–16].

HPV - rappel

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HPV - rappel

Tableau 1

Nombre moyen de cas et taux d'incidence (pour 100 000 personnes-années, standardisé sur l'âge) de nouveaux diagnostics de cancer en Suisse (période: 2007–2011, NICER [17]) et proportion des cas de cancer induits par les HPV16/18 (estimation sur la base de données recueillies à l'échelle internationale [9;12]). En raison du faible nombre de cas, le NICER ne publie pas de données sur les cancers du pénis, de la vulve et du vagin.

	Hommes	Femmes
Oropharynx, amygdales, base de la langue (ICD-10 C01, C09-10)	274 cas/année[a] Incidence: 6,2/100 000[a] HPV16/18: 12–50 %[c]	92 cas/année[a] Incidence: 1,9/100 000[a] HPV16/18: 12–50 %[c]
Anus et canal anal (ICD-10 C21)	57 cas/année[b] Incidence: 1,2/100 000[b] HPV16/18: 81 %[c]	121 cas/année[b] Incidence: 2,3/100 000[b] HPV16/18: 81 %[c]
Cervix (ICD-10 C53)		252 cas/année[b] Incidence: 5,3/100 000[b] HPV16/18: >70 %[c]
Total	331 cas/année	465 cas/année
Total des cas associés aux HPV16/18 et donc théoriquement évitables par la vaccination	79–183 cas/année	285–320 cas/année

HPV - rappel

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Cervix (ICD-10 C53)		252 cas/année[b] Incidence: 5,3/100 000[b] HPV16/18: >70 %[c]
Total	331 cas/année	465 cas/année
Total des cas associés aux HPV16/18 et donc théoriquement évitables par la vaccination	79–183 cas/année	285–320 cas/année

Les cancers ORL liés à l'HPV

- Cancers HPV+ de plus en plus fréquents, mais heureusement de meilleur pronostic
- D'où actuellement de multiples études en cours cherchant à «désescalader» les traitements de ces cancers en ORL, via:
  - Moins (ou pas) de chimio
  - Moins (ou pas) de RT
    - Doses moins élevées
    - Volumes moins étendues

Présentation clinique

- Douleurs pharyngées ou buccales (ou parfois référées au niveau de l'oreille)
- Masse dans la gorge/bouche ou dans le cou (adénopathies)
- Modification de la voix
- Fausses-routes
- Parésies ou pertes de sensibilité dans la région ORL ou de la face
- Perte de poids
- Obstruction nasale
- Etc…

Investigations cliniques

- Examen sphère ORL et cou
- Nasofibroscope
- Biopsie tumeur +/- ganglions suspects
  - Cas spécial = adénopathie «sans porte d'entrée» (unknown primary) → examen cutané, biopsies dirigées par la radiologie ou parfois à l'aveugle de la base de langue et amygdalectomie bilatérale

Bilan d'extension

- Panendoscopie (recherche tumeur synchrone bronches ou œsophage)
- Radiologie = en général:
  - IRM, pour l'extension locale et atteinte ganglionnaire
  - PET-CT (ou CT thoraco-abdominal), pour l'atteinte régionale ou à distance
  - Pas forcément de bilan poussé pour une tumeur précoce du larynx
- Les cancers ORL sont de façon général très lymphophiles, avec des atteintes métastatiques ganglionnaires fréquentes
- Atteintes à distance moins fréquentes (mais cancers synchrones p. ex. du poumon c/o le patient tabagique classique)

Staging selon TNM (complexe…)

Table 3
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancers)

Oropharynx (p16-)

TX		Primary tumor cannot be assessed
Tis		Carcinoma *in situ*
T1		Tumor 2 cm or smaller in greatest dimension
T2		Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3		Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4		Moderately advanced or very advanced local disease
	T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*
	T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

**Note:* Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Hypopharynx

TX		Primary tumor cannot be assessed
Tis		Carcinoma *in situ*
T1		Tumor limited to one subsite of hypopharynx and/or 2 cm or smaller in greatest dimension
T2		Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures larger than 2 cm but not larger than 4 cm in greatest dimension without fixation of hemilarynx
T3		Tumor larger than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophageal mucosa
T4		Moderately advanced or very advanced local disease
	T4a	Moderately advanced local disease Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophageal muscle or central compartment soft tissue
	T4b	Very advanced local disease Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

**Note:* Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

Continued

Staging selon TNM (complexe…)

Table 3 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N)	
Clinical N (cN) - Oropharynx (p16-) and Hypopharynx	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Continued

Staging selon TNM (complexe…)

Table 3 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N):
Pathological N (pN) – Oropharynx (p16-) and Hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+) *or* a single contralateral node of any size and ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Prognostic Stage Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Continued

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Staging selon TNM (complexe…)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Head and Neck Cancers

NCCN Guidelines Index
Table of Contents
Discussion

Table 4
American Joint Committee on Cancer (AJCC)
TNM Staging System for HPV-Mediated (p16+) Oropharyngeal Cancer (8th ed., 2017)
(Not including: P16-negative (p16-) cancers of the oropharynx)

Primary Tumor (T)
T0 No primary identified
T1 Tumor 2 cm or smaller in greatest dimension
T2 Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3 Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced local disease
Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond*

Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Regional Lymph Nodes (N)
Clinical N (cN)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 One or more ipsilateral lymph nodes, none larger than 6 cm
N2 Contralateral or bilateral lymph nodes, none larger than 6 cm
N3 Lymph node(s) larger than 6 cm

Pathological N (pN)
NX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in 4 or fewer lymph nodes
pN2 Metastasis in more than 4 lymph nodes

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
No grading system exists for HPV-mediated oropharyngeal tumors

Prognostic Stage Groups

Clinical

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage III	T0,T1,T2,T3	N3	M0
	T4	N0,N1,N2,N3	M0
Stage IV	Any T	Any N	M1

Pathological

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3,T4	N0,N1	M0
Stage III	T3,T4	N2	M0
Stage IV	Any T	Any N	M1

Continued

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Staging selon TNM (complexe…)

Table 5
American Joint Committee on Cancer (AJCC) TNM Staging System for the Larynx (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone and cartilage, and mucosal melanoma of the lip and oral cavity are not included)

Primary Tumor (T)

TX Primary tumor cannot be assessed
Tis Carcinoma *in situ*

Supraglottis

T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4 Moderately advanced or very advanced
T4a Moderately advanced local disease
Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3 Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4 Moderately advanced or very advanced
T4a Moderately advanced local disease
Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottis

T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation and/or inner cortex of the thyroid cartilage
T4 Moderately advanced or very advanced
T4a Moderately advanced local disease
Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Continued

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Approche thérapeutique – principes généraux

- En général une approche multidisciplinaire associant potentiellement:
  - Chirurgie
  - Radiothérapie
  - Chimiothérapie
- Idéalement une modalité unique dans les cas précoces
- Plusieurs buts de la prise en charge:
  - La guérison
  - La préservation de la fonction
  - Minimiser la toxicité surtout séquellaire

Discussion multidisciplinaire

- Idéalement, discussion de chaque cas dans le cadre d'une réunion multidisciplinaire impliquant:
  - Radiologues
  - Pathologues
  - Chirurgiens ORL et maxillo-faciaux
  - Radio-oncologues
  - Oncologues
  - Dentistes

Stratégie selon la localisation

- En général:
  - Nasopharynx: radio-chimiothérapie
  - Cavité buccale/cavité nasale/glandes salivaires:
    - Chirurgie +/- radio(chimio)thérapie adjuvante
    - Alternative pour la cavité buccale = curiethérapie, fréquente en France mais rare en CH (compétences, culture)
  - Oro- et hypopharynx : RCT ou RT, parfois chirurgie (amygdale)
  - Larynx: chirurgie ou RT pour cas précoces, RCT pour cas avancés

La radiothérapie - stratégies

- Deux situations:
  - Exclusive
  - Adjuvante (post-opératoire), selon facteurs de risque pathologiques:
    - Tranches de section positives ou proches
    - Adénopathies multiples
    - Dépassement capsulaire ganglionnaire
    - Invasion lympho-vasculaire ou périnerveuse
    - Status HPV pour les tumeurs oropharyngés

La radiothérapie – considérations générales

- Une fois l'indication à la RT posée, plusieurs questions:
  - Locale (larynx) ou locorégionale (presque toujours)
    - Niveaux ganglionnaires à inclure?
  - Irradiation régionale bilatérale (en général) ou unilatérale (cas particuliers)
  - Avec ou sans chimiothérapie (ou cetuximab)
  - Fractionnement standard ou «altéré»

- Et plusieurs évaluations pré-RT
  - Besoin d'un soutien nutrionnel (selon perte de poids préalable, traitement prévu)
  - Evaluation du status dentaire et mesures prophylactiques

Le soutien nutrionnel

- Impliquer tôt un/e diététicien/ne ou nutritionniste
- Mesures allant du plus simple à des plus compliquées:
  - Conseils diététiques
  - Suppléments nutritifs oraux (SNO)
  - Sonde naso-gastrique (SNG)
  - Percutaneous endoscopic gastrostomy tube (PEG)

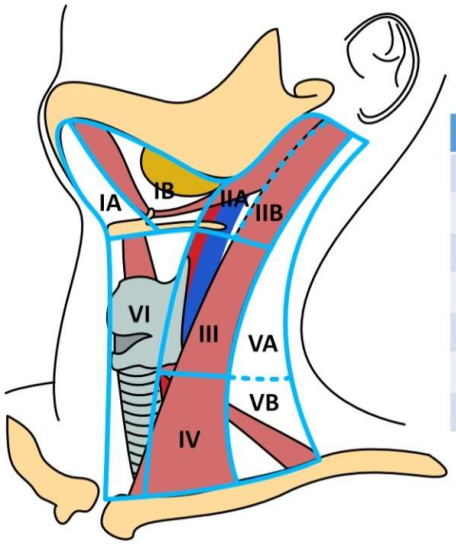
- Pas de consensus dans le débat SNG vs PEG, y compris en Suisse romande (HUG vs CHUV)

Bilan dentaire

- Une des complications les plus graves de la radiothérapie dans la sphère ORL et *l'ostéoradionécrose*
- Facteurs de risque:
  - Mauvaise hygiène buccale et état dentaire
  - Extractions ou infections futures
  - Xérostomie séquellaire à la RT
  - Moins bonne perfusion mandibulaire suite à la RT
  - Dose mandibulaire (Dmax = points chauds)
- Avec une bonne prévention (extractions prophylactiques, gouttières), risque très faible

Irradiation cervicale élective

- Niveaux à prendre de chaque côté du cou selon:
  - Localisation tumorale
  - Stade N (= atteinte ganglionnaire radiologique ou pathologique) +/- niveaux N+
  - En général, RT plus étendue du côté atteint, et moins étendue (ou pas du tout) du côté controlatéral



Level	Possible site of malignancy
IA	Lower lip, floor of mouth, lower gum
IB	Face, nose, paranasal sinuses, oral cavity, submandibular gland
II	Oral cavity, oropharynx, nasopharynx, hypopharynx, supraglottic larynx
III	Thyroid, larynx, hypopharynx, cervical esophagus
IV	Hypopharynx, larynx, thyroid, vervical esophagus
V	Nasopharynx, thyroid, esophagus, lung, breast
VI	Lower lip, oral cavity, thyroid, glottic and subglottic larynx, apex of piriform sinus, cervical esophagus

Atlas de consensus pour les contours…

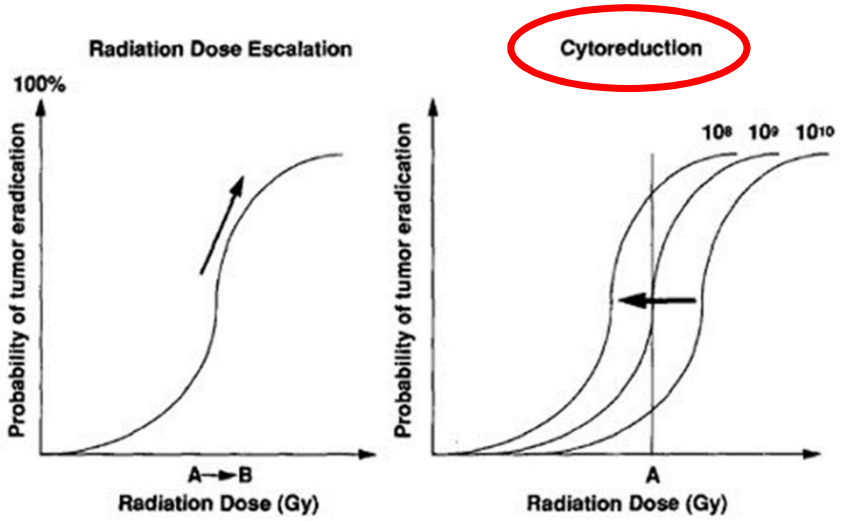
CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines

Vincent Grégoire[a,*,1], Peter Levendag[b,1], Kian K. Ang[c], Jacques Bernier[d], Marijel Braaksma[b], Volker Budach[e], Cliff Chao[c], Emmanuel Coche[f], Jay S. Cooper[c], Guy Cosnard[f], Avraham Eisbruch[c], Samy El-Sayed[g], Bahman Emami[c], Cai Grau[h], Marc Hamoir[i], Nancy Lee[c], Philippe Maingon[j], Karin Muller[b], Hervé Reychler[k]

Irradiation unilatérale

- Pour certaines tumeurs de la cavité buccale ou de l'oropharynx (amygdale) bien latéralisées, avec une atteinte ganglionnaire limitée
- Tumeurs HPV+ de l'amygdale par exemple

L’intérêt de la chimiothérapie



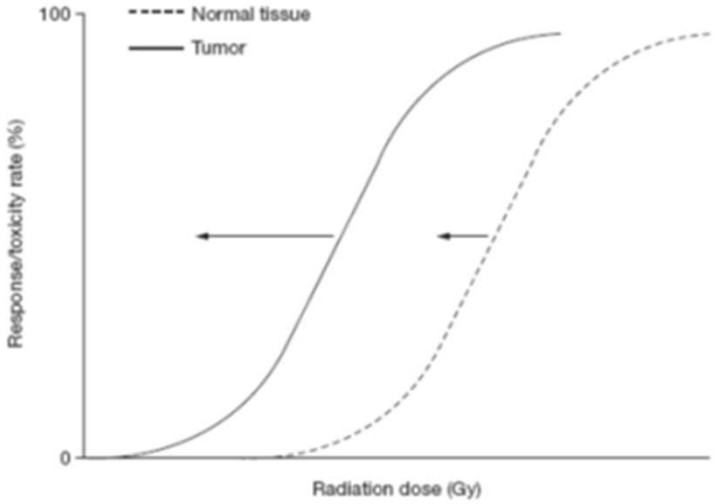
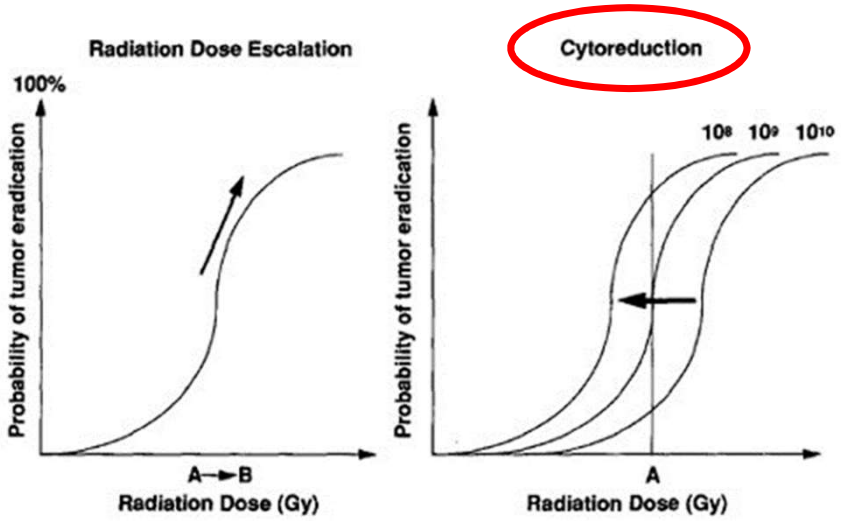
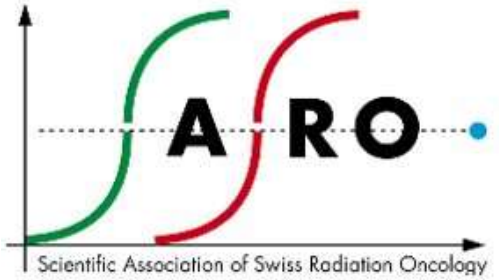


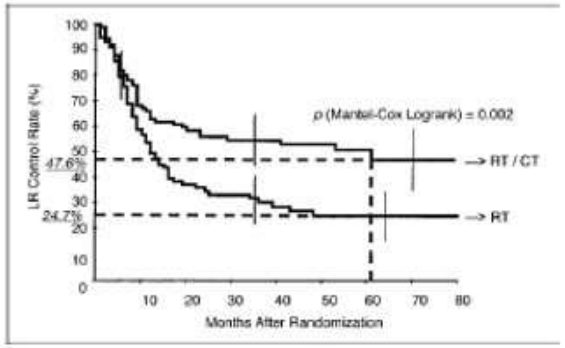
Figure 3 Schematic dose–response curves for tumor and normal tissue damage with radiation. The offset between the two curves indicates the therapeutic range. Chemoradiotherapy leads to a shift of both curves to the left, ideally with a stronger shift of the tumor curve (as indicated by the longer arrow), increasing overall efficacy of treatment (radiation enhancement).[120]

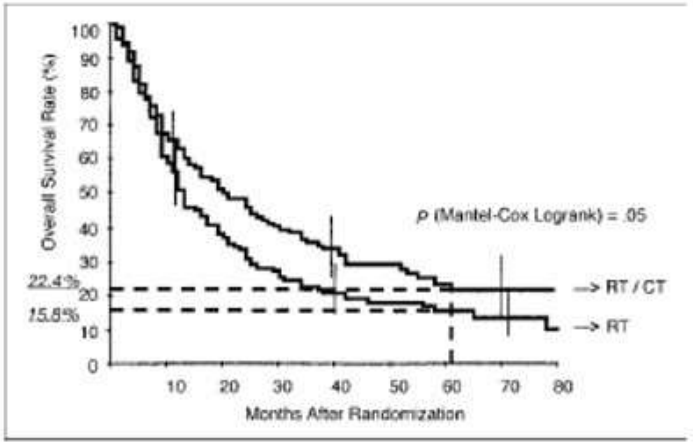
L’intérêt de la chimiothérapie





La radio-chimiothérapie





La radio-chimiothérapie

- Méta-analyse MACH-NC
- > 100 études randomisées
- > 18’000 patients
- Conclusion: la chimiothérapie «concomitante» (cisplatine) augmente la survie globale à 5/10 ans ans d’environ 6,5/3,4%
- Seulement pour <u>concomitante</u>, pas en adjuvant ou induction

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 2, Supplement, pp. S112–S114, 2007

0360-3016/07/$–see front matter

doi:10.1016/j.ijrobp.2007.04.088

HEAD AND NECK CANCER SYMPOSIUM

META-ANALYSES OF CHEMOTHERAPY IN HEAD AND NECK CANCER (MACH-NC): AN UPDATE

JEAN-PIERRE PIGNON, M.D., PH.D.,* AURÉLIE LE MAÎTRE, M.SC.,* AND JEAN BOURHIS, M.D., PH.D.,† ON BEHALF OF THE MACH-NC COLLABORATIVE GROUP

*Biostatistics and Epidemiology Unit and †Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France

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La radio-chimiothérapie

- Aussi en post-opératoire…

Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

Jacques Bernier, M.D., Ph.D., Christian Domenge, M.D., Mahmut Ozsahin, M.D., Ph.D., Katarzyna Matuszewska, M.D., Jean-Louis Lefèbvre, M.D., Richard H. Greiner, M.D., Jordi Giralt, M.D., Philippe Maingon, M.D., Frédéric Rolland, M.D., Michel Bolla, M.D., Francesco Cognetti, M.D., Jean Bourhis, M.D., Anne Kirkpatrick, M.Sc., and Martine van Glabbeke, Ir., M.Sc., for the European Organization for Research and Treatment of Cancer Trial 22931

La radio-chimiothérapie

- Aussi en post-opératoire…

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Toxicité de la RCT: négligée?

