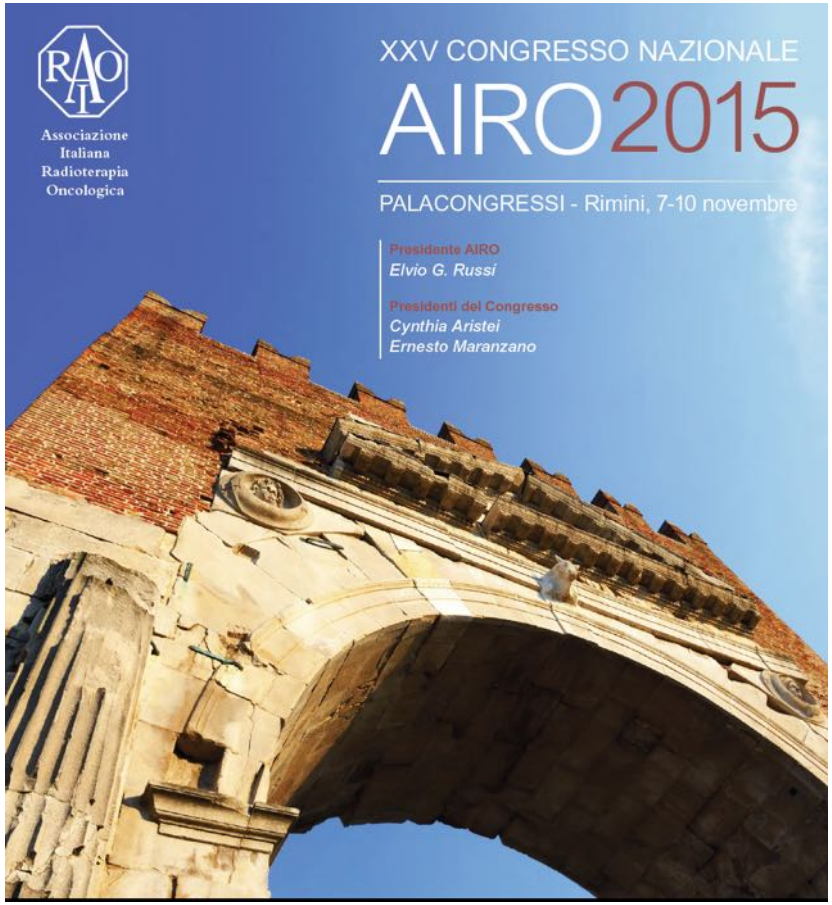



# Grandangolo in Radioterapia Oncologica:

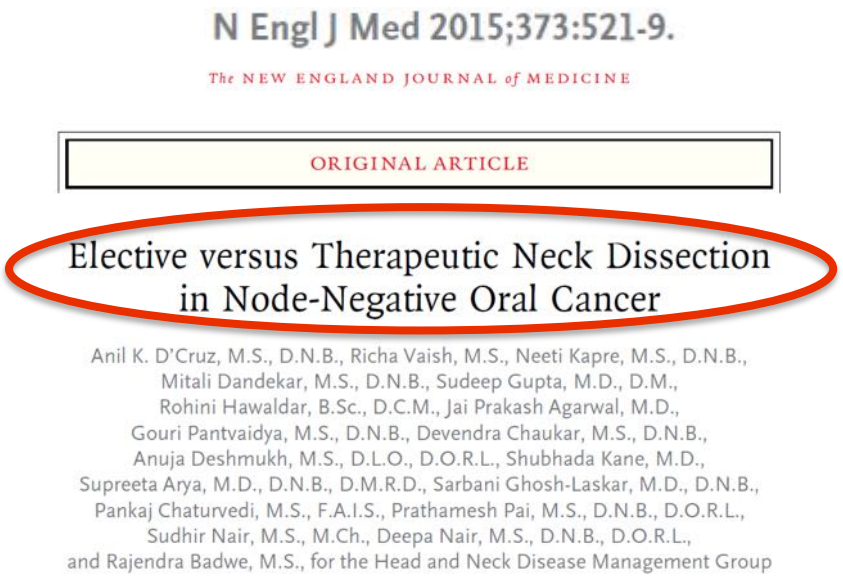
# Tumori Cervico-Facciali
# Sarcomi

**Marco Krengli**

**Università del Piemonte Orientale**
**AOU Maggiore della Carità**
**Novara**

# Tumori cervico-facciali

- Neck dissection
- Fractionation
- Induction chemotherapy
- Organ Preservation
- Target Therapy
- HPV e deintensification
- Nasopharynx
- Protons / ions


N Engl J Med 2015;373:521-9.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer

Anil K. D'Cruz, M.S., D.N.B., Richa Vaish, M.S., Neeti Kapre, M.S., D.N.B., Mitali Dandekar, M.S., D.N.B., Sudeep Gupta, M.D., D.M., Rohini Hawaldar, B.Sc., D.C.M., Jai Prakash Agarwal, M.D., Gouri Pantvaidya, M.S., D.N.B., Devendra Chaukar, M.S., D.N.B., Anuja Deshmukh, M.S., D.L.O., D.O.R.L., Shubhada Kane, M.D., Supreeta Arya, M.D., D.N.B., D.M.R.D., Sarbani Ghosh-Laskar, M.D., D.N.B., Pankaj Chaturvedi, M.S., F.A.I.S., Prathamesh Pai, M.S., D.N.B., D.O.R.L., Sudhir Nair, M.S., M.Ch., Deepa Nair, M.S., D.N.B., D.O.R.L., and Rajendra Badwe, M.S., for the Head and Neck Disease Management Group

**ASCO 2015:**

- High quality phase III surgical study
- Unequivocal results :
  - Increase of OS and DFS after elective neck dissection
  - Reduction by 36% of the risk of death after elective neck dissection
- Change of clinical practice :

elective neck dissection become the standard of treatment

# **Neck dissection** before or after RCT in N+ patients *versus* neck dissection **based on PET findings** after RCT

| Complications | Planned neck dissection | | | Follow-up (PET) |
|---|---|---|---|---|
| | Before RCT | After RCT | Total | Total |
| N. of complications | 35 | 134 | *169 | *113 |
| N. of patients with at least 1 complication | 25 | 87 | 112 | 89 |
| % of patients with at least 1 complication | 32,5% | 42,4% | 39,7% | 37,6% |

*p=0,001

## Conclusions

- Survival rates are identical in the two arms with less complications in the follow-up arm (PET)
- PET-guided follow-up is not detrimental and becomes the standard

**Hi.M. Mehanna, et al., ASCO 2015, CSS 6009**

Radiotherapy and Oncology 117 (2015) 99–105

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

# Mature results from a Swedish comparison study of conventional versus accelerated radiotherapy in head and neck squamous cell carcinoma – The ARTSCAN trial

Björn Zackrisson[a,*], Elisabeth Kjellén[b], Karin Söderström[a], Eva Brun[b], Jan Nyman[c], Signe Friesland[d], Johan Reizenstein[e], Helena Sjödin[d], Lars Ekberg[b], Britta Lödén[f], Lars Franzén[a], Anders Ask[b], Gun Wickart-Johansson[d], Freddi Lewin[g], Thomas Björk-Eriksson[c], Erik Lundin[e], Tina Dalianis[h], Johan Wennerberg[i], Karl-Axel Johansson[j], Per Nilsson[b]

- November 1998 – June 2006,
- 650 pts, 83% stadio III-IV
- 2 Gy/day, 7 wks, 68 Gy vs.
  1.1 Gy + 2Gy/day, 4.5 wks, 68 Gy

## Conclusions:

- **No significant difference between the two arms**
- A trend for AF in oral cancer patients should be further investigated
- A larger cohort could allow to highlight some difference

Radiotherapy and Oncology 117 (2015) 91–98

Contents lists available at ScienceDirect

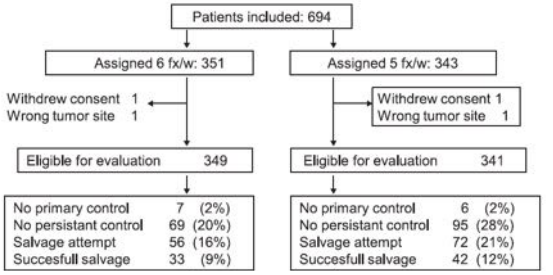
Radiotherapy and Oncology

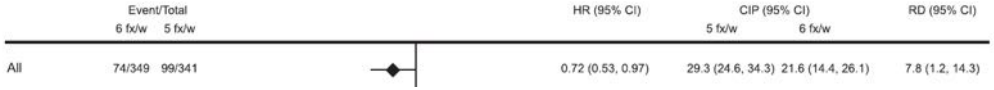
journal homepage: www.thegreenjournal.com

Phase III randomised trial

# The DAHANCA 6 randomized trial: Effect of 6 vs 5 weekly fractions of radiotherapy in patients with glottic squamous cell carcinoma ☆

Nina M. Lyhne [a,*], Hanne Primdahl [b], Claus A. Kristensen [c], Elo Andersen [d], Jørgen Johansen [e], Lisbeth J. Andersen [f], Jan Evensen [g], Hanna R. Mortensen [a], Jens Overgaard [a]

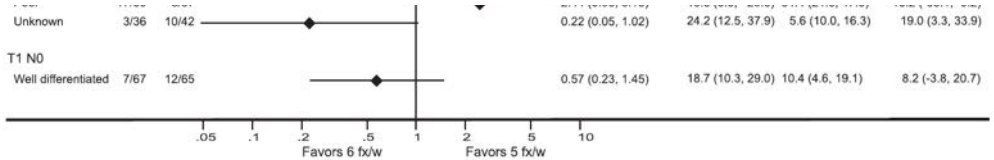


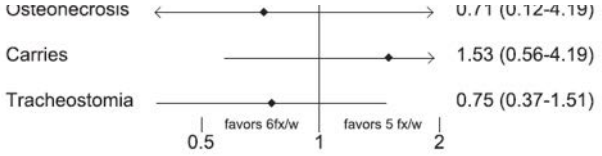




- January 1992 – December 1999
- T1-T2: 86%
- TD: 62-68 Gy in 5 vs. 6 days/wk

## Conclusions:

## Advantage for the 6 days schedule



Int J Radiation Oncol Biol Phys, Vol. 91, No. 5, pp. 916–924, 2015

**Hyperfractionated Accelerated Radiation Therapy (HART) of 70.6 Gy With Concurrent 5-FU/ Mitomycin C Is Superior to HART of 77.6 Gy Alone in Locally Advanced Head and Neck Cancer: Long-term Results of the ARO 95-06 Randomized Phase III Trial**

Volker Budach, MD,* Carmen Stromberger, MD,* Christoph Poettgen, MD,† Michael Baumann, MD,‡ Wilfried Budach, MD,§ Gerhard Grabenbauer, MD,|| Simone Marnitz, MD,* Heidi Olze, MD,¶ Klaus-Dieter Wernecke, PhD,# and Pirus Ghadjar, MD*

- March 1995 – June 1999,
- 384 pts
- 30 Gy (2 Gy/day) + 1.4 Gy bid up to 70.6Gy and MitC-5FU ***vs.*** 16 Gy (2 Gy/day) + 1.4 Gy bid up to 77.6Gy

## Conclusions:

**C-HART remains superior to HART in terms of LRC.**
**However, this effect may be limited to oropharyngeal cancer patients.**
**Acute toxicity but not late toxicity was increased .**

Clinical Oncology xxx (2015) 1–12

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

# Systematic Review and Meta-analysis of Conventionally Fractionated Concurrent Chemoradiotherapy versus Altered Fractionation Radiotherapy Alone in the Definitive Management of Locoregionally Advanced Head and Neck Squamous Cell Carcinoma

T. Gupta *†, S. Kannan †, S. Ghosh-Laskar *, J.P. Agarwal *

Only randomised controlled trials assigning HNSCC patients randomly to conventionally fractionated CCRT or AFRT alone were included.

**Conclusion:**

**There is moderate quality evidence that conventionally fractionated CCRT improves survival outcomes compared with AFRT alone in the management of locoregionally advanced HNSCC.**

**No form of acceleration can potentially compensate fully for the lack of concurrent chemotherapy.**

# Chemioterapia di Induzione

- Cohen et al, JCO, 2014: fase III, TPF pre-CRT in N2/N3 – **neg**
- Zhong et al, Oncotarget, 2015: fase III, TPF pre-CH in cavo orale – **neg**
- Marta et al, EJC, 2015: metanalisi, CT preCH +/-RT – **neg** (a parte forse cN2)

- **Zhang et al, Sci Rep, 2015: metanalisi, IC+CCRT vs. CCRT - neg**

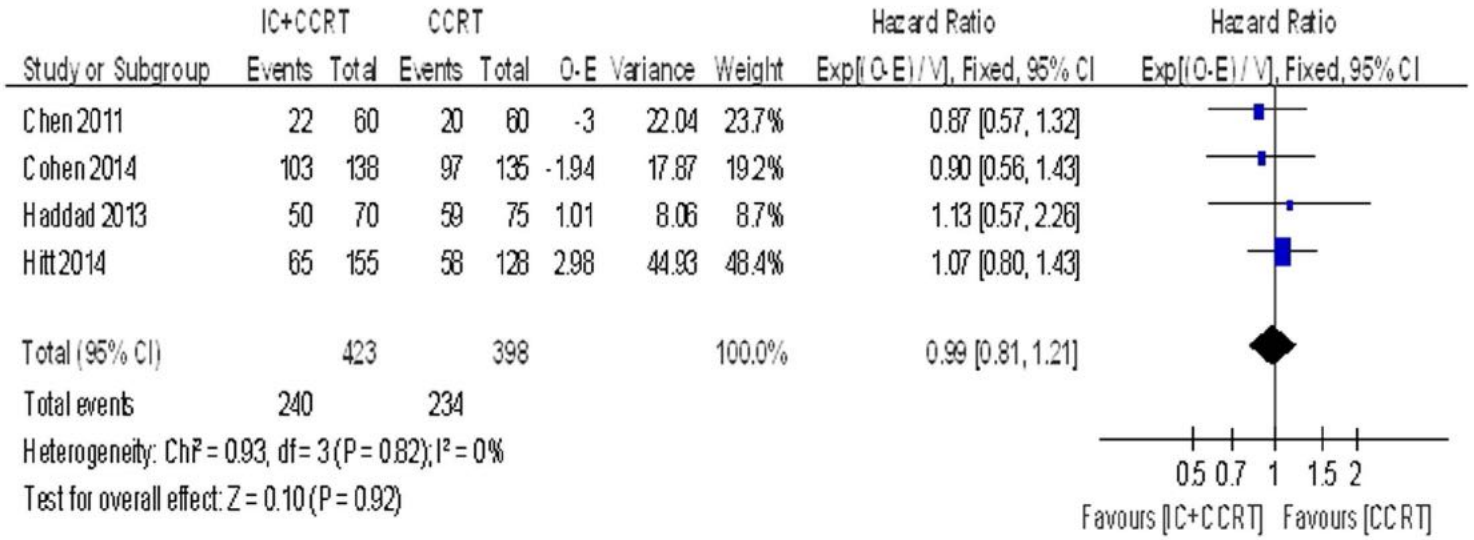



**Figure 3. Forest plots of hazard ratios (HRs) for 3-year overall survival (OS) in a fixed-effects model.**

# Preservazione d'Organo: Induzione

- **Janorary et al (GORTEC 2000-01), ASCO 2015:**

  213 pz, stadio III/IV laringe/ipofaringe

  **TPF vs. PF** seguito da RT (nei responders) aumenta la preservazione della laringe e sopravvivenza senza disfunzione laringea (67.2% a 5 aa) – ***raccomandato TPF + RT***

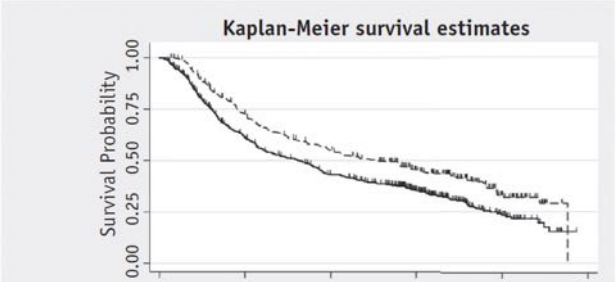
- **Mesia et al, ASCO 2015:**

  93 pz, stadio III/IVa laringe

  **TPF seguito da RT-cetuximab** (nei responders) dà alti tassi di sopravvivenza senza disfunzione laringo-esofagea (69.5% a 3aa) – ***merita fase III***

# Preservazione d'Organo: Il problema del T4 (laringe)

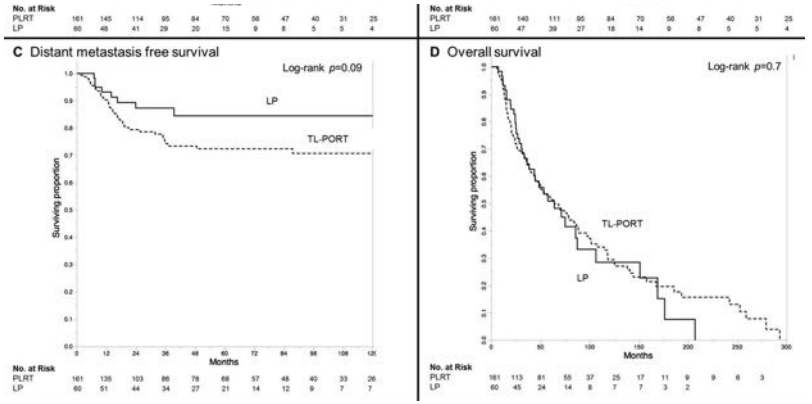
- ***Grover et al (U Penn), IJROBP 2015:***
  616 pz T4a preservazione




## T4 laringe → Chirurgia

vs.