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Evaluation of Early and Late Toxicities in Chemoradiation Trials

Søren M. Bentzen and Andrea Trotti

From the University of Wisconsin

efficacy is unthinkable, it is unfortunately still true that many, if not most, trial reports fail to document toxicity in sufficient detail.[9] Quan-

Toxicité: Bentzen

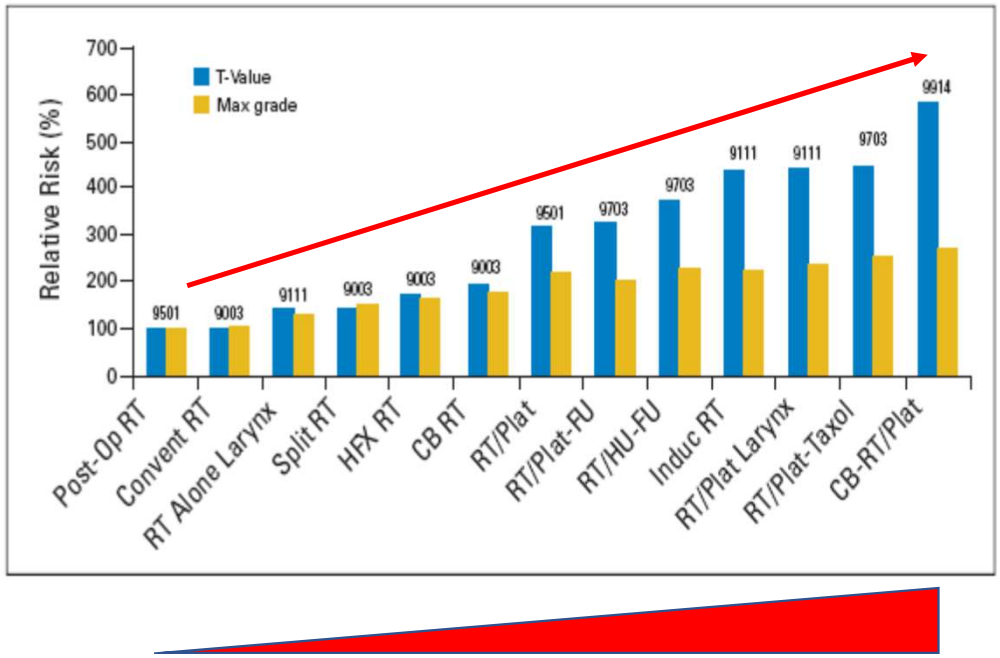
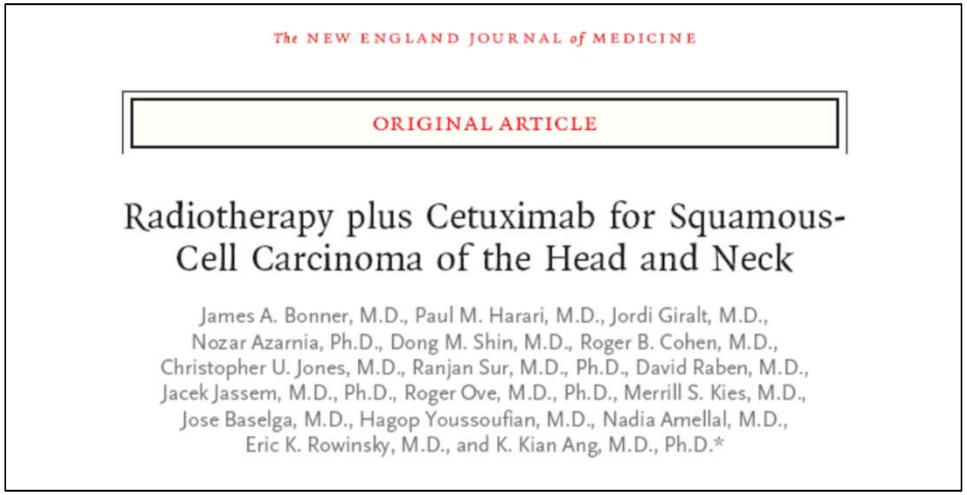


Fig 2. Toxicity burden measures: relative T-values versus relative maximum-grade values. Post-Op, postoperative; RT, radiotherapy; Convent, conventional; Plat, platinum; FU, fluorouracil; Induc, induction.

Le cetuximab (Erbitux®)

- Anticorps anti-EGFR
- Etudié comme alternative au cisplatine, avec résultats initiaux prometteurs (tout aussi efficace mais moins toxique?)
- Finalement, pas moins toxique (plus?), et moins efficace
- En voie de disparition…(?)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D., Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D., Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D., Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D., Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*

Cetuximab et RT: no toxicity?

Radiation Oncology

BioMed Central

Short report

Open Access

Severe skin reaction secondary to concomitant radiotherapy plus cetuximab

Bernhard Berger* and Claus Belka

Address: Department of Radiation Oncology, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany

Email: Bernhard Berger* - bernhard.berger@med.uni-tuebingen.de; Claus Belka - claus.belka@med.uni-tuebingen.de

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Received: 7 November 2007

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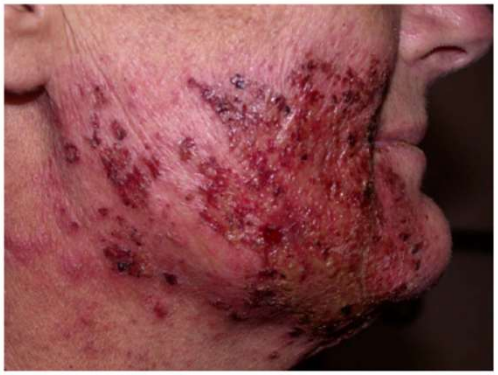
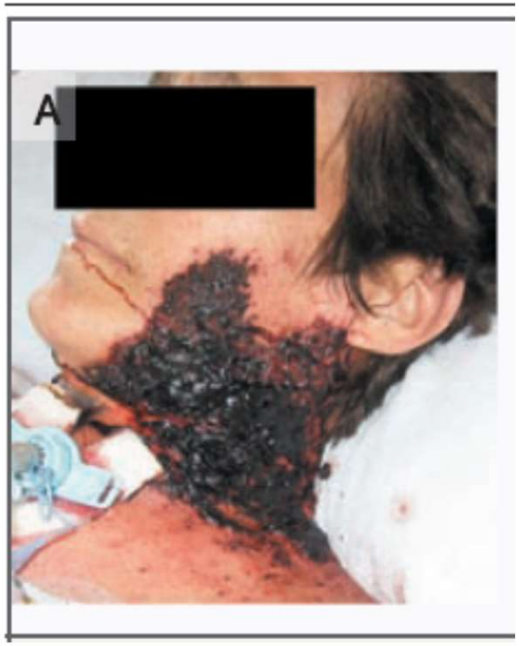


Figure 1
Exacerbated radiation dermatitis after cetuximab treatment.



Fractionnement standard

- Classiquement (1,8 à) 2 Gy/fraction
- Dose tumorale = 70 Gy
- Dose élective = 50 Gy
- Niveaux de dose intermédiaires possibles pour zones cN+ ou pour les traitements adjuvants:
  - 66 Gy dans les zones de TS positive ou dépassement capsulaire
  - 60 Gy dans les zones de marges proches ou les niveaux ganglionnaires pN+
  - Etc…

Fractionnement «altéré»

- Fractionnement standard:
  - Une fraction/jour sur environ 7 semaines, à environ 2 Gy/fraction
- Hyperfractionnement:
  - Une dose totale plus élevée délivrée sur un même temps de traitement total, en plus de fractions (2 ou 3 par jour) avec une dose réduite par fraction
- Fractionnement accéléré:
  - La même dose et nombre de fractions délivrés sur un temps de traitement total moins long
- Hypofractionnement ():
  - Une dose totale moins élevée délivrée en moins de fractions sur moins de temps, avec une dose par fraction plus élevé

Fractionnement «altéré»

- Fractionnement standard:
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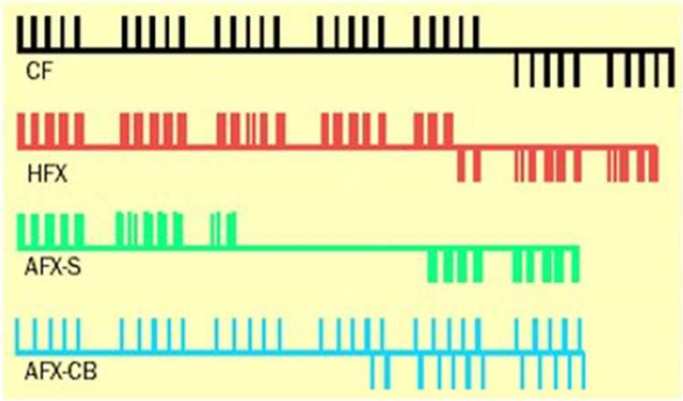
- Fractionnement accéléré:
  - La même dose et nombre de fractions délivrés sur un temps de traitement total moins long
- Hypofractionnement ():
  - Une dose totale moins élevée délivrée en moins de fractions sur moins de temps, avec une dose par fraction plus élevé

Fractionnement altéré



Fractionnement «accéléré»

- <u>L'importance du temps total de traitement</u> dans les cancers ORL (comme du col, canal anal, etc)
- Le «repopulation» accélérée, un des «5 R» de la radiobiologie
- A partir de la 4^{e} semaine de RT environ, un facteur de resistance
- D'où des stratégies pour accélérer la RT et diminuer le temps de traitement

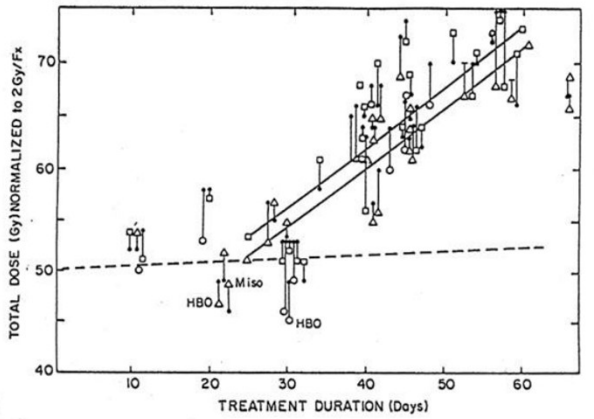


Fig. 1. TCD_{50} as a function of overall treatment time for squamous cell carcinomas of head and neck (Table 1). Data relate to T2 (○), T3 (□) or a combination of more than 2 stages (△). Total doses are normalized to the dose equivalent to that from a regimen of 2 Gy fractions using an α/β value of 25 Gy. Doses and times are best estimates of median values. The dose and control rate reported in the literature from which the TCD_{50} value was calculated is presented (●) to show the extent of the extrapolation. Rate of increase in TCD_{50} predicted from a 2 month clonogen doubling rate. (– – –). Estimated increase in TCD_{50} (——) with time for 'T3' (□) and mixed T stages (△) from independent scattergram analyses (Tables 2, 3) involving different data sets from those presented in this figure.

Fractionnement DAHANCA

- Deux séances le vendredi, séparées d'au moins 6 heures
- Raccourcit la durée totale de traitement d'une semaine, ce qui:
  - Augmente le contrôle loco-regional à 5 ans de 12%
  - Augmente la survie globale à 5 ans de 7%

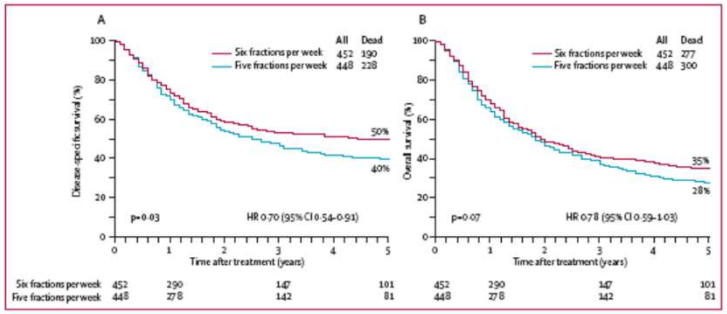


Figure 5: Disease-specific survival (A) and overall survival (B)

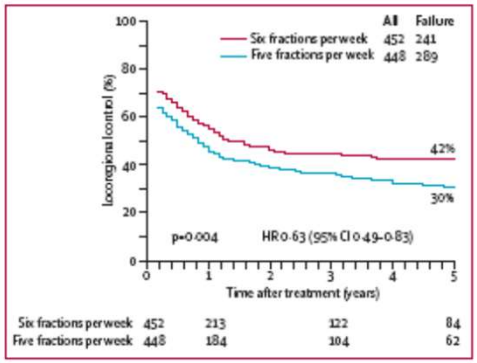


Figure 2: Locoregional tumour control

Méta-analyse MARCH

Lancet Oncol. 2017 September ; 18(9): 1221–1237. doi:10.1016/S1470-2045(17)30458-8.

Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis

Benjamin Lacas, MSc, Prof Jean Bourhis, MD, Prof Jens Overgaard, MD, Qiang Zhang, PhD, Prof Vincent Gregoire, MD, Matthew Nankivell, MSc, Prof Bjorn Zackrisson, MD, Zbigniew Szutkowski, MD, Prof Rafał Suwiński, MD, Prof Michael Poulsen, MD, Prof Brian O'Sullivan, MD, Prof Renzo Corvo, MD, Prof Sarbani Ghosh Laskar, MD, Prof Carlo Fallai, MD, Hideya Yamazaki, MD, Prof Werner Dobrowsky, MD, Kwan Ho Cho, MD, Prof Adam S Garden, MD, Prof Johannes A Langendijk, MD, Celia Maria Pais Viegas, MD, Prof John Hay, MBBChir, Prof Mohamed Lotayef, MD, Prof Mahesh K B Parmar, PhD, Anne Auperin, MD, Carla van Herpen, MD, Prof Philippe Maingon, MD, Prof Andy M Trotti, MD, Prof Cai Grau, MD, Jean-Pierre Pignon, MD[*], and Pierre Blanchard, MD[*] on behalf of the MARCH Collaborative Group[†]

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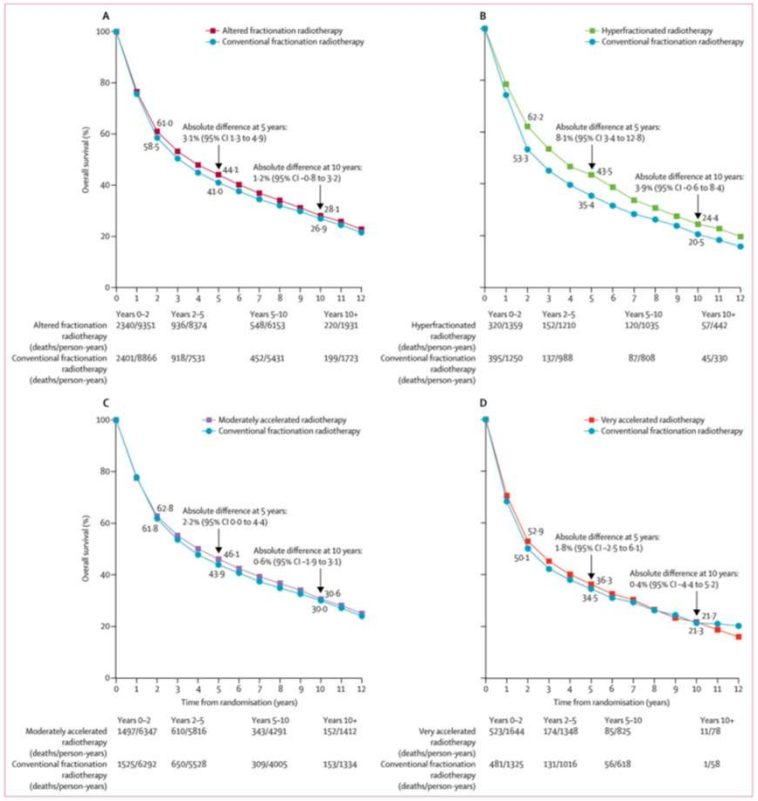
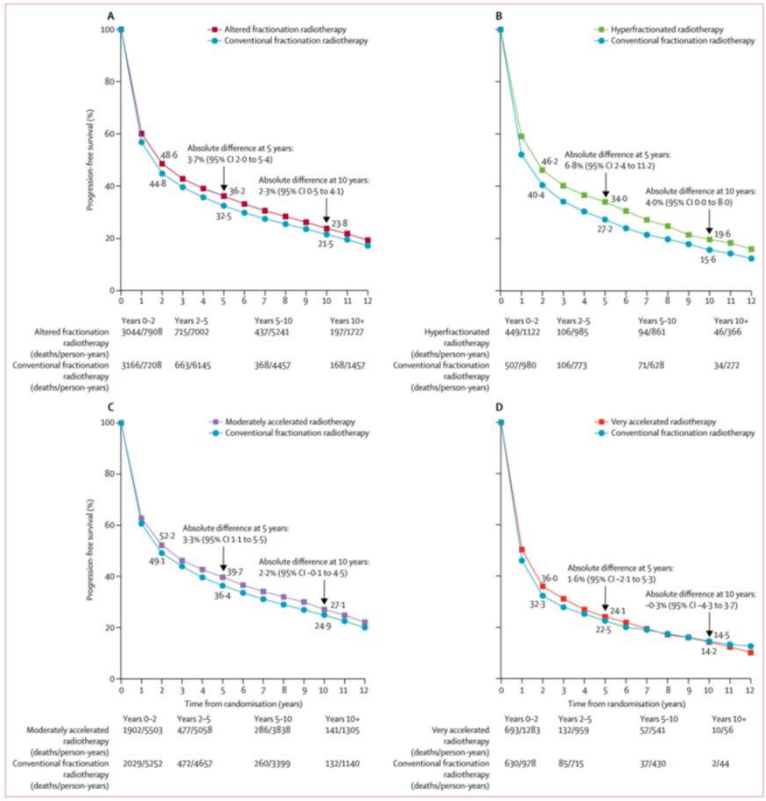
Résultats MARCH