161 pz T4 laringectomia

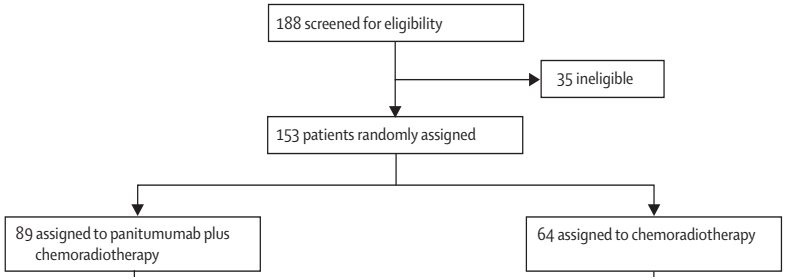


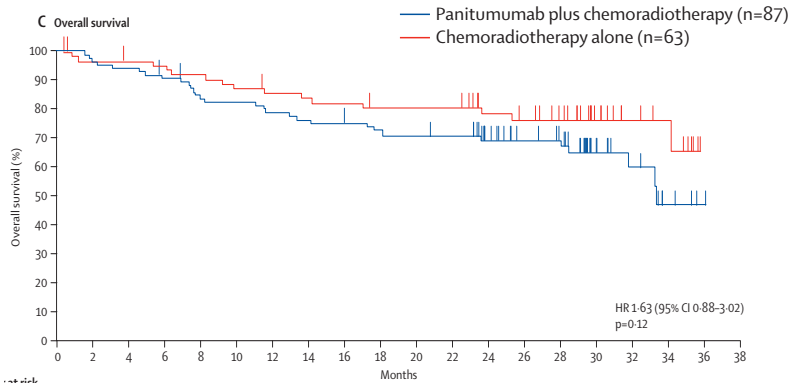
# Target Therapy: Panitumumab

*Lancet Oncol* 2015; 16: 208–20

## Chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-1): a randomised, controlled, open-label phase 2 trial

*Ricard Mesía, Michael Henke, Andre Fortin, Heikki Minn, Alejandro Cesar Yunes Ancona, Anthony Cmelak, Avi B Markowitz, Sebastien J Hotte, Simron Singh, Anthony T C Chan, Marco C Merlano, Krzysztof Skladowski, Alicia Zhang , Kelly S Oliner, Ari VanderWalde, Jordi Giralt*



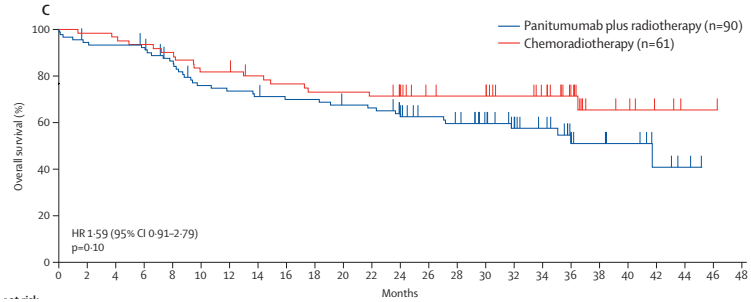



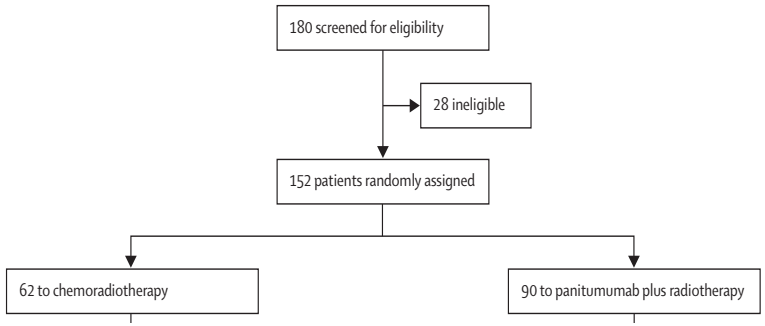

Conclusions: the addition of panitunumab to standard RT and cisplatin do not confer any benefit and has a higher toxicity

*Lancet Oncol* 2015; 16: 221–32

## Panitumumab plus radiotherapy versus chemoradiotherapy in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-2): a randomised, controlled, open-label phase 2 trial

*Jordi Giralt, Jose Trigo, Sandra Nuyts, Mahmut Ozsahin, Krzysztof Skladowski, Georges Hatoum, Jean-Francois Daisne, Alejandro César Yunes Ancona, Anthony Cmelak, Ricard Mesía, Alicia Zhang, Kelly S Oliner, Ari VanderWalde*



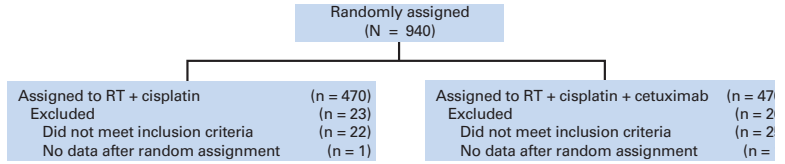

Conclusions: panitumumab cannot replace cisplatin in combined treatment with RT

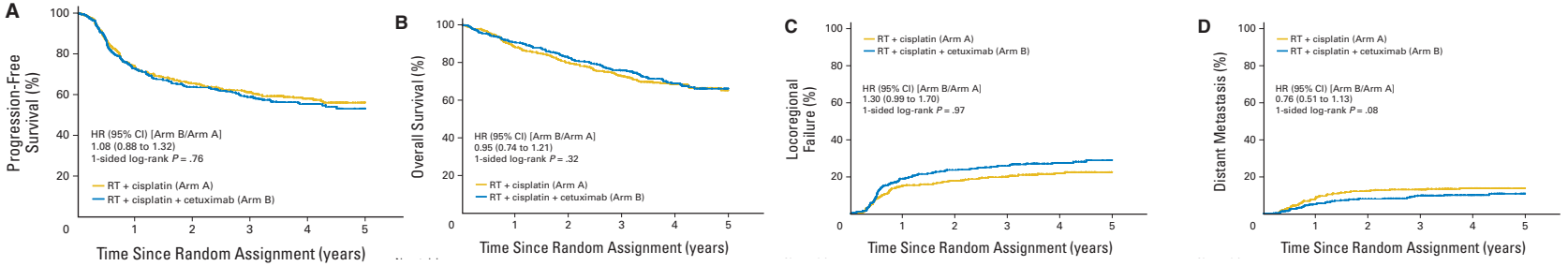
# Target Therapy: Cetuximab

VOLUME 32 · NUMBER 27 · SEPTEMBER 20 2014
JOURNAL OF CLINICAL ONCOLOGY

## Randomized Phase III Trial of Concurrent Accelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522

*K. Kian Ang,† Qiang Zhang, David I. Rosenthal, Phuc Felix Nguyen-Tan, Eric J. Sherman, Randal S. Weber, James M. Galvin, James A. Bonner, Jonathan Harris, Adel K. El-Naggar, Maura L. Gillison, Richard C. Jordan, Andre A. Konski, Wade L. Thorstad, Andy Trotti, Jonathan J. Beitler, Adam S. Garden, William J. Spanos,† Sue S. Yom, and Rita S. Axelrod*




**Conclusions: the addition of cetuximab to RT and cisplatin did not confer any benefit**

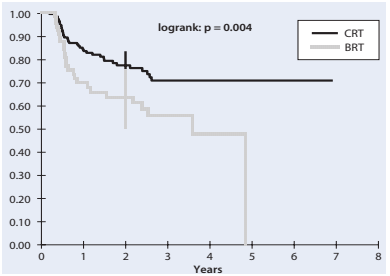
Strahlenther Onkol 2014 · 190:823–831

## Concurrent use of cisplatin or cetuximab with definitive radiotherapy for locally advanced head and neck squamous cell carcinomas

Antonin Levy[1] · Pierre Blanchard[1] · Sara Bellefqih[1] · Nacéra Brahimi[1] · Joël Guigay[2] · François Janot[3] · Stéphane Temam[3] · Jean Bourhis[1,4] · Eric Deutsch[1] Nicolas Daly-Schveitzer[1] · Yungan Tao[1]

- March 2006 – October 2012
- 597pts
- 194 CRT (Cisplatin+RT)
- 71 BRT (Cetuximab+RT)

Local Control




**Conclusions: better LRC and DC were observed in patients receiving CRT as compared with those receiving BRT**

**Postoperative Adjuvant Lapatinib and Concurrent Chemoradiotherapy Followed by Maintenance Lapatinib Monotherapy in High-Risk Patients With Resected Squamous Cell Carcinoma of the Head and Neck: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study**

Kevin Harrington, Stephane Temam, Hisham Mehanna, Anil D'Cruz, Minish Jain, Ida D'Onofrio, Georgy Manikhas, Zsuzsanna Horvath, Yan Sun, Stefan Dietzsch, Pavol Dubinsky, Petra Holeckova, Iman El-Hariry, Natalie Franklin, Nigel Biswas-Baldwin, Philippe Legenne, Paul Wissel, Thelma Netherway, John Farrell, Catherine Ellis, Jing Wang-Silvanto, Mayur Amonkar, Nazma Ahmed, Sergio Santillana and Jean Bourhis

Volume 33, Issue 31 -November 1, 2015


## CONCLUSION:

**Addition of lapatinib to chemoradiotherapy and its use as long-term maintenance therapy does not offer any efficacy benefits and had additional toxicity compared with placebo in patients with surgically treated high-risk SCCHN.**

JOURNAL OF CLINICAL ONCOLOGY J Clin Oncol 33. © 2015

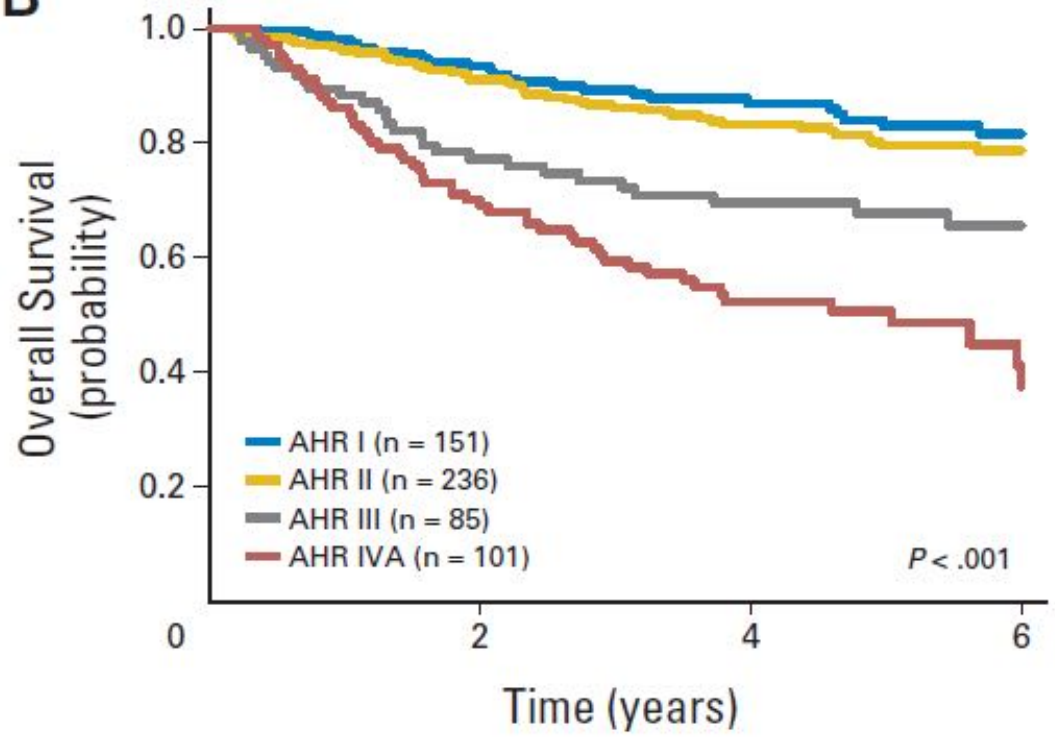
# Refining American Joint Committee on Cancer/Union for International Cancer Control TNM Stage and Prognostic Groups for Human Papillomavirus–Related Oropharyngeal Carcinomas

*Shao Hui Huang, Wei Xu, John Waldron, Lillian Siu, Xiaowei Shen, Li Tong, Jolie Ringash, Andrew Bayley, John Kim, Andrew Hope, John Cho, Meredith Giuliani, Aaron Hansen, Jonathan Irish, Ralph Gilbert, Patrick Gullane, Bayardo Perez-Ordonez, Ilan Weinreb, Fei-Fei Liu, and Brian O'Sullivan*

**HPV +**

**Alternative stage grouping on adjusted for age, smoking and treatment.**
**OS for alternative stage grouping (A); grid for alternative stage grouping (B)**

B




C

| AHR stage | T1 | T2 | T3 | T4 |
|---|---|---|---|---|
| N0 | I | I | II | III |
| N1 | I | I | II | III |
| N2a | I | I | II | III |
| N2b | I | II | II | IVA |
| N2c | II | II | III | IVA |
| N3 | III | III | IVA | IVA |

# HPV + e deintensificazione

THE AMERICAN JOURNAL OF HEMATOLOGY/ONCOLOGY MAY 2015

## Treatment De-Intensification for Locally Advanced HPV-Associated Oropharyngeal Cancer

Charles E. Rutter, MD, Zain A. Husain, MD, and Barbara Burtness, MD

**RTOG 1333 trial**: a randomized Phase II Trial for Patients With p16 Positive, Non-smoking Associated, Locoregionally Advanced Oropharyngeal Cancer ⇒ RT alone VS RT plus cisplatin in non/light smokers

**RTOG 1016**: phase III Trial of Radiotherapy Plus Cetuximab Versus Chemoradiotherapy in HPV-Associated Oropharynx Cancer ⇒

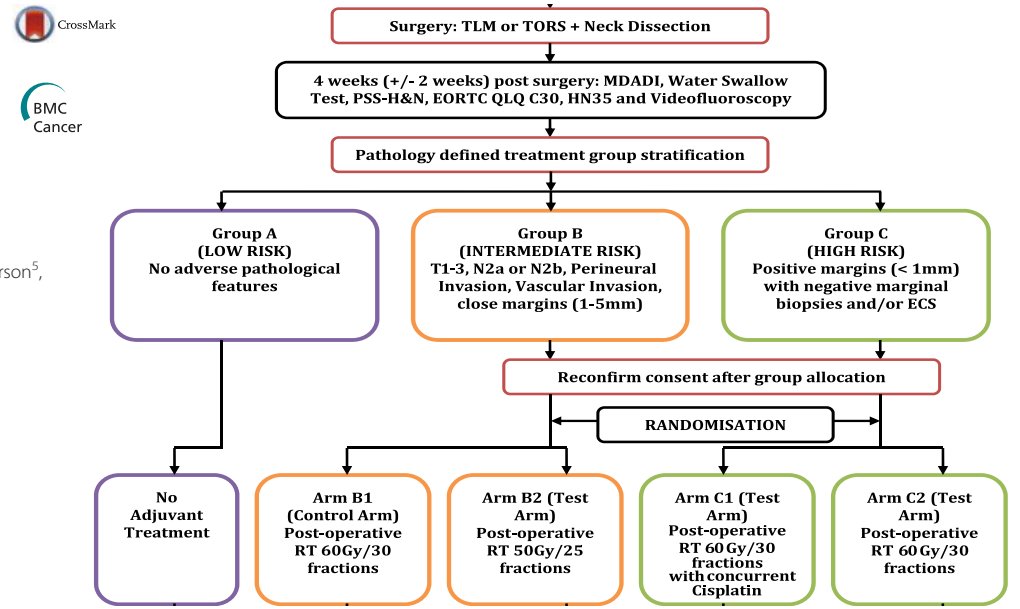
987 pts stage III/IV p16+

- IMRT 70 Gy (6 weeks) + Cetuximab
- RT (6 weeks) + CDDP 1-21 (2 doses)

*Nolan, ASTRO 2015*
***CDDP-RT better***

## PATHOS: a phase II/III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for Human papillomavirus (HPV) positive oropharyngeal cancer

Waheeda Owadally[1], Chris Hurt[2*], Hayley Timmins[2], Emma Parsons[3], Sarah Townsend[4], Joanne Patterson[5], Katherine Hutcheson[6], Ned Powell[7], Matthew Beasley[8], Nachi Palaniappan[1], Max Robinson[9], Terence M. Jones[10] and Mererid Evans[1]




**Cmelak *et al.*, ASCO 2015, PD 6021**
**TP+cetuximab + cetuximab and RT**
**TD: 69.3 Gy vs. 54 Gy**

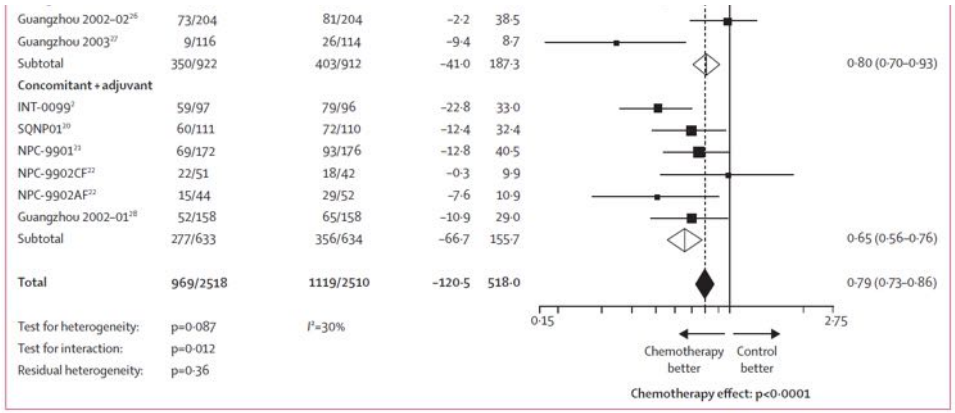
*Lancet Oncol* 2015; 16: 645–55

# Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis

*Pierre Blanchard, Anne Lee, Sophie Marguet, Julie Leclercq, Wai Tong Ng, Jun Ma, Anthony T C Chan, Pei-Yu Huang, Ellen Benhamou, Guopei Zhu, Daniel T T Chua, Yong Chen, Hai-Qiang Mai, Dora L W Kwong, Shie Lee Cheah, James Moon, Yuk Tung, Kwan-Hwa Chi, George Fountzilas, Li Zhang, Edwin Pun Hui, Tai-Xiang Lu, Jean Bourhis, Jean Pierre Pignon, on behalf of the MAC-NPC Collaborative Group**