MARCH – conclusions

- Le fractionnement accéléré améliore le contrôle loco-régional mais n'augmente pas de façon générale la survie globale
- L'hyperfractionnement améliore les deux
- Alors…pourquoi est-ce que tous les patients ORL ne sont pas traités par hyperfractionnement?
  - Problèmes logistiques
  - Pas de bénéfice en présence d'une chimiothérapie concomitante
  - Toxicité ++
  - --> en général, fractionnement(s) standard(s) en association avec la chimiothérapie

Fractionnement DAHANCA

- Deux séances le vendredi, séparées d'au moins 6 heures
- Raccourcit la durée totale de traitement d'une semaine, ce qui:
  - Augmente le contrôle loco-regional à 5 ans de 12%
  - Augmente la survie globale à 5 ans de 7%

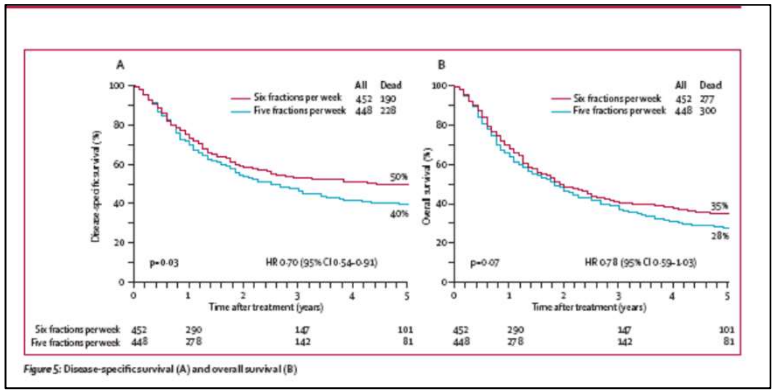


Figure 5: Disease-specific survival (A) and overall survival (B)

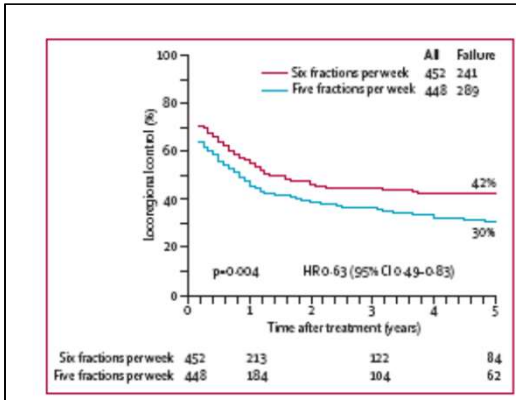
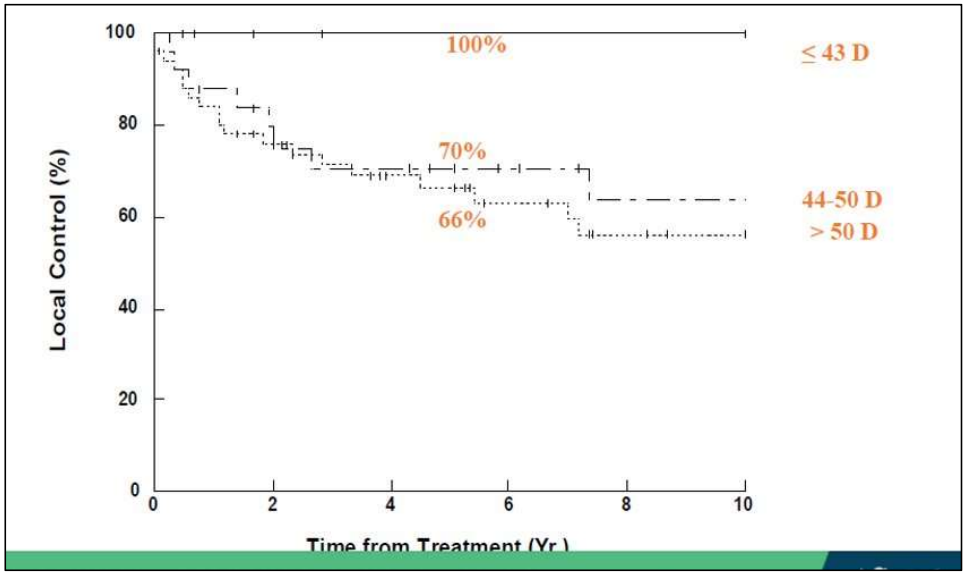


Figure 2: Locoregional tumour control

L’exemple des cancers précoces du larynx

- Meilleurs résultats surtout pour les tumeurs T2, mais aussi T1 avec 2,25 Gy/fraction
- Réduit le temps total de traitement...



L’exemple des cancers précoces du larynx

Table 1. Patient allocation to Arm A and B

Arm	Tumor length <2/3 of glottis	Tumor length ≥2/3 of glottis
Arm A (2 Gy/fr)		
A-1 (n = 31)	60 Gy/30 fr/6 wk	
A-2 (n = 57)		66 Gy/33 fr/6.6 wk
Arm B (2.25 Gy/fr)		
B-1 (n = 31)	56.25 Gy/25 fr/5 wk	
B-2 (n = 61)		63 Gy/28 fr/5.6 wk

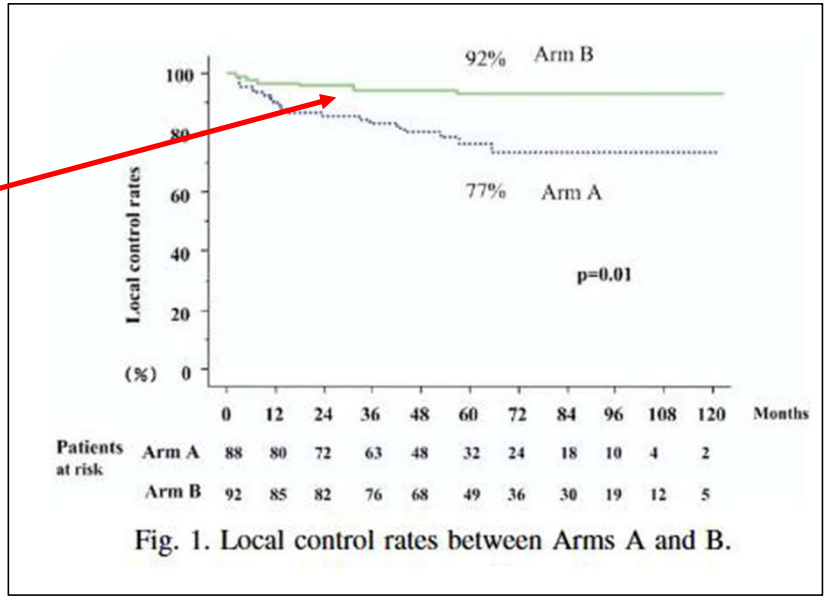
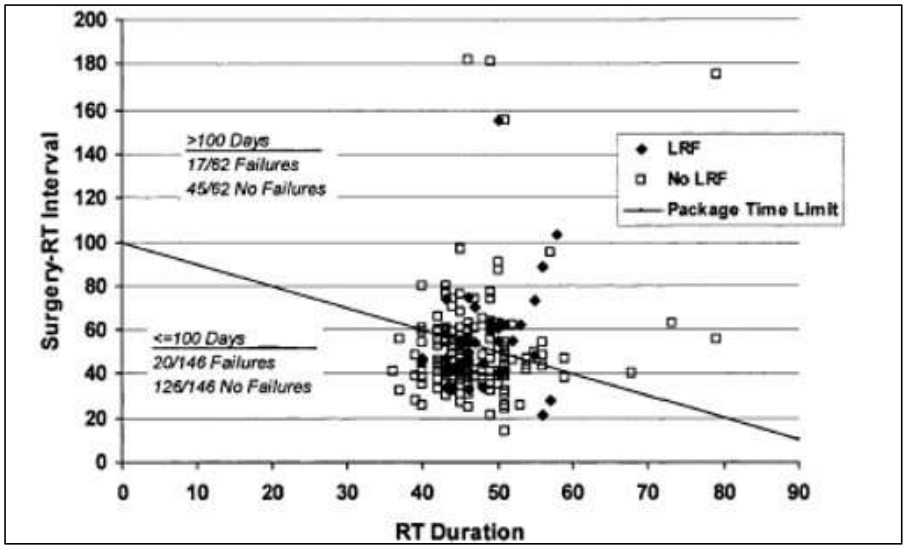


Fig. 1. Local control rates between Arms A and B.

Importance des délais aussi en adjuvant…

IMPORTANCE OF THE TREATMENT PACKAGE TIME IN SURGERY AND POSTOPERATIVE RADIATION THERAPY FOR SQUAMOUS CARCINOMA OF THE HEAD AND NECK

David I. Rosenthal, MD,[1] Li Liu, MD,[1] Jason H. Lee, MD,[1] Neha Vapiwala,[2]
Ara A. Chalian, MD,[3] Gregory S. Weinstein, MD,[3] Irina Chilian, MD,[1]
Randal S. Weber, MD,[3] Mitchell Machtay, MD[1]



Qu’en est-il de l’hypofractionnement?

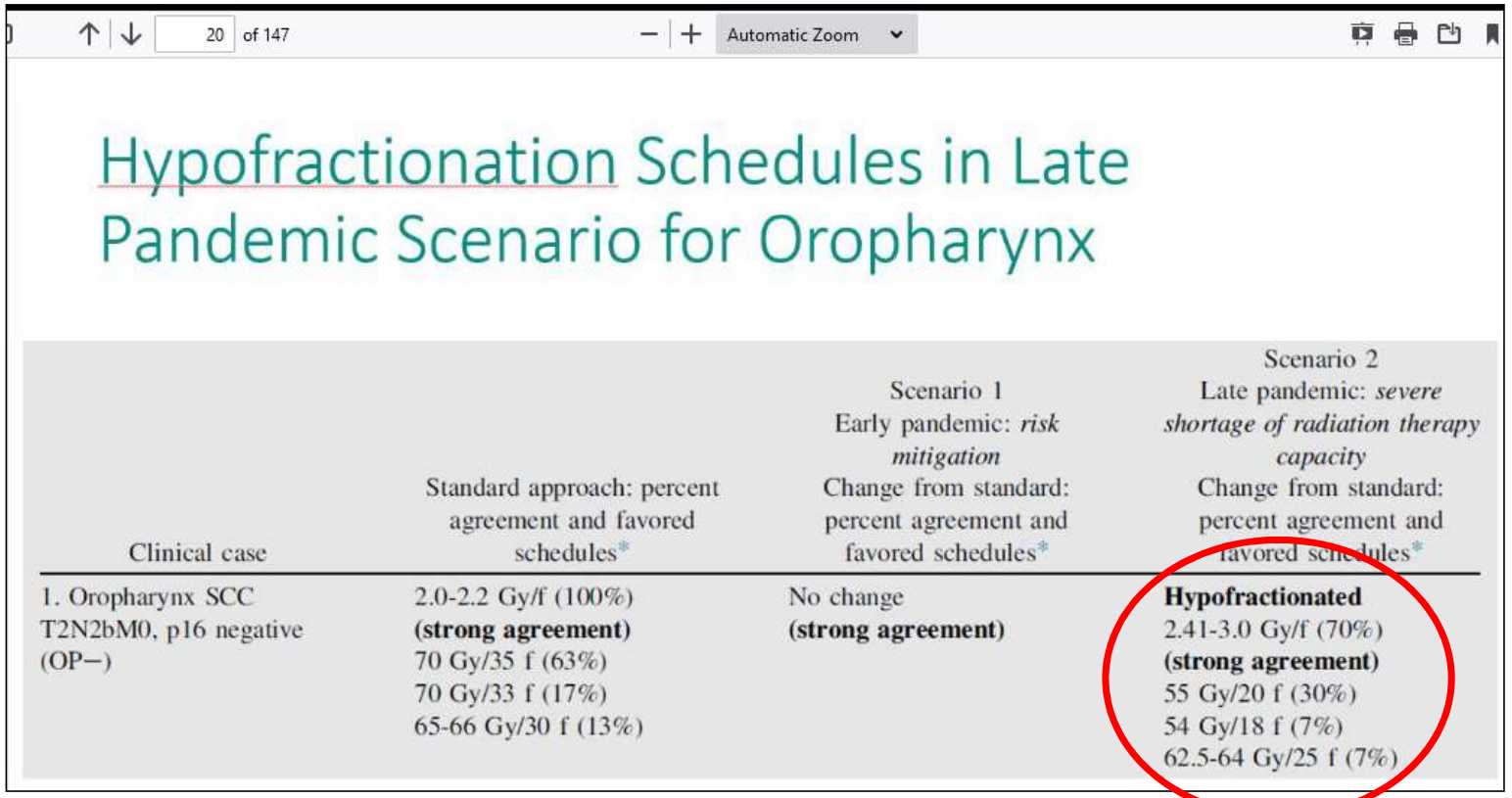
Practice Recommendations for Risk-Adapted Head and Neck Cancer Radiation Therapy During the COVID-19 Pandemic: An ASTRO-ESTRO Consensus Statement

Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1–10, 2020
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2020.04.016

In scenario 2, risk mitigation with severely reduced radiation therapy capacity:

Use a hypofractionated radiation schedule.	**Strong agreement**
Reserve concomitant chemotherapy for use with conventional or mildly hypofractionated radiation therapy (≤2.4 Gy/f).	Agreement
Do not use induction chemotherapy to delay initiation of treatment.	Majority, near-agreement

Consensus sur le principe, pas les détails…



20 of 147 — Automatic Zoom

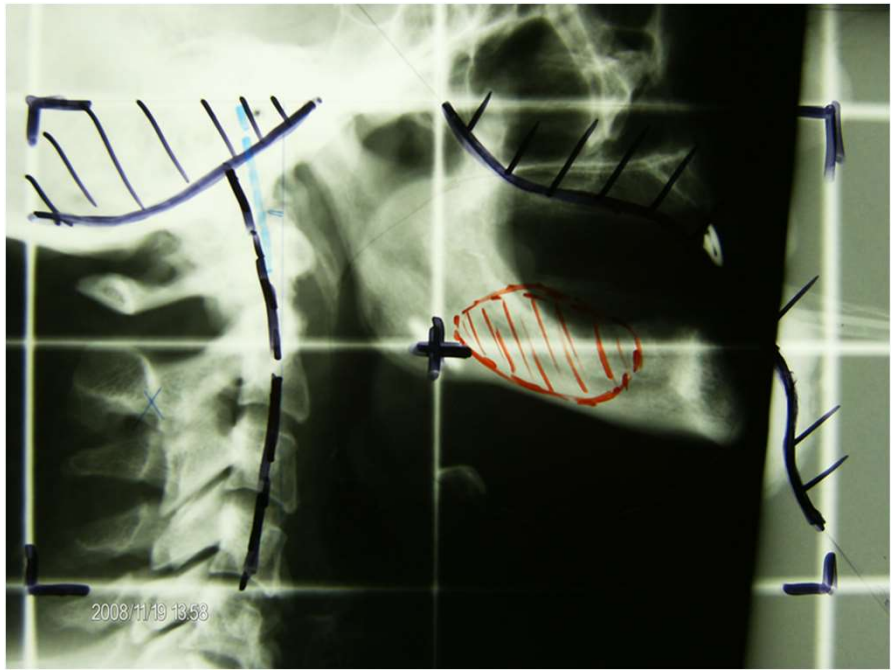
Hypofractionation Schedules in Late Pandemic Scenario for Oropharynx

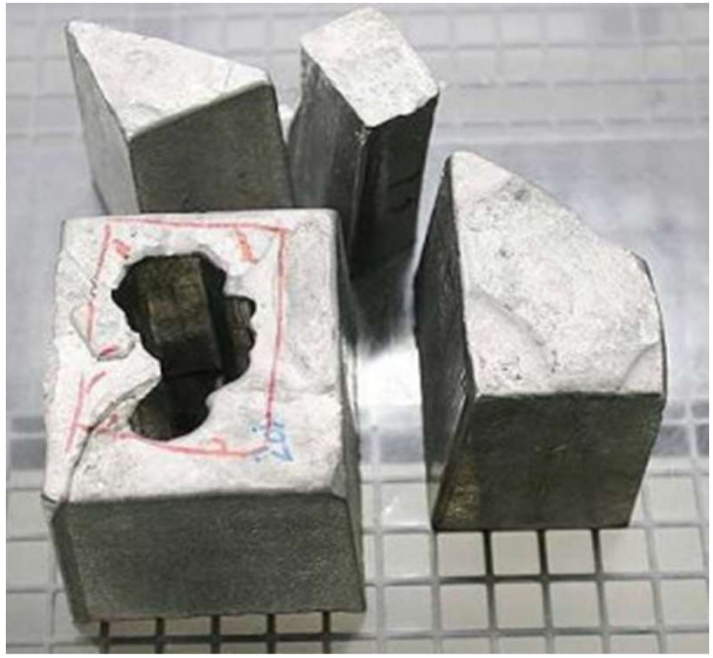
Clinical case	Standard approach: percent agreement and favored schedules*	Scenario 1 Early pandemic: *risk mitigation* Change from standard: percent agreement and favored schedules*	Scenario 2 Late pandemic: *severe shortage of radiation therapy capacity* Change from standard: percent agreement and favored schedules*
1. Oropharynx SCC T2N2bM0, p16 negative (OP−)	2.0-2.2 Gy/f (100%) **(strong agreement)** 70 Gy/35 f (63%) 70 Gy/33 f (17%) 65-66 Gy/30 f (13%)	No change **(strong agreement)**	**Hypofractionated** 2.41-3.0 Gy/f (70%) **(strong agreement)** 55 Gy/20 f (30%) 54 Gy/18 f (7%) 62.5-64 Gy/25 f (7%)

Hypofractionnement

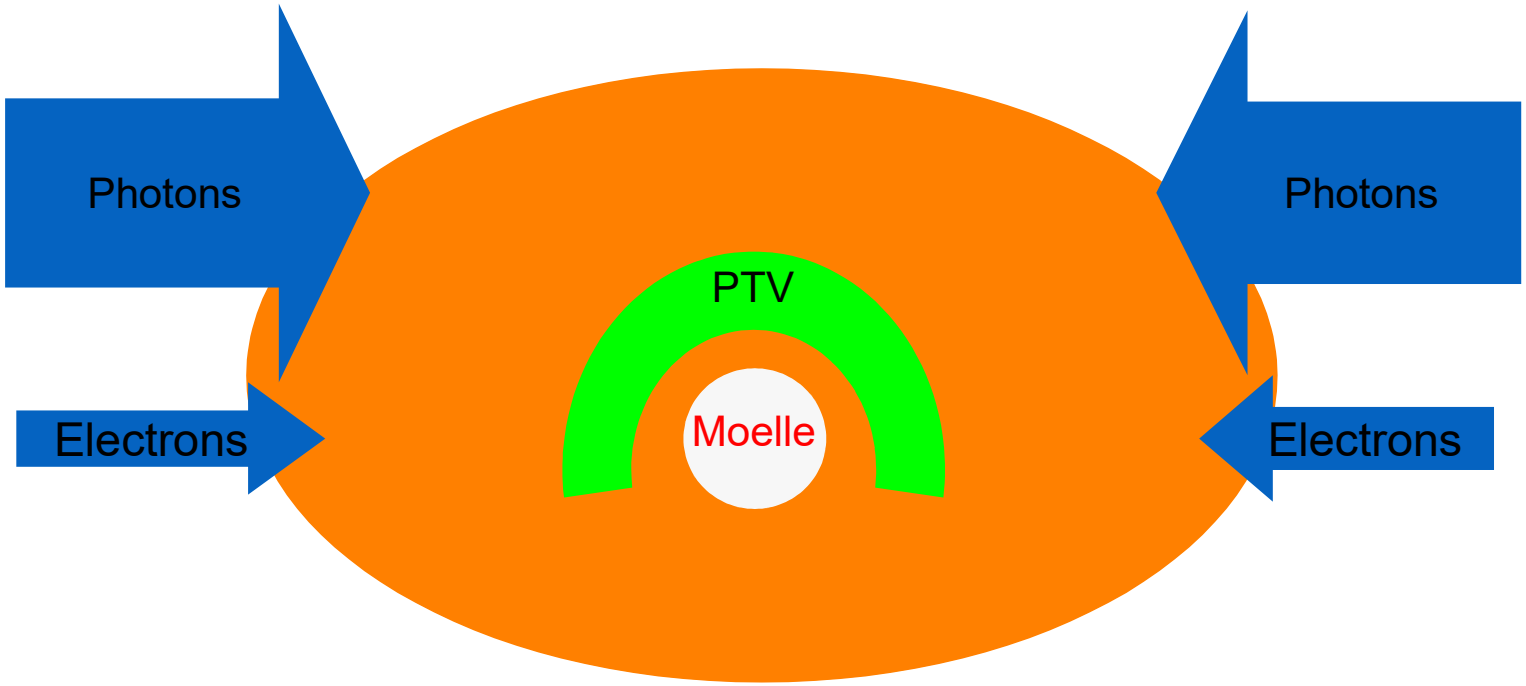
- En résumé, à part pour les tumeurs précoces du larynx, pas de vraie place en ORL pour le moment
- (Il en est de même pour la SBRT (récidives?))
- Par contre, rappel (!):
  - Le fractionnement standard pour les irradiations mammaires est actuellement 40-42,5 Gy en 15 ou 16 fractions sur 3 semaines
  - Le fractionnement standard pour les irradiations prostatiques est actuellement 60-70 Gy en 20 à 28 fractions sur 4 à 5,5 semaines
  - Il n'existe plus aucun argument médical ou éthique pour faire autrement, malgré les comportements et pratiques assez désolants en Suisse romande…

Considérations techniques:
Il n’y a pas si longtemps…

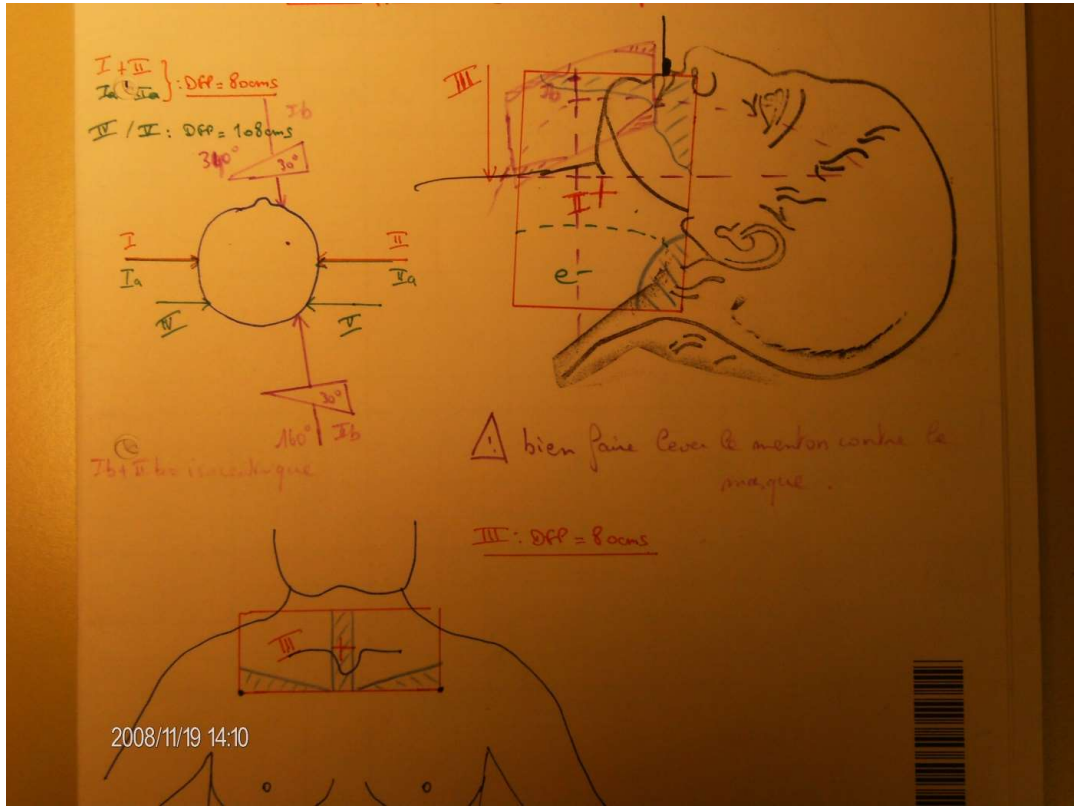




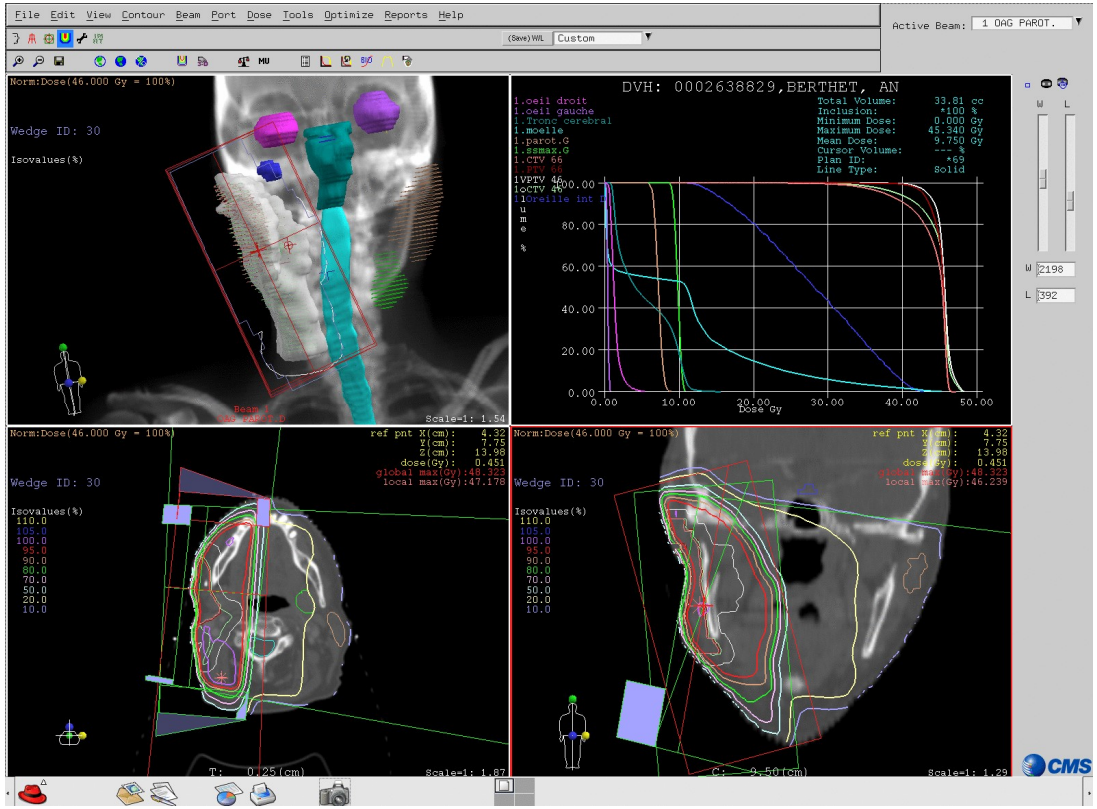
Planification 2D



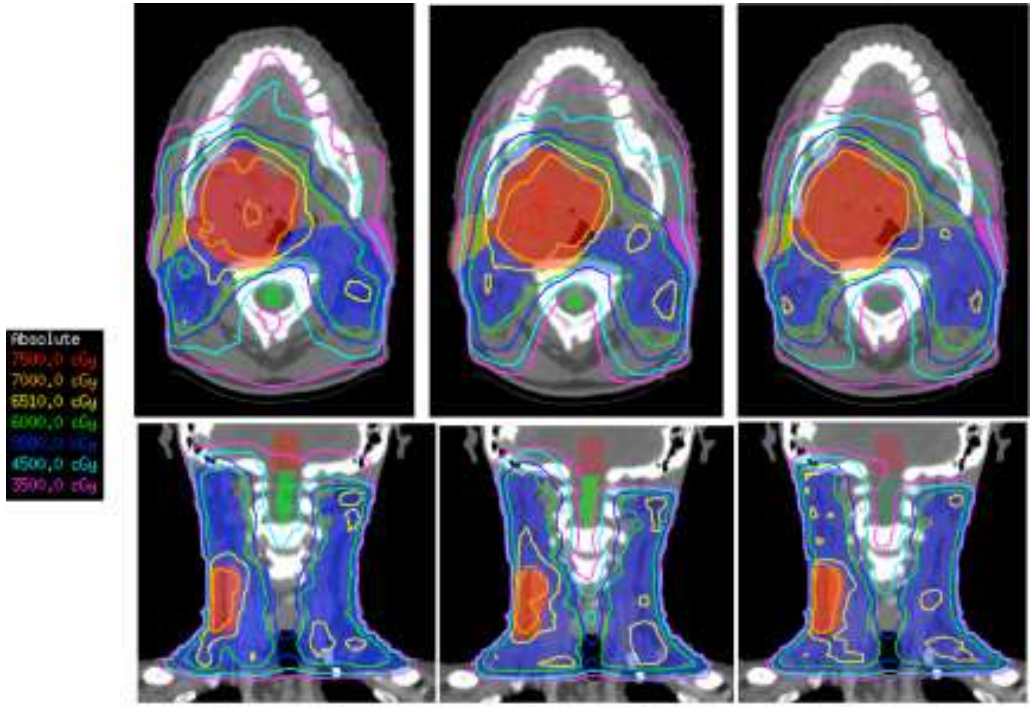
Plan de ttt circa 1990…



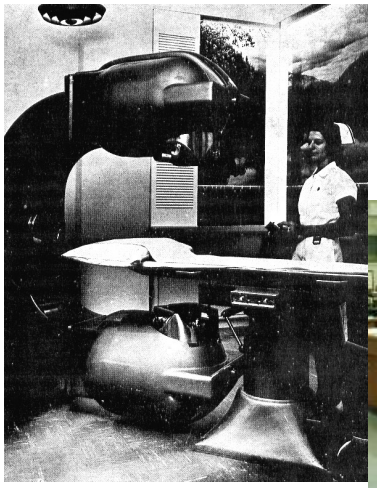
Circa 2000…


File Edit View Contour Beam Port Dose Tools Optimize Reports Help
Active Beam: 1 OAG PAROT.
Norm:Dose(46.000 Gy = 100%)
Wedge ID: 30
Isovalues(%)
DVH: 0002638829,BERTHET, AN
Total Volume: 33.81 cc
Inclusion: *100 %
Minimum Dose: 0.000 Gy
Maximum Dose: 45.340 Gy
Mean Dose: 9.750 Gy
Cursor Volume: --- %
Plan ID: *69
Line Type: Solid
Dose Gy
CMS

Aujourd’hui


Absolute
7500,0 cGy
7000,0 cGy
6510,0 cGy
6000,0 cGy
4500,0 cGy
3500,0 cGy
7 Field IMRT
Single Arc VMAT
Two Arc VMAT

Progrès techniques: machines/imagerie/informatique

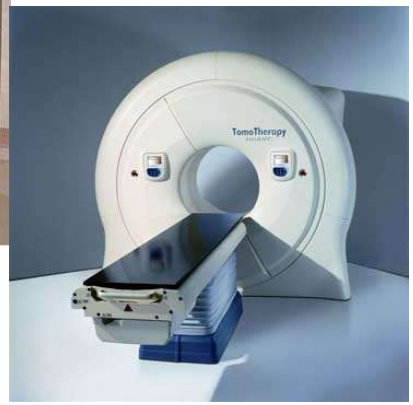


kilovoltage

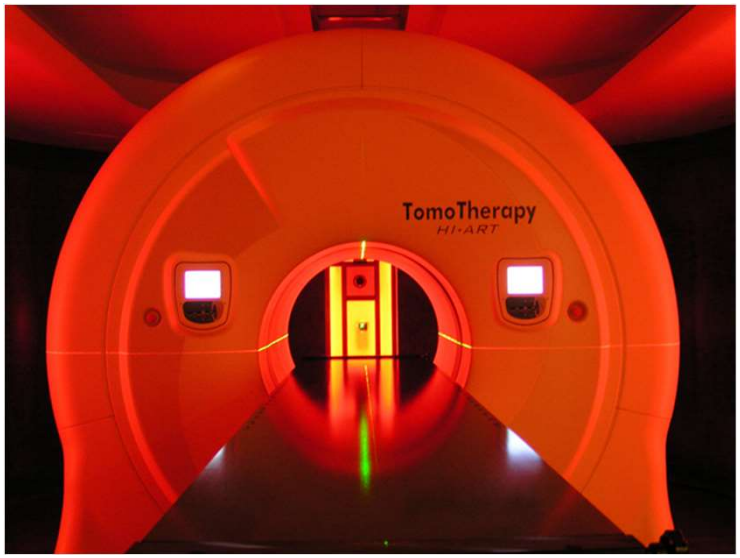
cobalt

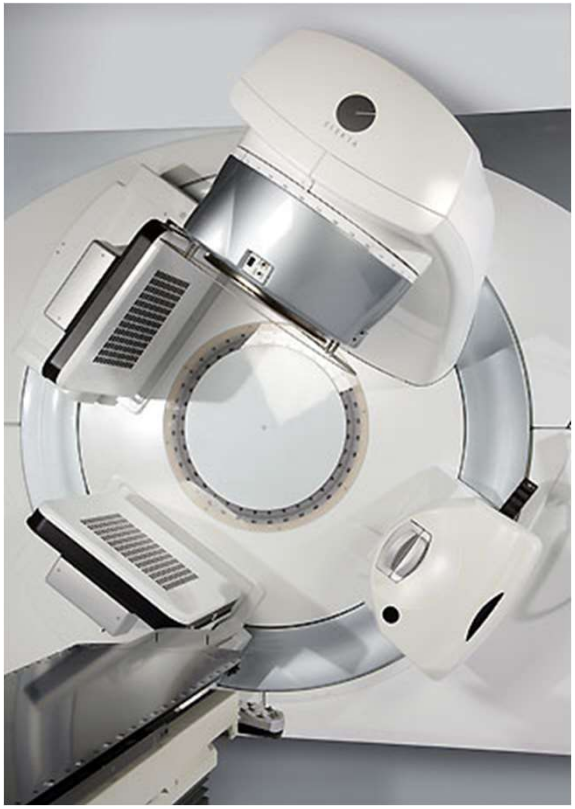
Linac (linear accelerator)

Tomotherapy®



Tomotherapy vs. Linac





Tomotherapy vs. Linac

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 3, pp. 917–923, 2006

0360-3016/06/$–see front matter

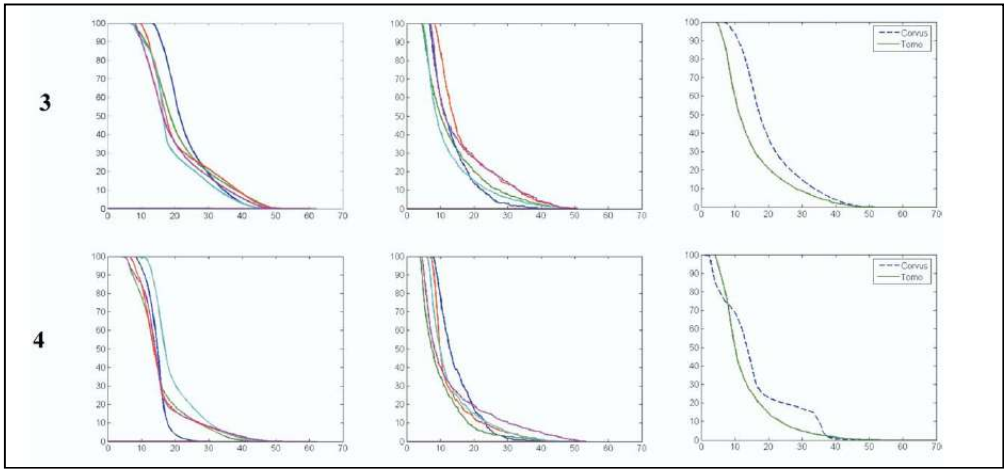
doi:10.1016/j.ijrobp.2006.02.038

PHYSICS CONTRIBUTION

INTENSITY-MODULATED RADIATION THERAPY (IMRT) DOSIMETRY OF THE HEAD AND NECK: A COMPARISON OF TREATMENT PLANS USING LINEAR ACCELERATOR–BASED IMRT AND HELICAL TOMOTHERAPY

KE SHENG, PH.D.,* JANELLE A. MOLLOY, PH.D.,*† AND PAUL W. READ, PH.D., M.D.*

*Department of Radiation Oncology, University of Virginia, Charlottesville, VA; †Department of Radiation Oncology, Mayo Clinic, Rochester, MN



Fractionnement

- Classiquement en plusieurs phases avec boost(s) séquentiels (p.ex. 50 Gy + boost 20 Gy, le tout en 35 fractions)
- Avec l'IMRT/VMAT, nous sommes dans l'ère des SIB (boosts simultanés intégrés), avec pas mal de variations locales…
- En SIB, typiquement:
  - 70/66/59.4/54(52.8) Gy en 33 fractions de 2.12/2/1.8/1.64(1.6) Gy
  - 66/60/52.5 Gy en 30 fractions de 2.2/2/1.75 Gy
  - Etc…
  - Doses électives estimées comme biologiquement equivalentes aux doses classiques, en general env. 0.5 Gy/j de plus pour compenser temps plus long

Your SIB, or mine?