19 trials, 4806 pz, (prec. MAC-NPC: 8 trials, 1753 pz), F/U mediano 7.7 aa


## RT-CT concomitante migliora significativamente la sopravvivenza



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*Pierre Blanchard, Anne Lee, Sophie Marguet, Julie Leclercq, Wai Tong Ng, Jun Ma, Anthony T C Chan, Pei-Yu Huang, Ellen Benhamou, Guopei Zhu, Daniel T T Chua, Yong Chen, Hai-Qiang Mai, Dora L W Kwong, Shie Lee Cheah, James Moon, Yuk Tung, Kwan-Hwa Chi, George Fountzilas, Li Zhang, Edwin Pun Hui, Tai-Xiang Lu, Jean Bourhis, Jean Pierre Pignon, on behalf of the MAC-NPC Collaborative Group**

- **Il beneficio della chemioterapia sulla OS è stato maggiore per i pazienti più anziani (>50 aa) con stadi avanzati.**
- **Chemioterapia concomitante associata ad adiuvante è stata associata a maggiore tossicità acuta.**
- **Fra le tossicità tardive solo deficit dei nervi cranici e uditivo sono stati aumentati dalla chemioterapia.**

- ***Studio randomizzato (Ng et al. ASTRO 2015) in T2N0 e T1N1 non dimostra vantaggio per CT-RT rispetto a RT (IMRT)***

# Meta-analysis on Sinonasal Tumors

*Lancet Oncol* 2014; 15: 1027–38

**Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis**

*Samir H Patel, Zhen Wang, William W Wong, Mohammad Hassan Murad, Courtney R Buckey, Khaled Mohammed, Fares Alahdab, Osama Altayar, Mohammed Nabhan, Steven E Schild, Robert L Foote*

## Conclusions:

**Charged particle therapy might be associated with better outcomes for malignant diseases of the nasal cavity and paranasal sinuses. Prospective studies are strongly encouraged.**

# Take home…

- **“Neck dissection”:** sì in cavo orale N0; sì in base a PET in F/U
- **Iperfrazionamento accelerato:** positivo per ca. glottico T1-2
- **Chemioterapia di induzione:** non dà vantaggi
- **Preservazione d’organo:** utile TPF di induzione; no T4,
- **Target Therapy:** risultati deludenti
- **HPV e deintensificazione:** nuova classificazione; studi in corso
- **Rinofaringe:** chemioterapia concomitante a RT (in stadi avanzati)
- **Protoni / ioni:** attesi ampi studi clinici con dati più solidi

# Sarcomi

- Estremità : tecnica di RT
  riduzione dei volumi di RT
  RT: preop o postop
- Retroperitoneo: linee guida per “contouring”
  RT preoperatoria
  IORT
- Cordoma sacrale: Ioni carbonio

VOLUME 32 · NUMBER 29 · OCTOBER 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Comparison of Local Recurrence With Conventional and Intensity-Modulated Radiation Therapy for Primary Soft-Tissue Sarcomas of the Extremity

*Michael R. Folkert, Samuel Singer, Murray F. Brennan, Deborah Kuk, Li-Xuan Qin, Wendy K. Kobayashi, Aimee M. Crago, and Kaled M. Alektiar*

A B S T R A C T

**Purpose**
The use of intensity-modulated radiation therapy (IMRT) in the treatment of soft tissue sarcoma (STS) of the extremity is increasing, but no large-scale direct comparison has been reported between conventional external-beam radiation therapy (EBRT) and IMRT.

**Methods**
Between January 1996 and December 2010, 319 consecutive adult patients with primary nonmetastatic extremity STS were treated with limb-sparing surgery and adjuvant radiotherapy (RT) at a single institution. Conventional EBRT was used in 154 patients and IMRT in 165 with similar dosing schedules. Median follow-up time for the cohort was 58 months.

**Results**
Treatment groups were comparable in terms of tumor location, histology, tumor size, depth, and use of chemotherapy. Patients treated with IMRT were older ($P = .08$), had more high-grade lesions ($P = .05$), close (< 1 mm) or positive margins ($P = .04$), preoperative radiation ($P < .001$), and nerve manipulation ($P = .04$). Median follow-up was 90 months for patients treated with conventional EBRT and 42 months for patients treated with IMRT. On multivariable analysis adjusting for patient age and tumor size, IMRT retained significance as an independent predictor of reduced LR (hazard ratio = 0.46; 95% CI, 0.24 to 0.89; $P = .02$).

**Conclusion**
Despite a preponderance of higher-risk features (especially close/positive margin) in the IMRT group, IMRT was associated with significantly reduced local recurrence compared with conventional EBRT for primary STS of the extremity.

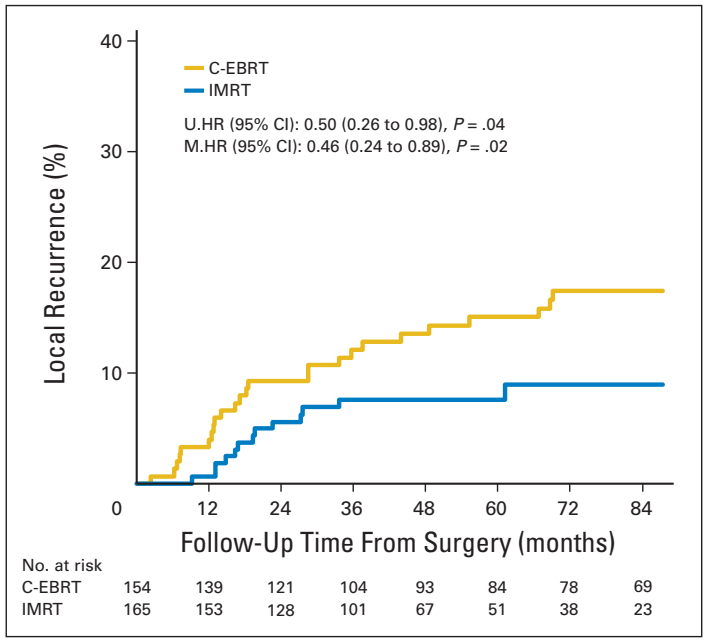


**Fig 2.** Cumulative incidence curve for local recurrence by radiation treatment group. C-EBRT, conventional external-beam radiation therapy; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; M, multivariable; U, univariable.

- **January 1996 to December 2010**
- **319 patients,**
  **EBRT in 154 and IMRT in 165**

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial

*Dian Wang, Qiang Zhang, Burton L. Eisenberg, John M. Kane, X. Allen Li, David Lucas, Ivy A. Petersen, Thomas F. DeLaney, Carolyn R. Freeman, Steven E. Finkelstein, Ying J. Hitchcock, Manpreet Bedi, Anurag K. Singh, George Dundas, and David G. Kirsch*

**VORTEX**: Randomised trial of volume of post-operative radiotherapy given to adult patients with extremity soft tissue sarcoma

**Aims/Objectives:** The aim of this trial is to assess if a reduced volume of post-operative radiotherapy increases limb function without compromising local control

**Outcomes:**
**Primary:** Limb functionality and time to local recurrence
**Secondary**: Soft tissue and bone toxicity, disease free-survival, overall survival time and overall level of disability

# Pre or Postoperative RT in Extremity Sarcoma?

Journal of Surgical Oncology 2015;111:133–134

EDITORIAL

**Individualizing the Use/Non-Use of Radiation Therapy (RT) in Soft Tissue Sarcoma (STS): When Abstention Is Better Than Care**

ALESSANDRO GRONCHI, MD*
*Sarcoma Service, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Pre-operative RT was shown to be associated to less long-term side effects. Although no differences in the overall local control rate between pre- or post-operative RT, an uncontrolled retrospective evidence favors the use of preoperative RT (alone or in combination with chemotherapy) whenever surgery is expected to be marginal and/or the tumor has a high risk of relapse.