Acta Oncologica
2008, 1–9, iFirst article

informa
healthcare

ORIGINAL ARTICLE

IMRT dose fractionation for head and neck cancer: Variation in current approaches will make standardisation difficult

KEAN F. HO[1], JACK F. FOWLER[2], ANDREW J. SYKES[3], BENG K. YAP[3], LIP W. LEE[3] & NICK J. SLEVIN[3]

[1]*Academic Department of Radiation Oncology, University of Manchester, Manchester, UK,* [2]*Emeritus, Department of Human Oncology and Medical Physics, University of Wisconsin, Wisconsin, USA and* [3]*Department of Clinical Oncology, Christie Hospital NHS Foundation Trust, Manchester, UK*

Dose fractionation radiotherapy trials in head and neck cancer over the past 20 years have established clinical benefits for a variety of modified fractionation schedules compared to the conventional 2 Gy per day to a total of 70 Gy over 7 weeks. When concurrent chemoradiation is used, there is further variation over the choice of optimum fractionation schedule. IMRT, with its potential for Simultaneous Integrated Boost (SIB), further adds to this uncertainty [1] such that there is an increasing lack of uniformity of practice with no single 'standard of care'.

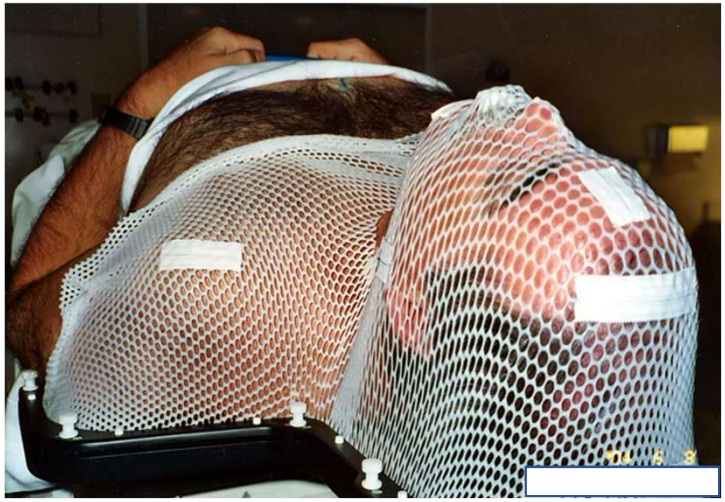
In SIB, each target volume is treated to the same number of fractions and therefore receives a different dose per fraction. Planning studies suggest that this method produces the most conformal dose distribution compared with using sequential IMRT plans [2]. Although this offers the distinct advantage of tailoring the appropriate dose to each target volume according to risk, it is a departure from the uniform fraction size conventionally employed.

There are now several published series of patients treated with head and neck IMRT which together demonstrate a plethora of fractionation regimes. It is apparent that single institutions are developing not only protocols that are 'in-house' but which are also evolving and changing with experience. We aim to examine the international practice of IMRT used for head and neck cancer through a survey of IMRT dose fractionation currently used in cancer centres around the world. A radiobiological comparison of the schedules is made. The variability of IMRT practice that currently exists is discussed with suggestions of possible reasons for this diversity in approach.

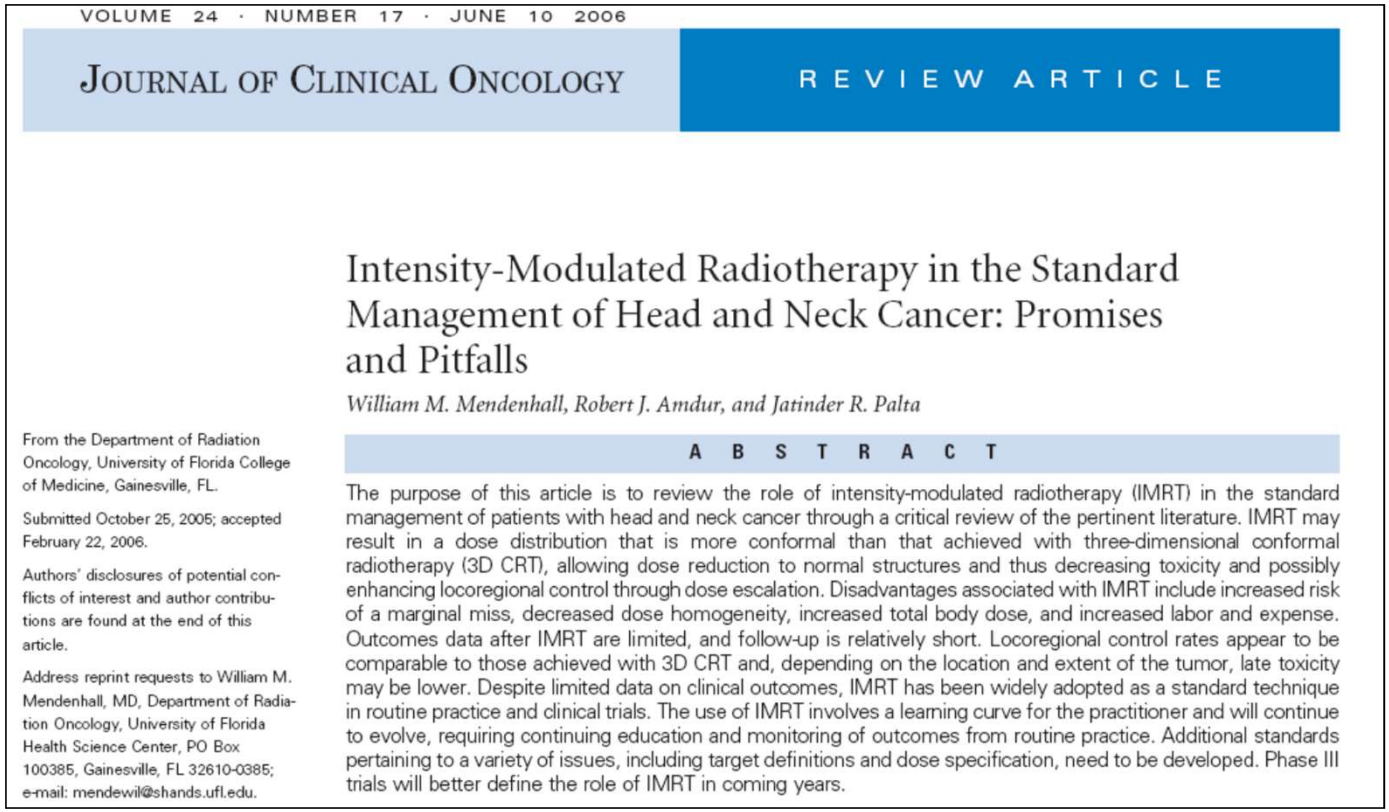
Contours

- GTV si traitement exclusif, selon IRM/CT/PET-CT et examen clinique y compris description/dessins faits par l'ORL lors de son examen et la panendoscopie
- CTV tumoral
  - GTV + marges généreuses (1-1,5 cm en exclusif recommandé)
  - En adjuvant, lit tumoral/ADP + marges généreuses
- CTV électif
  - Niveaux ganglionnaires selon tumeur et stade
- PTV = en général CTV + 3-5 mm (masque et imagerie → peu de mouvement inter- ou intrafraction)

Immobilisation



L'IMRT…trop précise?



VOLUME 24 · NUMBER 17 · JUNE 10 2006

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Intensity-Modulated Radiotherapy in the Standard Management of Head and Neck Cancer: Promises and Pitfalls

William M. Mendenhall, Robert J. Amdur, and Jatinder R. Palta

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Submitted October 25, 2005; accepted February 22, 2006.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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A B S T R A C T

The purpose of this article is to review the role of intensity-modulated radiotherapy (IMRT) in the standard management of patients with head and neck cancer through a critical review of the pertinent literature. IMRT may result in a dose distribution that is more conformal than that achieved with three-dimensional conformal radiotherapy (3D CRT), allowing dose reduction to normal structures and thus decreasing toxicity and possibly enhancing locoregional control through dose escalation. Disadvantages associated with IMRT include increased risk of a marginal miss, decreased dose homogeneity, increased total body dose, and increased labor and expense. Outcomes data after IMRT are limited, and follow-up is relatively short. Locoregional control rates appear to be comparable to those achieved with 3D CRT and, depending on the location and extent of the tumor, late toxicity may be lower. Despite limited data on clinical outcomes, IMRT has been widely adopted as a standard technique in routine practice and clinical trials. The use of IMRT involves a learning curve for the practitioner and will continue to evolve, requiring continuing education and monitoring of outcomes from routine practice. Additional standards pertaining to a variety of issues, including target definitions and dose specification, need to be developed. Phase III trials will better define the role of IMRT in coming years.

Target delineation discrepancies

Strahlentherapie
und Onkologie

Original Article

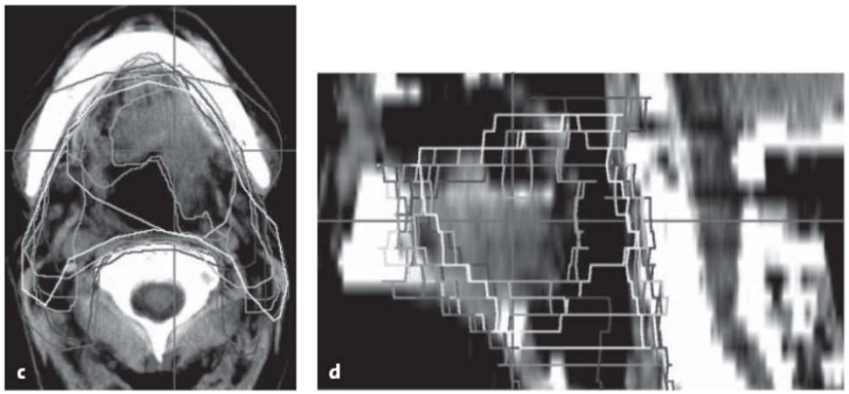
The Reasons for Discrepancies in Target Volume Delineation

A SASRO Study on Head-and-Neck and Prostate Cancers

Wendy Jeanneret-Sozzi[1], Raphaël Moeckli[2], Jean-François Valley[2], Abderrahim Zouhair[1], Esat Mahmut Ozsahin[1], René-Olivier Mirimanoff[1] on Behalf of SASRO[3]

Purpose: To understand the reasons for differences in the delineation of target volumes between physicians.
Material and Methods: 18 Swiss radiooncology centers were invited to delineate volumes for one prostate and one head-and-neck case. In addition, a questionnaire was sent to evaluate the differences in the volume definition (GTV [gross tumor volume], CTV [clinical target volume], PTV [planning target volume]), the various estimated margins, and the nodes at risk. Coherence between drawn and stated margins by centers was calculated. The questionnaire also included a nonspecific series of questions regarding planning methods in each institution.

Jeanneret-Sozzi et al.



Figures 1a to 1d. Demonstration of the variations in the CTV delineation on axial and sagittal planes for the prostate (a, b) and the head-and-neck case (c, d).

Lymph node areas	Yes, homolateral	Yes, bilateral	No
Supraclavicular	0	8	2
Inferior jugular	0	7	2
Midjugular	1	9	0
Subdigastric	0	10	0
Superior jugular	0	10	0
Spinal	0	9	1
Submaxillary	0	9	1

Conclusion

In this study, we confirmed that wide interobserver variations exist in the delineation of GTV, CTV and PTV, in two different oncologic cases.

Data to explain these discrepancies are scarce in the literature and suggest multifactorial and complex reasons. We suggest that part of these are due to:

(1) a variable knowledge and/or interpretation in the basic ICRU definitions;
(2) difficulties in the identification of GTV due to the available imaging quality;
(3) a variable understanding and/or concept for microscopic tumor extent (CTV);
(4) a variable knowledge and/or concept in the estimation of variations in position and movement of the CTV (GTV);
(5) a variable coherence between the theoretical knowledge (stated margins) and the practice (drawn margins).

Conceivably, measures can be taken to decrease discrepancies and, hopefully, improve interobserver coherence. To start with, a better and more comprehensive diffusion and understanding of ICRU recommendations in the radiation oncology community should be promoted. In parallel, continuous research in cancer imaging, in the knowledge of microscopic tumor extent and in a more systematic and individualized estimation of physiological motion should be supported.

Organes à risque

CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines

Radiotherapy and Oncology, 2015-10-01, Volume 117, Issue 1, Pages 83-90,

Charlotte L. Brouwer, Roel J.H.M. Steenbakkers, Jean Bourhis, Wilfried Budach, Cai Grau, Vincent Grégoire, Marcel van

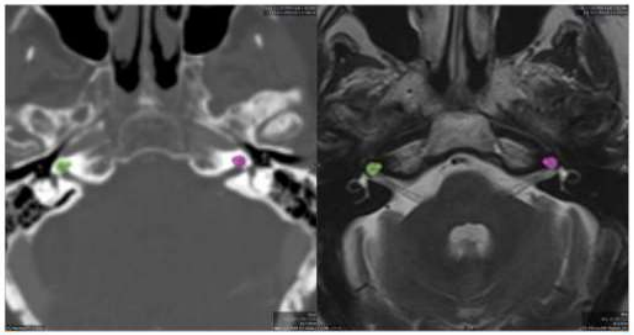


Fig. 2

Delineation of the cochlea in CT bone settings (left), matched to MRI-T2 (right).

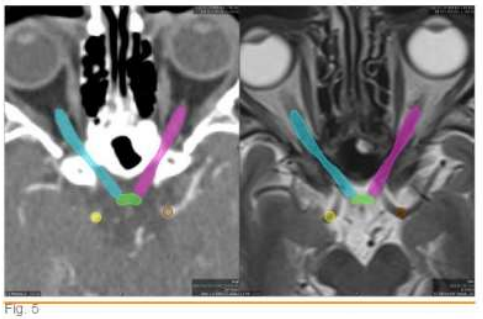
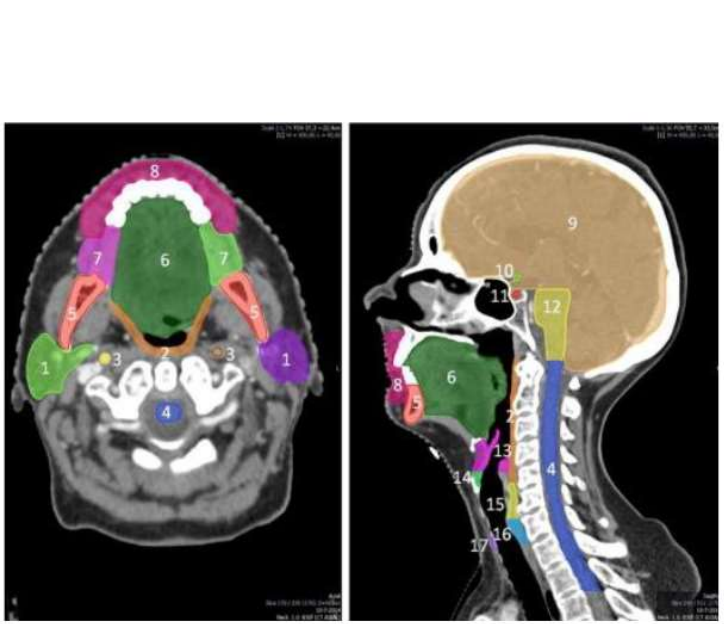


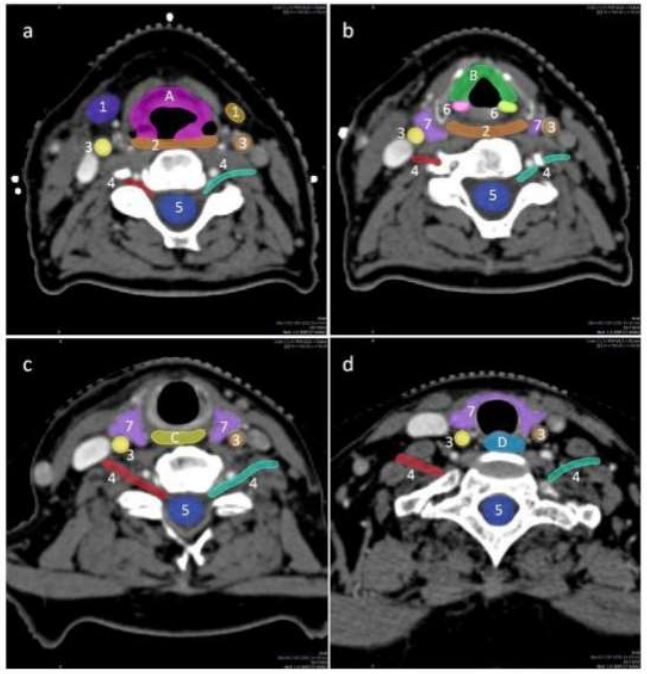
Fig. 5

Delineation of the optic nerves (blue and purple), optic chiasm (green) and carotid arteries (yellow and brown) on CT (left) and MRI-T2 (right).

De nombreuses structures à considérer…

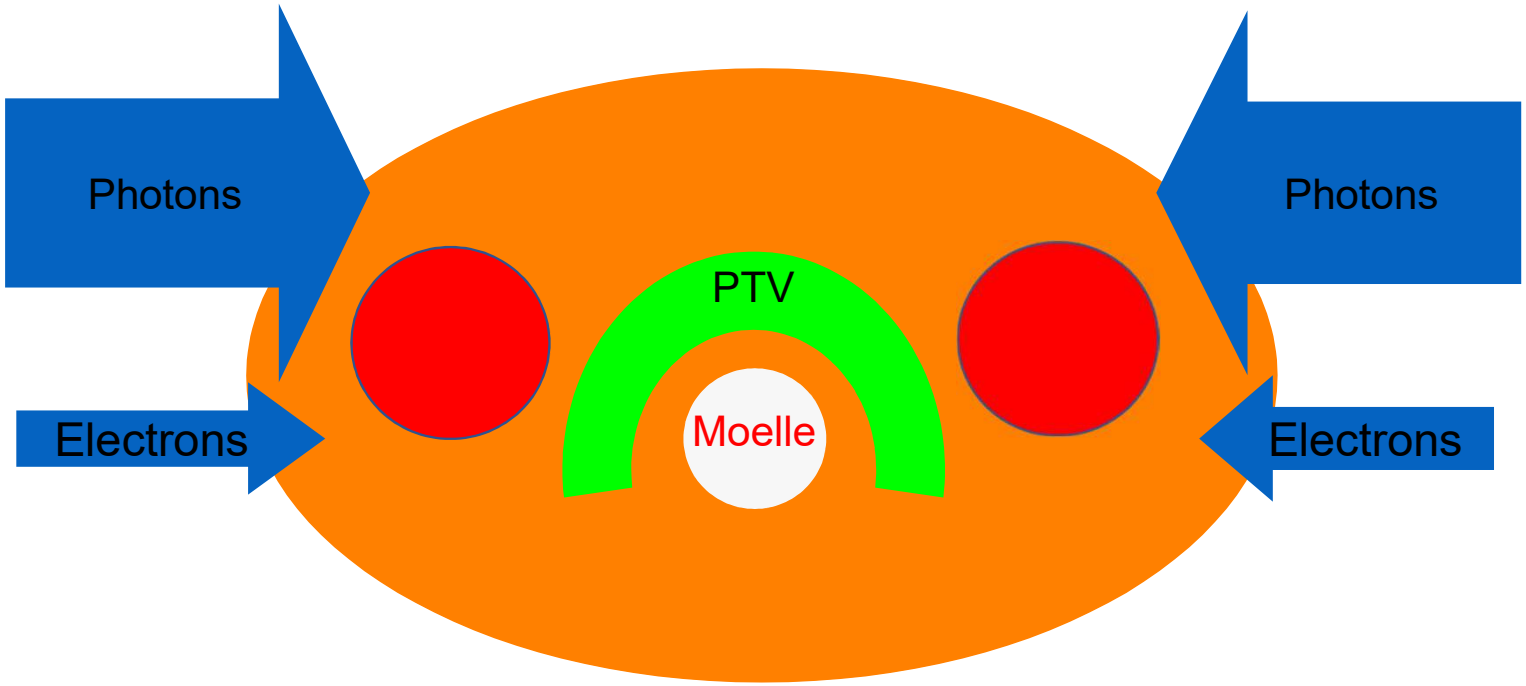


Axial (left) and sagittal (right) view of the consensus delineations of the parotid glands (1), pharyngeal constrictor muscles (2), carotid arteries (3), spinal cord (4), mandible (5), extended oral cavity (6), buccal mucosa (7), lips (8), brain (9), chiasm (10), pituitary gland (11), brainstem (12), supraglottic larynx (13), glottic area (14), crico-pharyngeal inlet (15), cervical esophagus (16) and thyroid (17). (For the full atlas, the reader is referred to the Supplemental material .)

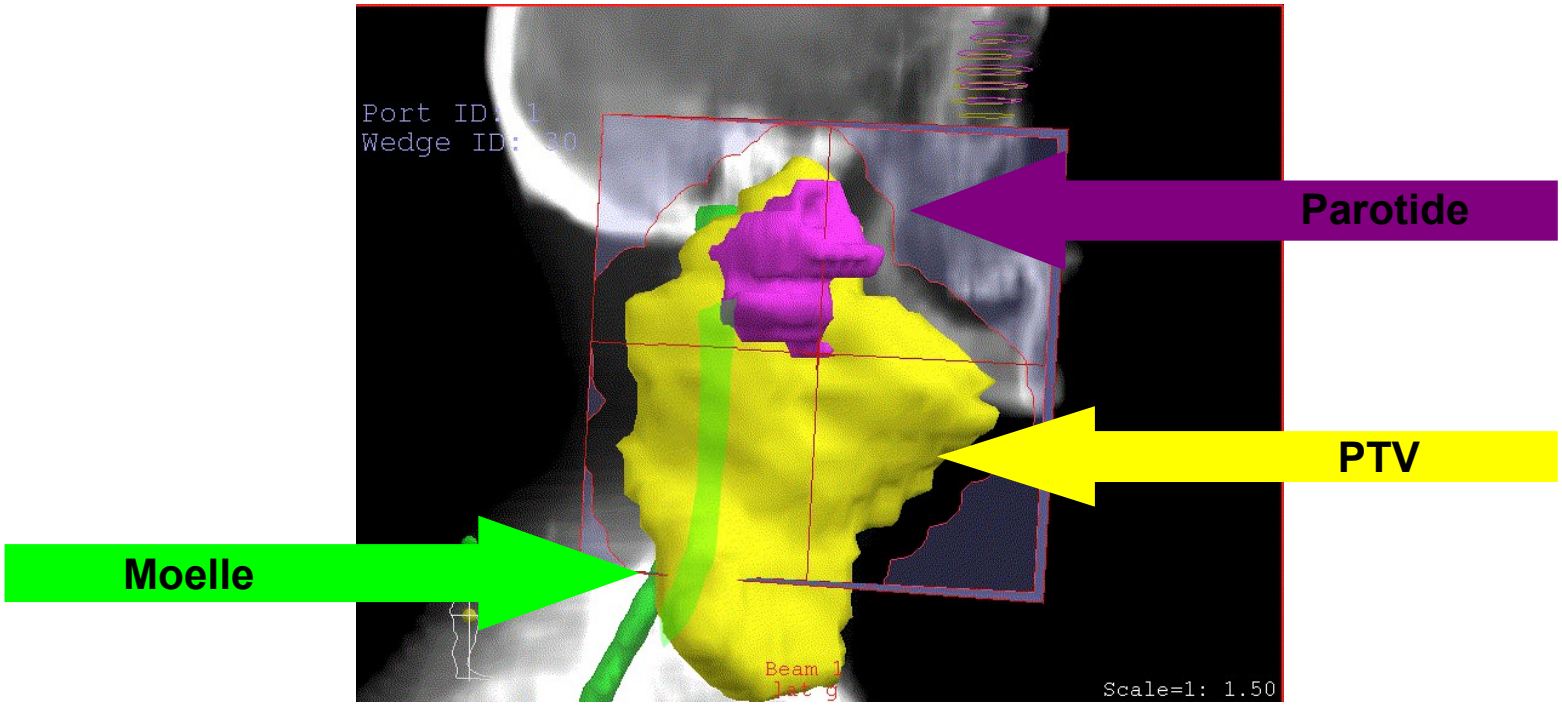


Axial CT slices showing the delineation of the supraglottic larynx (A) (a), glottic area (B) (b), crico-pharyngeal inlet muscle (C) (c), and cervical esophagus (D) (d). Other organs at risks visible are the submandibular glands (1), pharyngeal constrictor muscles (2), carotid arteries (3), brachial plexus (4), spinal cord (5), arytenoids (6) and thyroid

Les parotides



Les parotides



2D vs IMRT

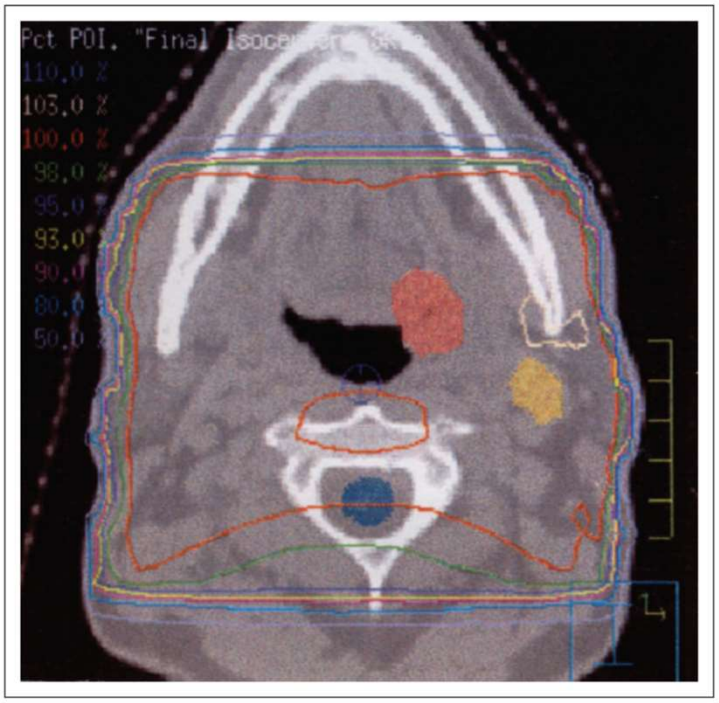


Fig 1. Axial dose distribution for a 49-year-old man with a T2N2C squamous cell carcinoma of the left tonsillar fossa. The patient received 76.8 Gy at 1.2 Gy per fraction twice daily with three-dimensional conformal radiotherapy followed by a

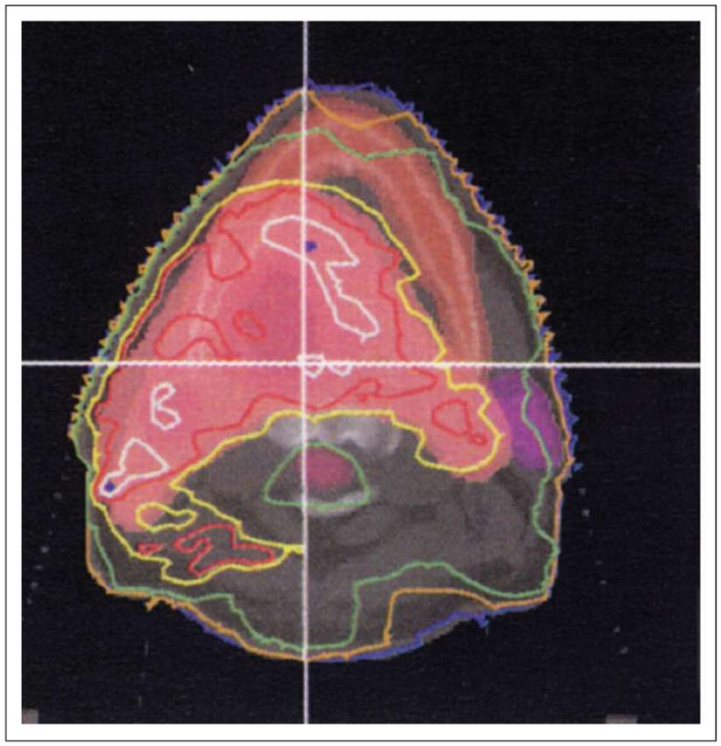


Fig 2. Axial dose distribution for a 56-year-old man with a T3N2B squamous cell

Parotid-sparing IMRT

Int. J. Radiation Oncology Biol. Phys., Vol. 67, No. 3, pp. 660–669, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.09.021

CLINICAL INVESTIGATION **Head and Neck**

THE IMPACT OF DOSE ON PAROTID SALIVARY RECOVERY IN HEAD AND NECK CANCER PATIENTS TREATED WITH RADIATION THERAPY

YUN LI, M.S.,* JEREMY M. G. TAYLOR, PH.D.,*† RANDALL K. TEN HAKEN, PH.D.,† AND AVRAHAM EISBRUCH, M.D.†

*Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI; †Department of Radiation Oncology, School of Medicine, University of Michigan, Ann Arbor, MI

Results: Parotids receiving higher radiation produce less saliva. The largest reduction is at 1–3 months after RT followed by gradual recovery. When mean doses are lower (e.g., <25 Gy), the model-predicted average stimulated saliva recovers to pretreatment levels at 12 months and exceeds it at 18 and 24 months. For higher doses (e.g., >30 Gy), the stimulated saliva does not return to original levels after 2 years. Without stimulation, at 24 months, the predicted saliva is 86% of pretreatment levels for 25 Gy and <31% for >40 Gy. We do not find evidence to support that the overproduction of stimulated saliva at 18 and 24 months after low dose in 1 parotid gland is the result of low saliva production from the other parotid gland.

Conclusions: Saliva production is affected significantly by radiation, but with doses <25–30 Gy, recovery is substantial and returns to pretreatment levels 2 years after RT.

Prudence…

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 3, pp. 660–665, 2008

0360-3016/08/$–see front matter

doi:10.1016/j.ijrobp.2007.09.018

RAPID COMMUNICATION

RECURRENCE IN REGION OF SPARED PAROTID GLAND AFTER DEFINITIVE INTENSITY-MODULATED RADIOTHERAPY FOR HEAD AND NECK CANCER

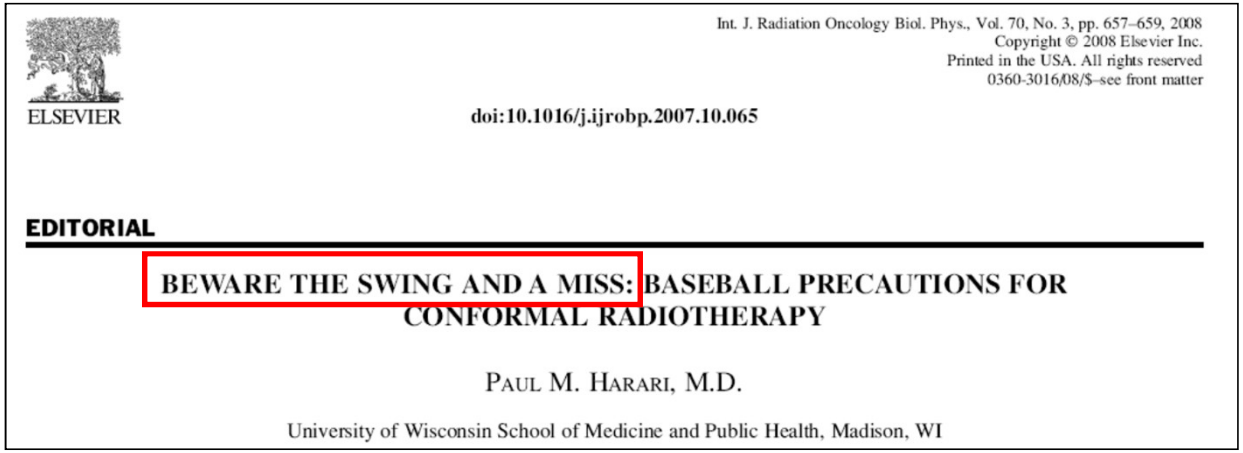
DONALD M. CANNON, B.S.,* AND NANCY Y. LEE, M.D.†

*Weill-Cornell Medical College, New York, NY; and †Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

Results: All patients had treatment failure in the region of a spared parotid gland. Failure in the 2 patients with bilateral multilevel nodal involvement occurred in the periparotid lymph nodes. The third patient developed a dermal metastasis near the tail of a spared parotid gland. On pretreatment imaging, the 2 patients with nodal failure had small nonspecific periparotid nodules that showed no hypermetabolic activity on positron emission tomography.

Conclusion: For HNC patients receiving definitive IMRT, nonspecific positron emission tomography–negative periparotid nodules on pretreatment imaging should raise the index of suspicion for subclinical disease in the presence of multilevel or Level II nodal metastases. Additional evaluation of such nodules might be indicated before sparing the ipsilateral parotid gland. © 2008 Elsevier Inc.

Prudence…



Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 3, pp. 657–659, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.10.065

EDITORIAL

BEWARE THE SWING AND A MISS: BASEBALL PRECAUTIONS FOR CONFORMAL RADIOTHERAPY

PAUL M. HARARI, M.D.

University of Wisconsin School of Medicine and Public Health, Madison, WI

Despite the absence of Phase III trials rigorously comparing the long-term outcomes using highly conformal radiation techniques (intensity-modulated radiotherapy [IMRT], tomotherapy, proton therapy) vs. those using conventional techniques, there is a prevailing sentiment that improved dose conformality is "good"… good for the patient, good for normal tissues and toxicity profiles, and good for the discipline of radiation oncology. The published data and evolving pattion of new radiation delivery technologies in recent years. If radiation oncologists are reliably "hitting" all the tumor cells with radiation each day, and reliably sparing normal tissues, this improved conformality is indeed likely to be good (although questions remain unanswered regarding the long-range effect of radiation exposure to increased volumes of normal tissue). However, to use a baseball analogy, we would

Harari

Although idealized computer treatment plans with meticulous contours, sharp dose–volume histogram plots and steep isodose gradient profiles separating tumor from normal tissue are the norm in head-and-neck IMRT (particularly adjacent to the spinal cord and parotid glands), we know that the day-to-day variations in set up and delivery can degrade the integrity of idealized plans. It has been increasingly well appreciated

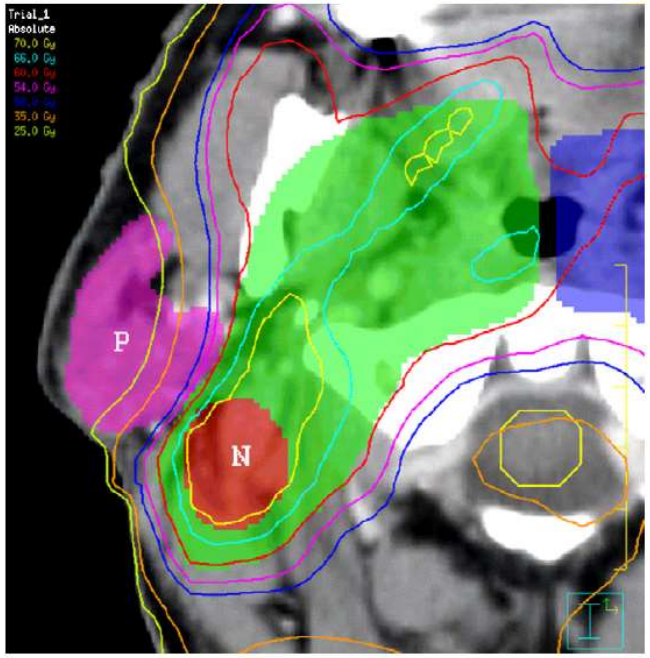


Fig. 1. Head-and-neck intensity-modulated radiotherapy plan illustrating steep dose gradient between metastatic superior jugular node (N) and right parotid gland (P). Tight juxtaposition between gross tumor (70 Gy prescription dose) and normal tissue avoidance structure (parotid gland, 26 Gy mean dose prescription) highlights potential risk that accompanies daily set-up and treatment variations during 30–35-fraction treatment course.

Harari

INADVERTENT OVEREMPHASIS ON SALIVA?

Parotid gland sparing in head-and-neck cancer treatment has emerged as a key objective for radiation oncologists in recent years. For decades previously, relatively little attention was paid to this issue because the available technology did not readily facilitate salivary gland sparing. For the most part, it was a given that patients would develop xerostomia after curative-intent radiotherapy for head and neck cancer. With our increasing capacity to spare salivary gland dose, the topic of xerostomia has taken center stage, with the desire to diminish toxicity and preserve better overall quality of life (3, 4). In the current era of highly conformal technology advancement, elegant normal tissue-sparing techniques sometimes attract as much, or more, attention as tumor eradication. For some patients with advanced head and neck cancer, this approach might not be warranted or safe despite the laudable desire to spare salivary gland function. Considerable

hensive radiation approaches. To paraphrase commentary from several head-and-neck cancer experts on this topic, "much better a dry mouth than a dead patient."

Un vrai bénéfice clinique…?