Consensus opinion

| Case summary | Clinician (number responded) | First treatment of choice | | |
|---|---|---|---|---|
| | | Preoperative radiotherapy | Surgery | Other |
| 70 year old lady, de-differentiated liposarcoma thigh, close to neurovascular bundle | Surgeon (9) | 4 | 5 | 0 |
| | Oncologist (17) | 12 | 5 | 0 |
| 40 year old male, myxoid liposarcoma thigh | Surgeon (8) | 6 | 2 | 0 |
| | Oncologist (16) | 12 | 4 | 0 |
| 59 year old lady, grade 2 spindle cell sarcoma thigh, close to neurovascular bundle | Surgeon (8) | 4 | 4 | 0 |
| | Oncologist (16) | 12 | 3 | 1 |
| 69 year old lady, liposarcoma grade 1 posterior thigh, encasing sciatic nerve | Surgeon (10) | 4 | 4 | 2 |
| | Oncologist (17) | 11 | 6 | 0 |

# Treatment Guidelines for Preoperative RT for Retroperitoneal Sarcoma

**Target volumes if 4D motion is assessed (recommended for all upper abdominal tumors)**
iGTV: contour GTV incorporating 4D motion; this accounts for internal margin (IM)
ITV = iGTV + 1.5 cm (CTV expansion) for upper abdominal tumors
Edit ITV at interfaces:
Retroperitoneal compartment, bone, kidney, liver: 0 mm
Bowel and air cavity: 5 mm
Under skin surface: 3-5 mm according to institutional preference
If tumor extends to inguinal canal, expand iGTV by 3 cm inferiorly
PTV = ITV + 5 mm (if frequent IGRT with volumetric imaging will be performed)
PTV = ITV + 9-12 mm (if no IGRT with volumetric imaging will be performed)

**Target volumes if 4D motion is NOT assessed and tumor has a significant component below the pelvic brim**
GTV: contour gross tumor volume
CTV = GTV + 1.5 cm for tumors below pelvic brim
Edit CTV at interfaces:
Retroperitoneal compartment, bone, kidney, liver: 0 mm
Bowel and air cavity: 5 mm
Under skin surface: 3-5 mm according to institutional preference
If tumor extends to inguinal canal, expand GTV by 3 cm inferiorly
PTV = CTV + 5 mm (if frequent IGRT with volumetric imaging will be performed)
PTV = CTV + 9-12 mm (if no IGRT with volumetric imaging will be performed)

**Target volumes if 4D motion is NOT assessed and tumor is in the upper abdomen (Note: 4D motion assessment is strongly recommended in this situation)**
GTV: contour gross tumor volume
CTV = GTV + 2-2.5 cm in cephalocaudal directions, 1.5-2 cm in radial directions
Edit CTV at interfaces:
Retroperitoneal compartment, bone, kidney, liver: 0 mm
Bowel and air cavity: 5 mm
Under skin surface: 3-5 mm according to institutional preference
If tumor extends to inguinal canal, expand GTV by 3 cm inferiorly
PTV = CTV + 5 mm (if frequent IGRT with volumetric imaging will be performed)
PTV = CTV + 9-12 mm (if no IGRT with volumetric imaging will be performed)

**Dose:**
50.4 Gy in 1.8 Gy fractions or 50 Gy in 2 Gy fractions

**Technique:**
IMRT preferred unless organ at risk dose constraints and target volume coverage can be achieved with a 3D-conformal technique.
Proton therapy is also acceptable in experienced centers.

Int J Radiation Oncol Biol Phys, Vol. 92, No. 3, pp. 602–612, 2015

Critical Review

## Treatment Guidelines for Preoperative Radiation Therapy for Retroperitoneal Sarcoma: Preliminary Consensus of an International Expert Panel

Elizabeth H. Baldini, MD, MPH,* Dian Wang, MD, PhD,† Rick L.M. Haas, MD, PhD,‡ Charles N. Catton, MD,§ Daniel J. Indelicato, MD,‖ David G. Kirsch, MD, PhD,¶ David Roberge, MD,# Kilian Salerno, MD,** Curtiland Deville, MD,†† B. Ashleigh Guadagnolo, MD, MPH,‡‡ Brian O'Sullivan, MD,§§ Ivy A. Petersen, MD,‖‖ Cecile Le Pechoux, MD, PhD,¶¶ Ross A. Abrams, MD,† and Thomas F. DeLaney, MD, PhD¶¶

*Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts; †Department of Radiation Oncology, Rush University Medical Center, Chicago, Illinois; ‡Department of Radiotherapy, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; §Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada; ‖Department of Radiation Oncology, University of Florida Medical Center, Jacksonville, Florida; ¶Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina; #Department of Radiation Oncology, Centre Hospitalier de l'Université de Montreal, Montreal, Quebec, Canada; **Department of Radiation Oncology, Roswell Park Cancer Institute, Buffalo, New York; ††Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins Sidney Kimmel Cancer Center, Washington, DC; ‡‡Department of Radiation Oncology, MD Anderson Cancer Center, Houston, Texas; §§Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; ‖‖Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France; and ¶¶Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts

# Validation of Contouring Guidelines

Int J Radiation Oncol Biol Phys, Vol. 92, No. 5, pp. 1053–1059, 2015

Clinical Investigation

## Retroperitoneal Sarcoma Target Volume and Organ at Risk Contour Delineation Agreement Among NRG Sarcoma Radiation Oncologists

**Elizabeth H. Baldini, MD, MPH,* Ross A. Abrams, MD,† Walter Bosch, DSc,‡ David Roberge, MD,§ Rick L.M. Haas, MD, PhD,‖ Charles N. Catton, MD,¶ Daniel J. Indelicato, MD,# Jeffrey R. Olsen, MD,‡ Curtiland Deville, MD,** Yen-Lin Chen, MD,†† Steven E. Finkelstein, MD,‡‡ Thomas F. DeLaney, MD, PhD,†† and Dian Wang, MD, PhD†**

***Department of Radiation Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, Massachusetts; †Department of Radiation Oncology, Rush University Medical Center, Chicago, Illinois; ‡Department of Radiation Oncology, Washington University, St. Louis, Missouri; §Department of Radiation Oncology, Centre Hospitalier de l'Universite de Montreal, Montreal, Quebec, Canada; ‖Department of Radiotherapy, Netherlands Cancer Institute, Amsterdam, The Netherlands; ¶Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada; #Department of Radiation Oncology, University of Florida Medical Center, Jacksonville, Florida; **Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania; ††Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts; ‡‡Translational Research Consortium, 21st Century Oncology, Scottsdale, Arizona***

This report showed that sarcoma radiation oncologists contoured RPS GTV, CTV, and most OARs with a high level of agreement. HR CTV contours were more variable.

**Table 1** Summary of kappa statistic agreement for RPS target and OAR volumes

| Contoured structure | Kappa agreement | |
|---|---|---|
| | RPS1 | RPS2 |
| GTV | 0.84 Almost perfect | 0.92 Almost perfect |
| CTV | 0.79 Substantial | 0.86 Almost perfect |
| HR CTV | 0.50 Moderate | 0.57 Moderate |
| Bowel bag | 0.82 Almost perfect | 0.79 Substantial |
| Small bowel | 0.73 Substantial | 0.78 Substantial |
| Colon | 0.73 Substantial | 0.82 Almost perfect |
| Stomach | 0.77 Substantial | 0.83 Almost perfect |
| Duodenum | 0.41 Moderate | 0.36 Fair |

*Abbreviations:* bowel bag = contour encompassing the contents of the peritoneal cavity to include small bowel and colon; CTV = clinical target volume; GTV = gross tumor volume; HR CTV = high-risk clinical target volume; OAR = organ at risk; RPS = retroperitoneal sarcoma.

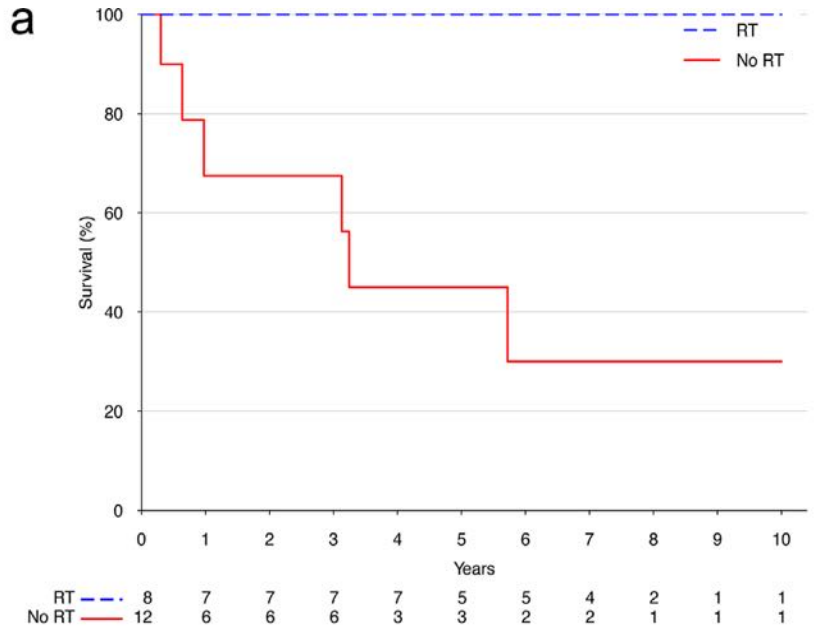
RPS1 is a patient with a right upper-quadrant de-differentiated (DD) liposarcoma (LPS) with a predominant, well-differentiated (WD) component. RPS2 is a patient with a left upper quadrant DD LPS with a minimal WD component.

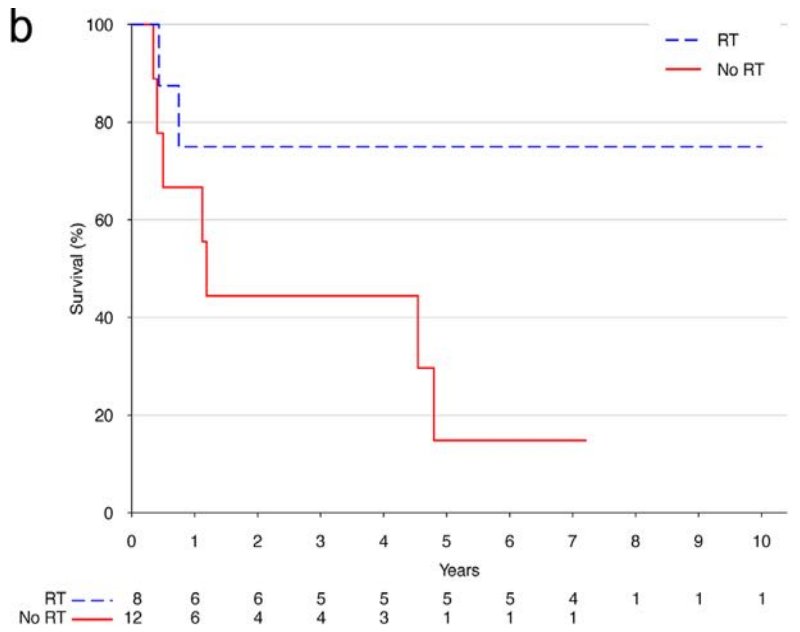
# Preoperative RT in Retroperitoneal Sarcoma?

Journal of Surgical Oncology 2015;112:352–358

## Analysis of Perioperative Radiation Therapy in the Surgical Treatment of Primary and Recurrent Retroperitoneal Sarcoma

WHITNEY O. LANE, MD,[1] CHRISTINA K. CRAMER, MD,[2] DANIEL P. NUSSBAUM, MD,[1]
PAUL J. SPEICHER, MD,[1] BRIAN C. GULACK, MD,[1] BRIAN G. CZITO, MD,[2] DAVID G. KIRSCH, MD, PhD,[1]
DOUGLAS S. TYLER, MD,[1] AND DAN G. BLAZER III, MD[1]*




| Estimate | Overall | No RT | RT | p-value |
|---|---|---|---|---|
| 1-year survival | 82.2% (65.8-100%) | 67.5% (43-100%) | 100% (100-100%) | |
| 5-year survival | 69.6% (50.4-96%) | 45% (21.8-92.7%) | 100% (100-100%) | <0.01 |

| Estimate | Overall | No RT | RT | p-value |
|---|---|---|---|---|
| 1-year survival | 70.6% (51.9-95.9%) | 66.7% (42-100%) | 75% (50.3-100%) | |
| 5-year survival | 44.1% (25.1-77.6%) | NA% (NA-NA%) | 75% (50.3-100%) | 0.05 |

Fig. 3. (a) Overall survival and (b) Recurrence-free survival in patients presenting with recurrent disease by the use of perioperative RT.

# Retroperitoneal Sarcoma: the ongoing STRASS Trial

| | |
|---|---|
| Trial No. | EORTC 62092-22092 |
| NCT No. (www.clinicaltrials.gov) | NCT01344018 |
| Trial Status | Recruiting |
| Date of activation | January 2012 |
| Estimated completion date | May 2015 |
| Phase | III |
| Randomized trial | Yes |
| Type | Adjuvant |
| Therapy/ies, treatment | Investigational arm:<br>Pre-operative radiotherapy 50.4 Gy (28 daily fractions) + large en-bloc curative-intent surgery<br>Control arm:<br>Large en-bloc curative-intent surgery alone |
| Planned no. of patients | 256 |
| Ages Eligible for Study | 18 Years and older |
| Type of cancer | Soft Tissue Sarcoma (STS) |
| Spec. subtype: | Retroperitoneal sarcoma (RPS) |
| Rationale | Radiation therapy uses high-energy x-rays to kill tumour cells. Giving radiation therapy before surgery may make the tumour smaller and reduce the amount of normal tissue that needs to be removed. It is not yet known whether surgery is more effective with or without radiation therapy in treating non metastatic retroperitoneal soft tissue sarcoma. |
| Purpose | This randomized phase III trial is studying radiation therapy followed by surgery to see how well it works compared with surgery alone in treating patients with previously untreated non metastatic retroperitoneal soft tissue sarcoma. |
| Primary Outcome Measures | Abdominal recurrence-free survival |
| Secondary Outcome Measures | - Acute toxicity profile of preoperative radiotherapy<br>- Perioperative complications<br>- Late complications<br>- Tumour response to preoperative radiotherapy<br>- Time to abdominal recurrence<br>- Metastasis-free survival<br>- Overall survival |
| Participating Groups | EORTC Soft Tissue and Bone Sarcoma Group (Coordinating Group)<br>EORTC Radiation Oncology Group |
| Participating countries | Italy, France, Germany, UK, Netherlands, Denmark, Norway, Sweden, Poland, Spain |

**Closure date: 01/09/2016**
**Recruitment: 56%**

# IORT and IMRT in Retroperitoneal Sarcoma

*BMC Cancer* 2014, **14**:617

RESEARCH ARTICLE Open Access

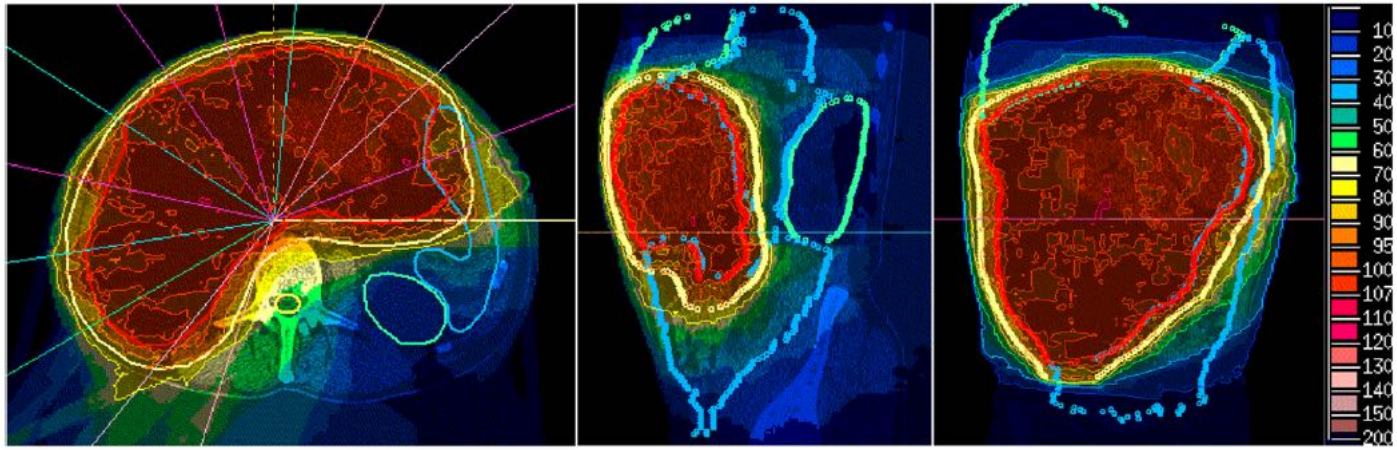
## Clinical Phase I/II trial to Investigate Preoperative Dose-Escalated Intensity-Modulated Radiation Therapy (IMRT) and Intraoperative Radiation Therapy (IORT) in patients with retroperitoneal soft tissue sarcoma: interim analysis

Falk Roeder[1,2,8*], Alexis Ulrich[3], Gregor Habl[2], Matthias Uhl[2], Ladan Saleh-Ebrahimi[1,8], Peter E Huber[1,2], Daniela Schulz-Ertner[4], Anna V Nikoghosyan[5], Ingo Alldinger[3], Robert Krempien[5], Gunhild Mechtersheimer[6], Frank W Hensley[2], Juergen Debus[1,2] and Marc Bischof[7]

- 2007 - 2013
- 27 patients
- Neoadjuvant IMRT

TD: 45-50 Gy to PTV and 50 56 Gy to GTV in 25 fxs

- Surgery
- IOERT (10 -12Gy)
- LC 72% @ 3 and 5 yrs
- PFS 40% @3 and 5 yrs



*Lancet Oncol* 2015; 16: e71–83

# Building a global consensus approach to chordoma: a position paper from the medical and patient community

*Silvia Stacchiotti, Josh Sommer, on behalf of a Chordoma global consensus group**

**En-bloc R0 resection is the recommended treatment** when feasible and sequelae are accepted by the patient. The expected 5-year relapse-free survival after R0 resection is in excess of 50% (**level of evidence IV, recommendation B**).