VOLUME 25 · NUMBER 31 · NOVEMBER 1 2007

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Reducing Xerostomia by IMRT: What May, and May Not, Be Achieved

Avraham Eisbruch, *Department of Radiation Oncology, University of Michigan, Ann Arbor, MI*

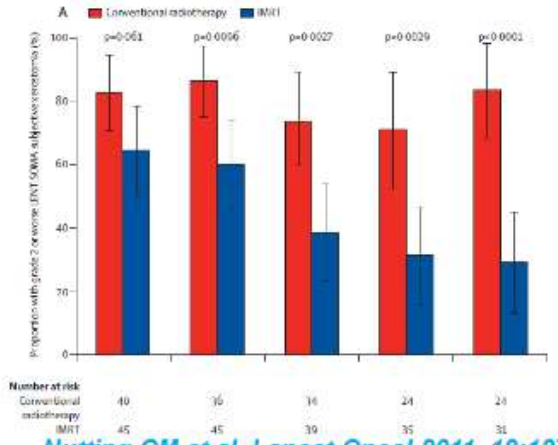
Kam et al[8] found that in the patients treated with IMRT, significantly lower parotid gland mean doses were achieved compared with patients treated with 2D RT, and the lower doses translated into higher stimulated salivary flow rates. Moreover, the salivary flows in the IMRT patients improved over time, compared with no improvement in the 2D RT patients. These findings corroborate what we have known: following 2D RT of HN cancer, the salivary output is meager and does not improve over time. By clear) by the part of the glands that received a low dose.[12] As the parotid salivary output is partially preserved and increasing over time, it has been predicted that parallel improvements in the symptoms of xerostomia would follow. However, this expected effect was found to be much more complex and uncertain. The uncer-

Etude PASSPORT

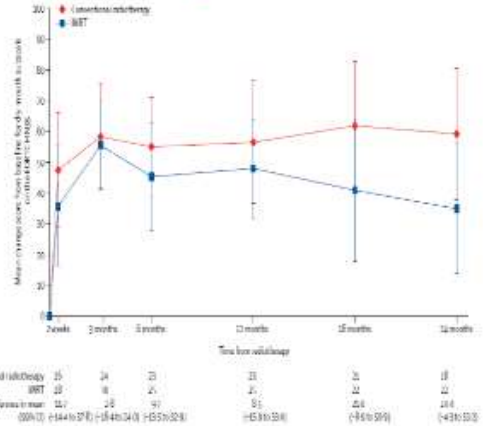
Parotid Sparing with IMRT Decreases Xerostomia: PASSPORT Trial

- 94 pts with OP/HP cancer randomized to IMRT vs 3DRT
- Whole contralateral parotid < 24Gy

Lent SOMA Score

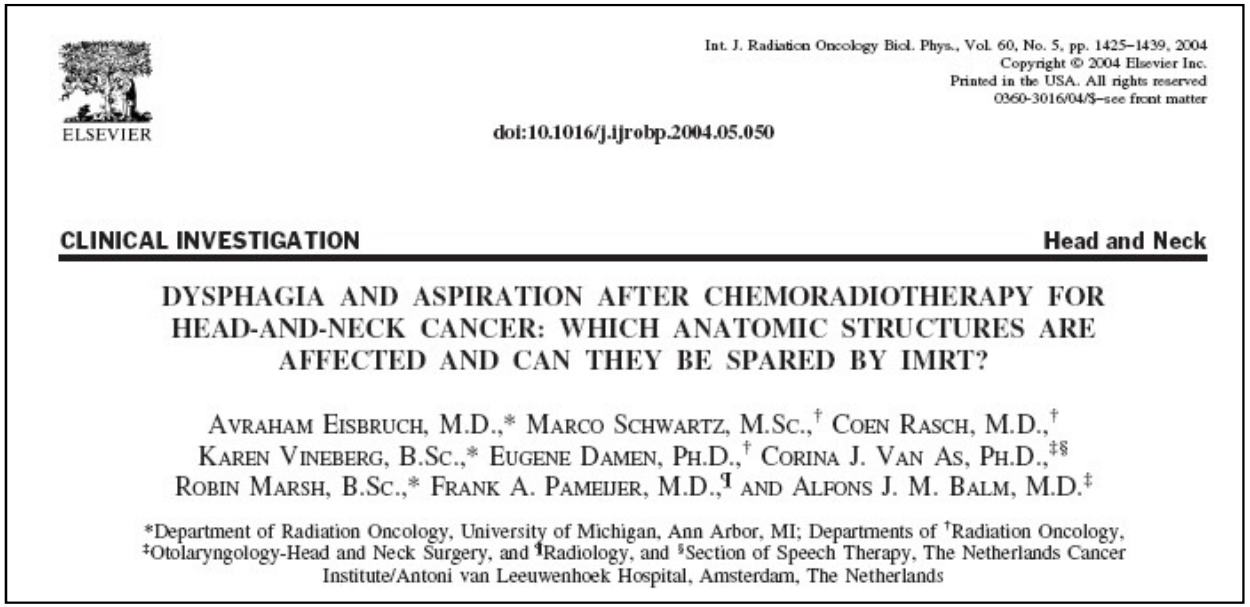


EORTC Dry Mouth Subscale



Nutting CM et al, Lancet Oncol 2011, 12:127

La prochaine étape…
Dysphagie et IMRT



Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 5, pp. 1425–1439, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.05.050

CLINICAL INVESTIGATION **Head and Neck**

DYSPHAGIA AND ASPIRATION AFTER CHEMORADIOTHERAPY FOR HEAD-AND-NECK CANCER: WHICH ANATOMIC STRUCTURES ARE AFFECTED AND CAN THEY BE SPARED BY IMRT?

AVRAHAM EISBRUCH, M.D.,* MARCO SCHWARTZ, M.SC.,† COEN RASCH, M.D.,†
KAREN VINEBERG, B.SC.,* EUGENE DAMEN, PH.D.,† CORINA J. VAN AS, PH.D.,‡§
ROBIN MARSH, B.SC.,* FRANK A. PAMEIJER, M.D.,¶ AND ALFONS J. M. BALM, M.D.‡

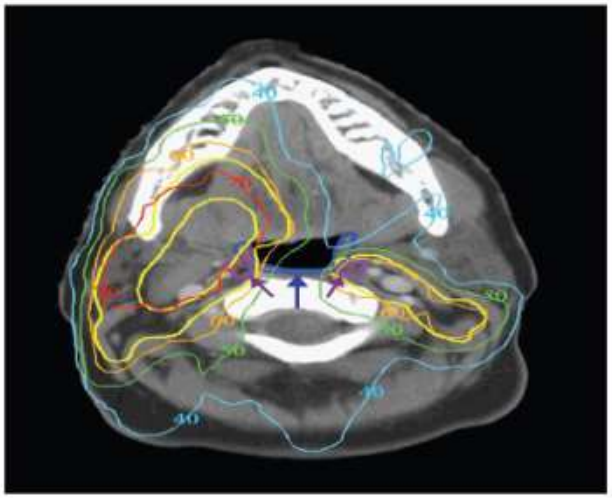
*Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; Departments of †Radiation Oncology, ‡Otolaryngology-Head and Neck Surgery, and ¶Radiology, and §Section of Speech Therapy, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Réduire la dysphagie

Intensity-Modulated Chemoradiotherapy Aiming to Reduce Dysphagia in Patients With Oropharyngeal Cancer: Clinical and Functional Results

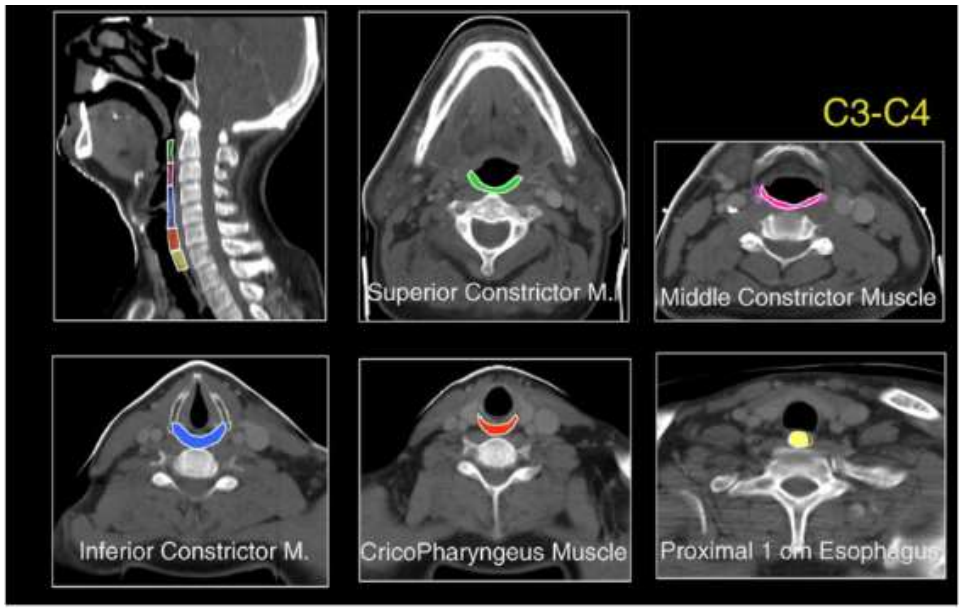
73 III/IV Opx 70Gy/7wks + taxol/carbo/wk

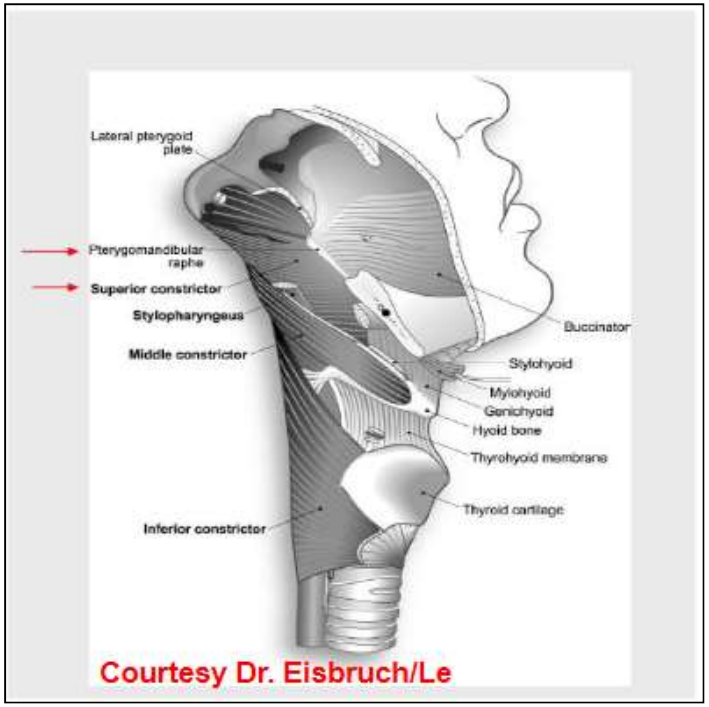
Med F/U 36mo 3yr LRC 96% DFS 88%



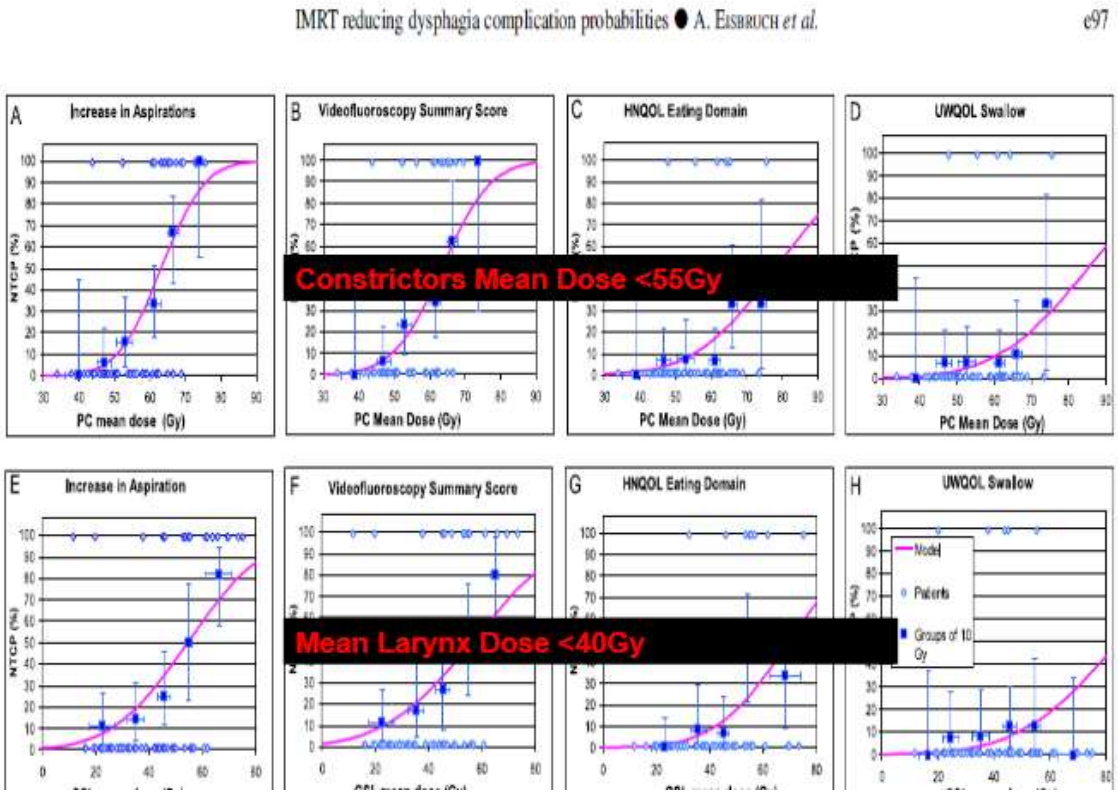
Feng JCO 2010

Muscles constricteurs pharyngés

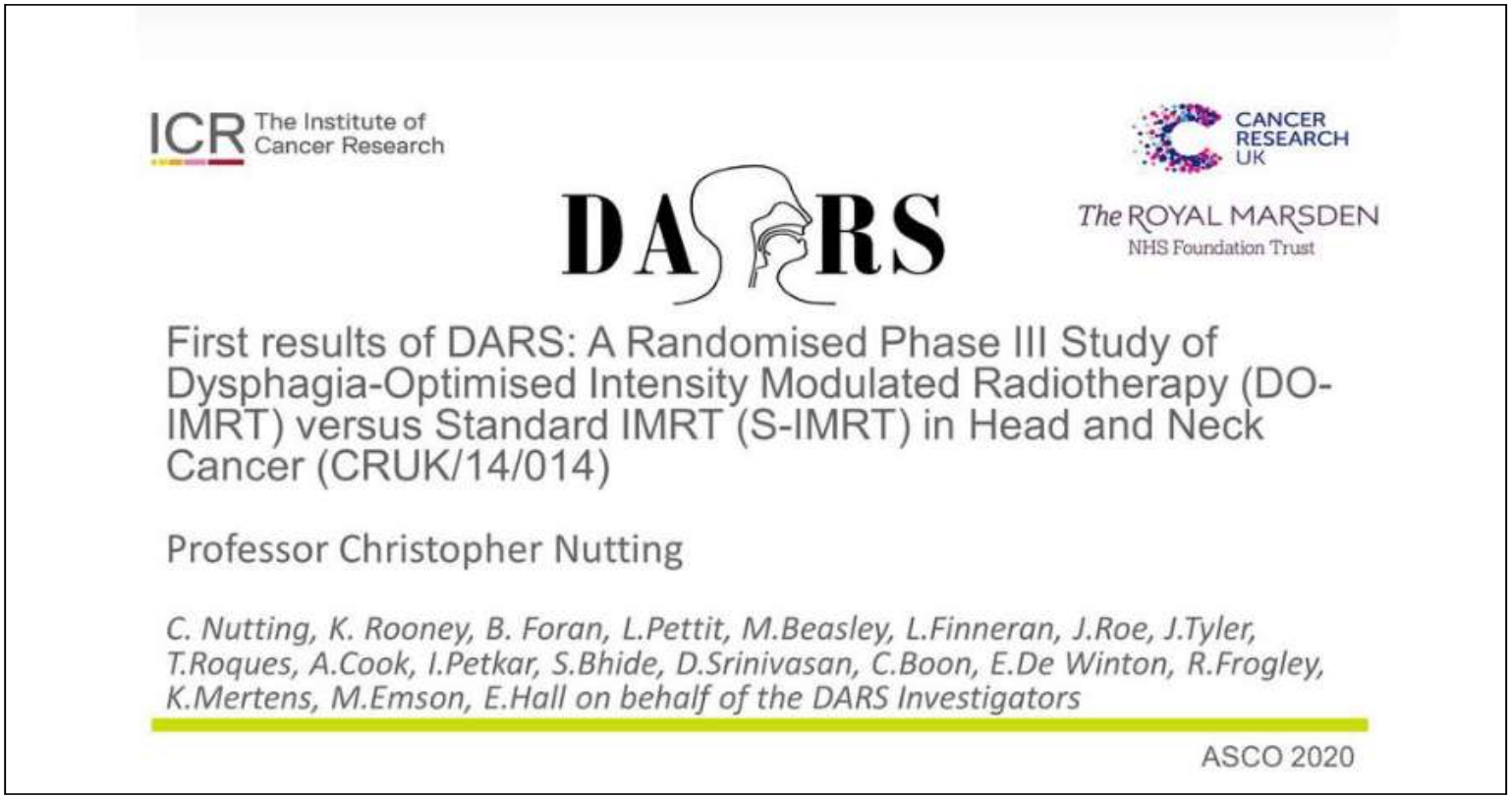




Dysphagia-optimized IMRT/VMAT

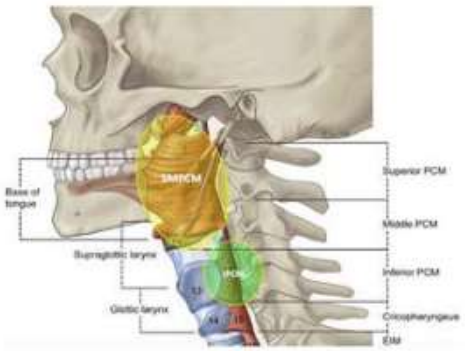


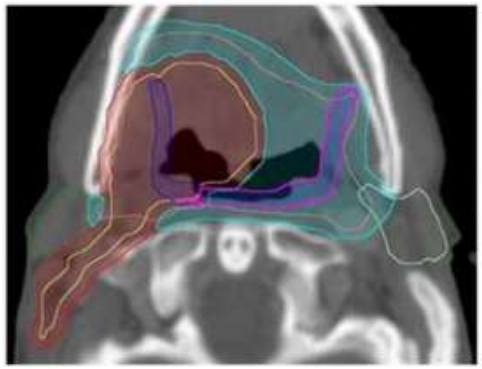
Etude DARS


ICR The Institute of Cancer Research
CANCER RESEARCH UK
DARS
The ROYAL MARSDEN NHS Foundation Trust
First results of DARS: A Randomised Phase III Study of Dysphagia-Optimised Intensity Modulated Radiotherapy (DO-IMRT) versus Standard IMRT (S-IMRT) in Head and Neck Cancer (CRUK/14/014)
Professor Christopher Nutting
C. Nutting, K. Rooney, B. Foran, L.Pettit, M.Beasley, L.Finneran, J.Roe, J.Tyler, T.Roques, A.Cook, I.Petkar, S.Bhide, D.Srinivasan, C.Boon, E.De Winton, R.Frogley, K.Mertens, M.Emson, E.Hall on behalf of the DARS Investigators
ASCO 2020