**If en-bloc R0 resection seems unfeasible** on the basis of location, or the patient does not accept the surgical morbidities, other options should be considered (i.e. RT). Salvage of nerve roots might be possible at the expense of a microscopically positive margin. Additionally, tumour extension into the spinal canal precludes a wide margin.

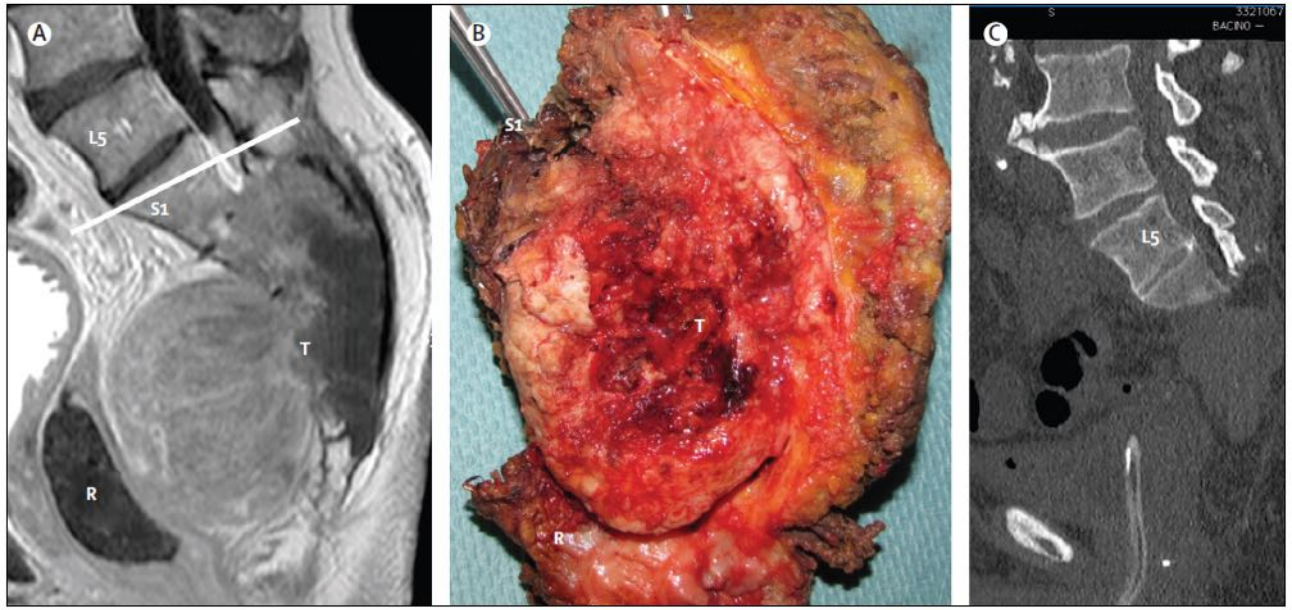
**Adjuvant radiotherapy should always be considered for skull base and cervical spine chordomas, and for sacral and mobile spine chordoma if microscopic positive margins (R1)** are noted in the final pathological examination and the tumour has not been spilled during surgery, while taking a biopsy sample, or decompression.

Moreover, **definitive radiotherapy alone (eg, without debulking) is an alternative to surgery** (**level of evidence V, recommendation C**).

For **tumours arising from S4 and below**, **surgery** should definitely be offered as the first choice to patients (**level of evidence IV, recommendation A**).

For **tumours originating from S3**, **surgery** is the standard treatment, especially if preservation of S2 roots is possible because the surgery could result in some neurological recovery (40% of the cases) (**level of evidence IV, recommendation A**).

For **tumours originating above S3**, **surgery** always results in important neurological sequelae and the chance of obtaining an R0 resection is lower compared to chordoma arising below S3. Therefore, the risks and benefits of surgery versus **radiation** alone should be discussed with the patient (**level of evidence IV, recommendation B**).



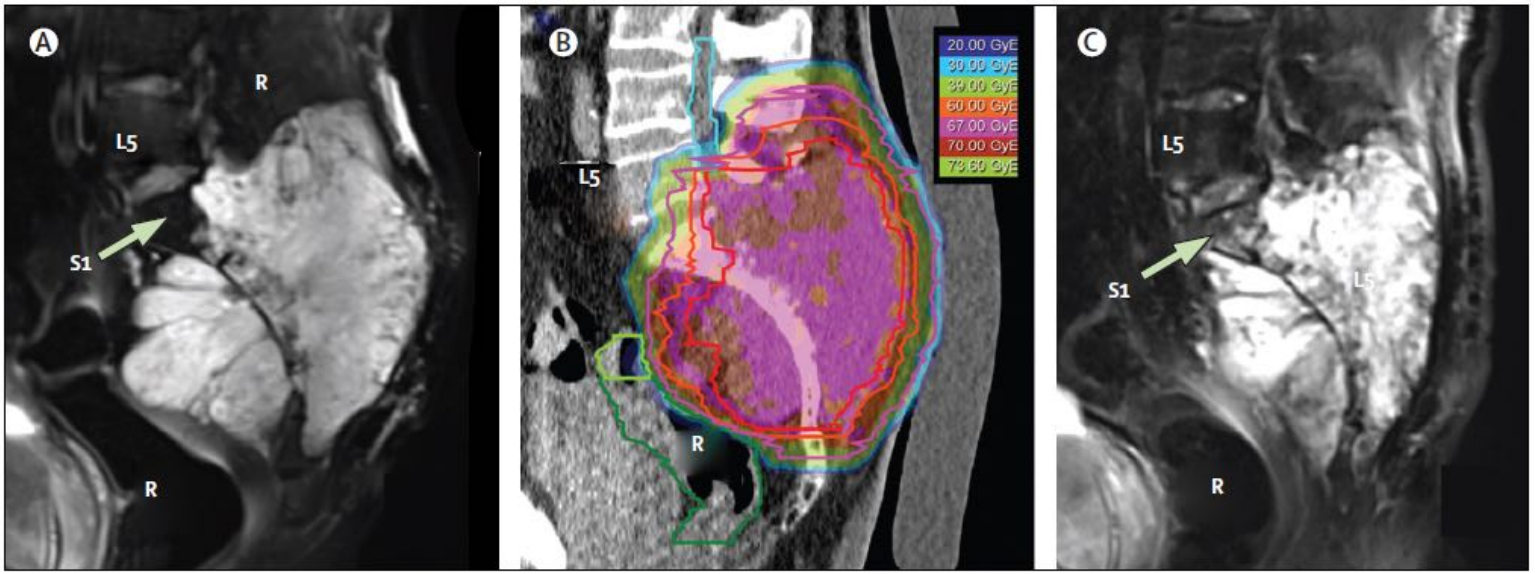
**RT Volume**

**In case of R1 resection**, **CTV2** needs to include the area of positive resection margin, as reconstructed by description of surgery and pathological changes report (**level of evidence V, recommendation A**). **After R2 resection**, **CTV2** needs to include areas of microscopic disease followed by a further cone down to **CTV3** to include visible tumours plus reduced margins (**level of evidence V, recommendation A**). **After R0 resection**, the role of a reduced volume boost on a CTV2 is still controversial (**level of evidence V, recommendation C**).

## RT Dose

In case of **macroscopic residual disease**, high-dose radiotherapy (**≥ 74 GyE**) with conventional fractionation (**photons and protons**) has to be delivered to the CTV2, and at least 50–54 GyE to the wider CTV1. In case of **R1/R0 resection**, the dose to high risk volume can be limited to **70 GyE** (**level of evidence V, recommendation A**).

In case of **macroscopic disease**, moderate hypofractionation is feasible (**3–4.4 GyE per fraction, in 22–16 fractions with carbon ions**) with the wider CTV1 receiving at least 36 GyE (**level of evidence V, recommendation A**).



# Take home…

**Sarcomi delle estremità:**

- IMRT (e IGRT) sono preferibili
- IGRT potrebbe consentire riduzione del volume (trial in corso)
- RT preoperatoria è preferibile alla postoperatoria

**Sarcomi del retroperitoneo:**

- Linee guida per contornamento
- Sarebbe preferibile la RT preoperatoria (trial in corso)
- IORT potrebbe essere utile

**Cordoma sacrale (e non solo)**

- Linee guida da Consensus Group

***Panel:*** **Level of evidence and grade of recommendation**

- I Evidence from at least one large randomised control trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomised trials without heterogeneity
- II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
- III Prospective cohort studies
- IV Retrospective cohort studies or case-control studies
- V Studies without control group, case reports, and experts' opinions
- A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
- B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
- C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (including adverse events and costs), optional
- D Moderate evidence against efficacy or for adverse outcome, generally not recommended
- E Strong evidence against efficacy or for adverse outcome, never recommended

To distinguish prospectively planned studies from retrospective case series, we assigned the level of evidence V followed by "*" to single-group prospective trials

The guidelines were adapted from the Infectious Diseases Society of America-US Public Health Service Grading System.[2]