DARS

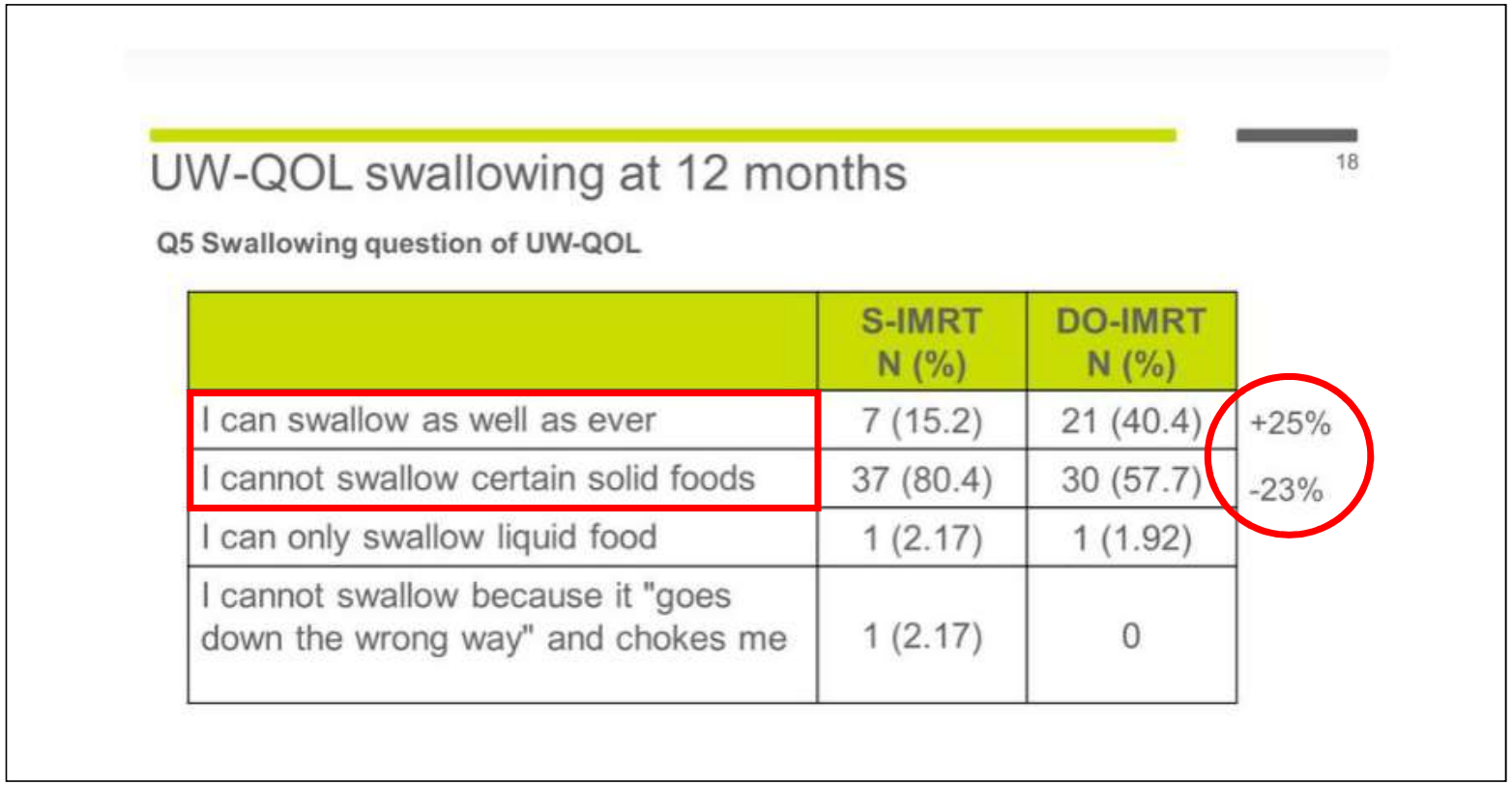
Dysphagia-Optimised IMRT





- The volume of the superior & middle pharyngeal constrictor muscle (PCM) or inferior PCM **lying outside the high-dose clinical target volume (CTV65)** was set a mandatory mean dose constraint (<50 Gy) in DO-IMRT

DARS



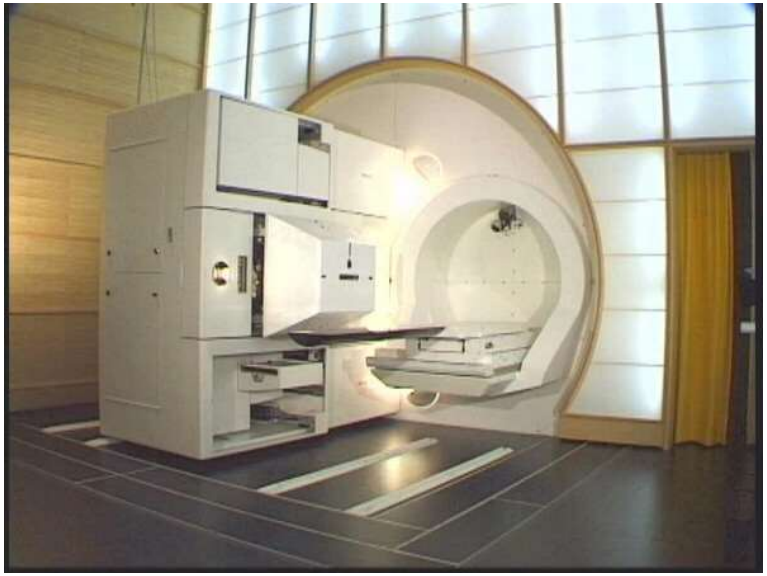
UW-QOL swallowing at 12 months

Q5 Swallowing question of UW-QOL

	S-IMRT N (%)	DO-IMRT N (%)	
I can swallow as well as ever	7 (15.2)	21 (40.4)	+25%
I cannot swallow certain solid foods	37 (80.4)	30 (57.7)	-23%
I can only swallow liquid food	1 (2.17)	1 (1.92)	
I cannot swallow because it "goes down the wrong way" and chokes me	1 (2.17)	0	

Quand l’IMRT ne suffit pas….

- Paul Scherrer Institute, Villigen



Some proton / IMXT comparisons - 4. maxillary sinus

MGH

3 Target Volumes

Gross volume: 76Gy

Subclinical: 66Gy

Microscopic: 54Gy

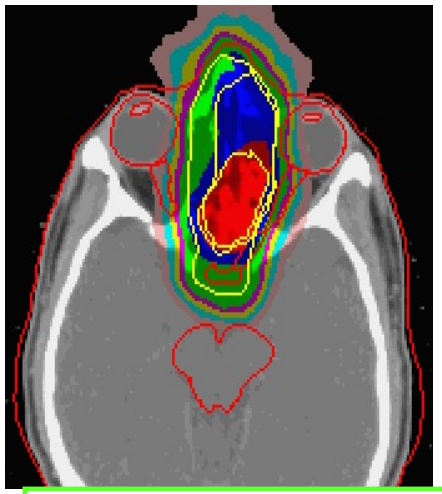
Nominal constraints

Optic nerves < 56Gy

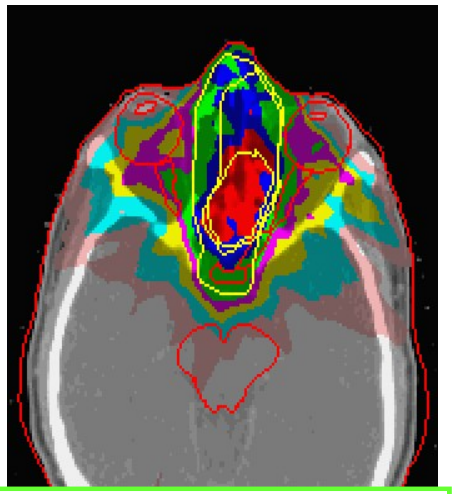
Brainstem < 53Gy

Eyes < 50Gy

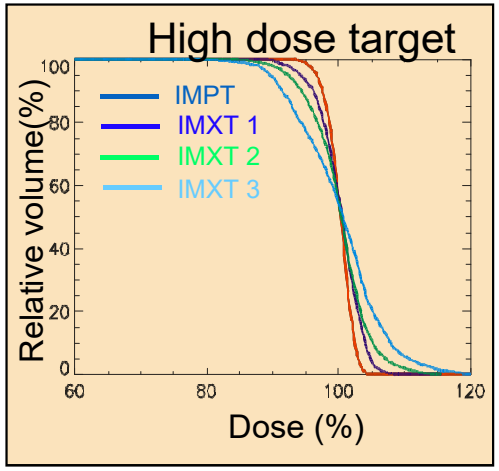
Nominal IMPT

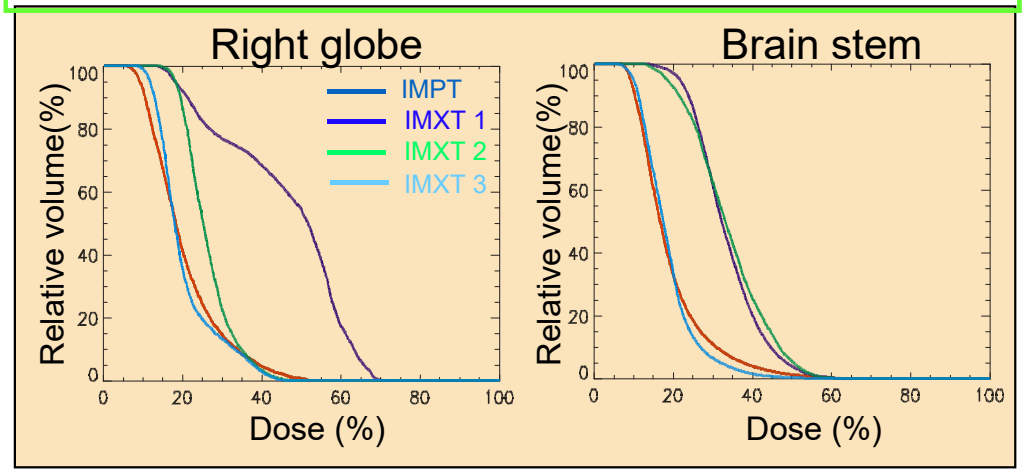


Nominal IMXT



Loss of dose homogeneity and conformity to target volumes





L’immunothérapie dans les cancers ORL?

Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy

Andrew B Sharabi, Michael Lim, Theodore L DeWeese, Charles G Drake

Lancet Oncology 2015; 16: e498-509

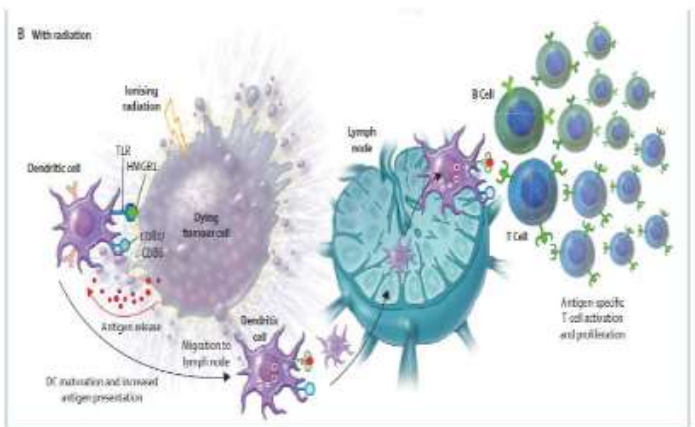


Figure 2: Radiation enhances cross-presentation of tumour antigens
(A) In the absence of danger signals, tumour antigen presentation is restricted or tolerogenic. (B) Radiation-induced danger signals enhance dendritic cell-mediated antigen presentation, resulting in activation and proliferation of tumour-specific CD8 T cells. TLR=Toll like receptor.

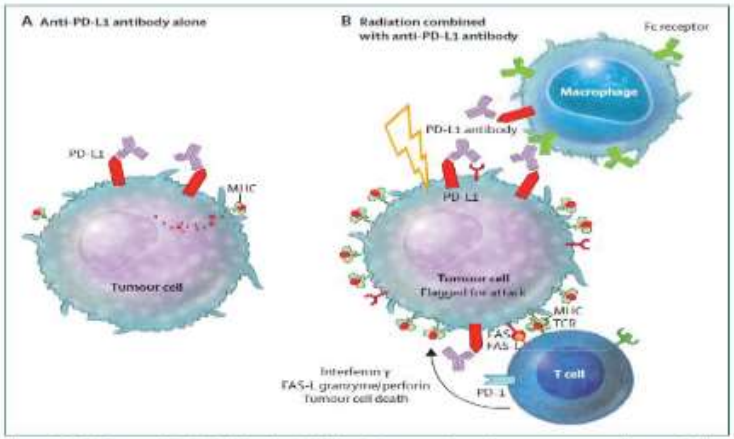
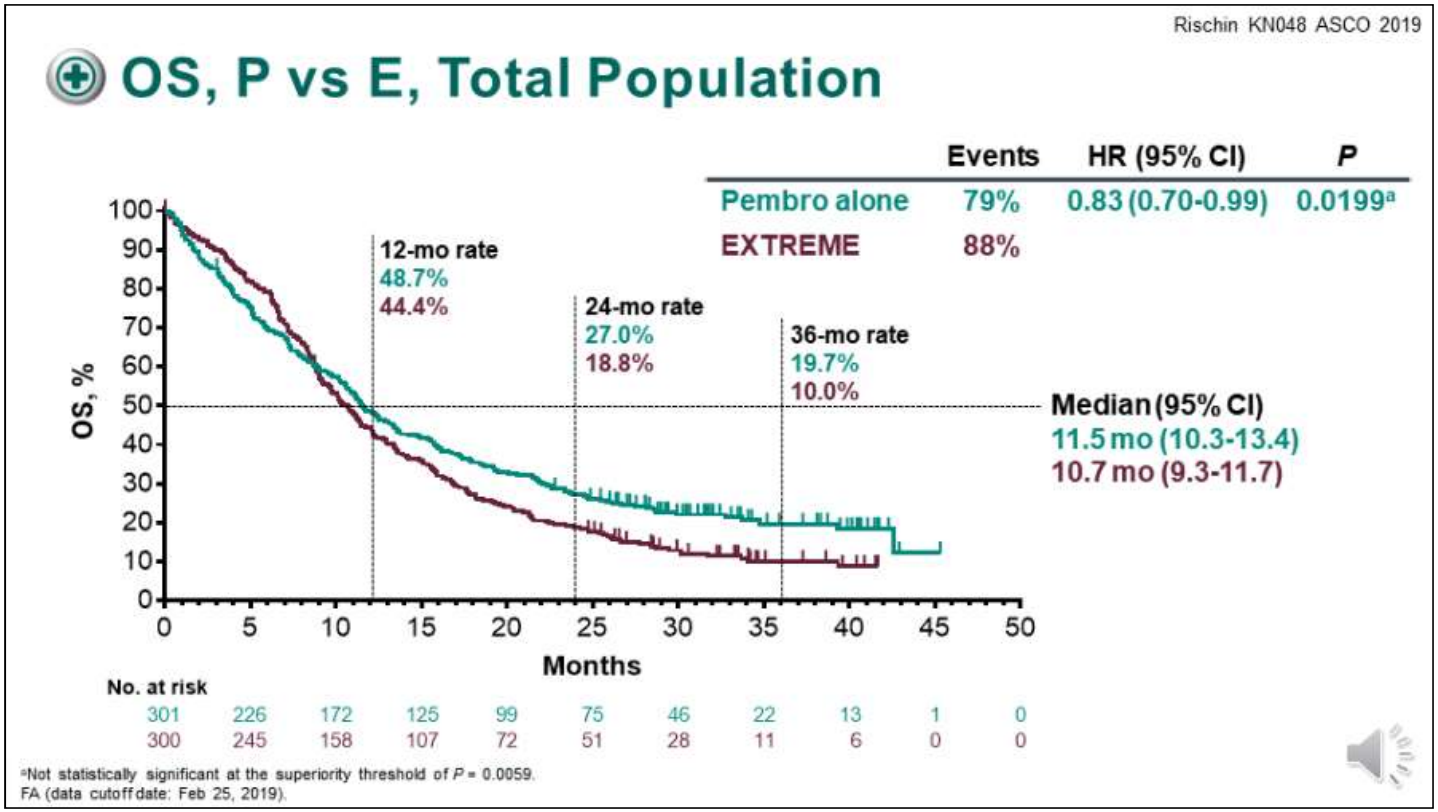


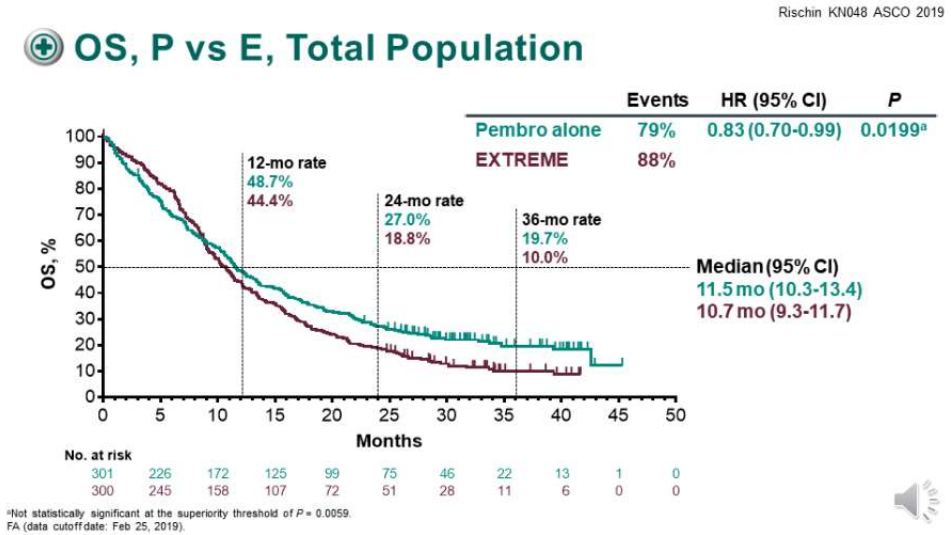
Figure 3: Radiation combined with checkpoint blockade immunotherapy increases tumour cell susceptibility to immune-mediated cell death
(A) Anti-PD-L1 alone is not predominantly cytotoxic. (B) Radiation combined with anti-PD-L1 upregulates MHC and FAS on tumour cells, increasing susceptibility to T-cell-mediated cytotoxicity. TCR=T-cell receptor.

KEYNOTE-048 pour patients métastatiques



Etude KEYNOTE-048

- A établi l'immunothérapie par pembrolizumab (Keytruda®) seul comme <u>nouveau standard en 1ère ligne métastatique</u>



Etude JAVELIN 100 et autres

- Données négatives, <u>aucun bénéfice de l'association immunothérapie et RT en situation curative</u>
- La chimiothérapie concomitante de cisplatine reste le standard
- Beaucoup de questions soulevées par ces résultats…