Indicazioni e rapporto/costo benificio nell'impiego clinico della IMRT

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Definitions

IMRT is an advanced form of 3D-CRT that uses non uniform radiation beam intensities that have been determined using various computer-based optimization techniques (NCI collaborative working group, IJROBP, 2001)

IMRT in the strict sense requires each field from a given direction to be spatially modulated (Webb and Lomax 2001)

Conceptually, IMRT is closely related to *inverse treatment planning*

The inverse planning is a method by which the radiation oncologist can specify a desired — but physically realistic or deliverable — dose distribution in both the target volume and in the adjacent normal tissue.

Potential advantages of IMRT

* Improved avoidance of critical tissues
* Improved dose homogeneity

} both may allow dose escalation

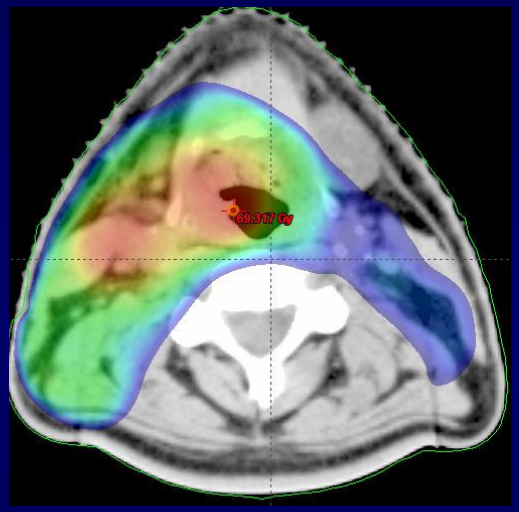
* Deliberate dose inhomogeneity

* Much greater power to put dose in certain places and avoid nearby structures

The IMRT clinical advantages

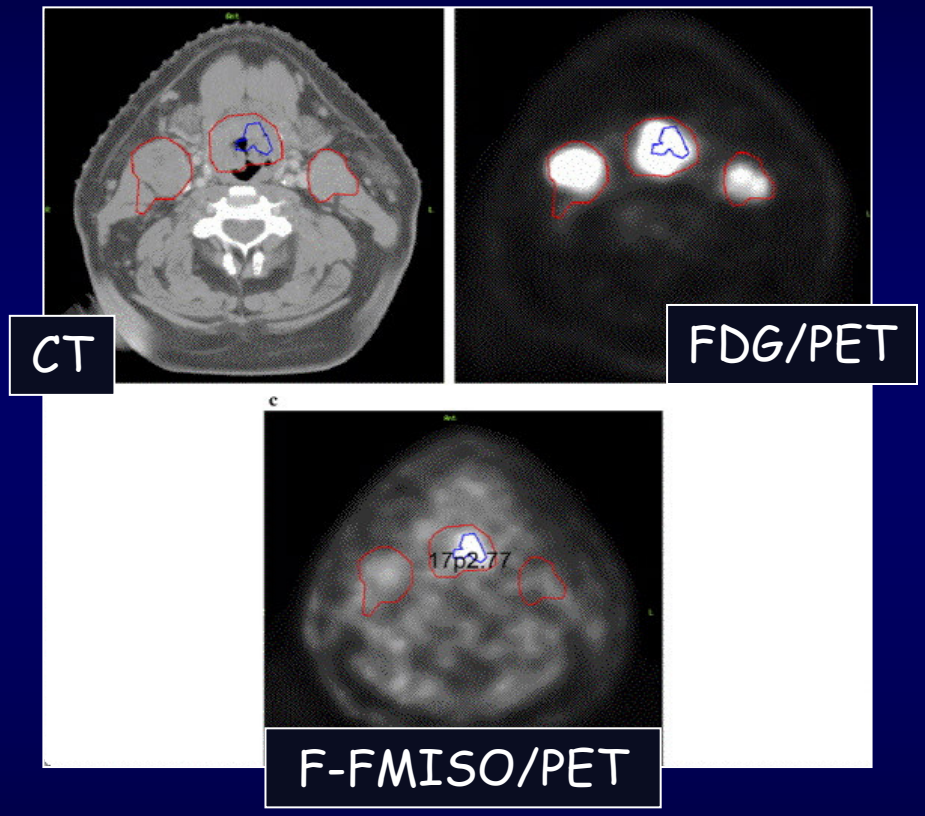
Improvements in dose distribution can:

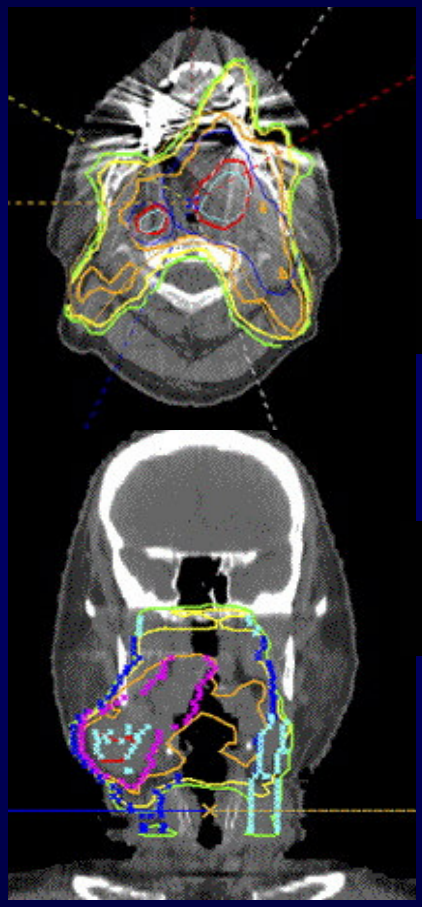
- increase local control and disease free survival, by mean of the dose escalation



- reduce early and late effects or RT
- make it possible to deliver a higher fraction size to the tumor while keeping the fraction size to the normal structures as low as possible (SIB)
- make it possible to re-treat patients who have failed locally and have been treated to the limit of tolerance with previous therapy
- make it possible the biological optimisation (Dose Painting)

Dose painting





84 Gy to hypoxic volume

105 Gy to hypoxic volume

Lee NY et al
IJROBP 2008

Potential negatives of IMRT

- Longer outlining - more resources
- Longer planning and plan checking - more resources
- (Longer delivery times - more resources and more time)
- Increased resources includes people and training

Potential negatives of IMRT

- IMRT is less tolerant of poor implementation than 'standard' techniques
- IMRT pose a *greater* risk of missing the target than traditional techniques of radiation therapy
- Misadministrations are harder to detect and may lead to worse outcomes for patients

IMRT: prescribed vs. planned dose

Das I, JNCI 2008

- Studied 803 patients at five institutions
- Treatment plans were done by experienced physicists (> 50 IMRT cases each)

IMRT: prescribed vs. planned dose

Das I, JNCI 2008

Results:

- In 46% of patients the plan delivered to **the** CTV a maximum dose more than 10% higher than prescribed by the MD (worst case: 40% higher).
- In 63% of patients the plan delivered to the CTV a minimum dose more than 10% lower than prescribed (worst case: 100% lower = zero).

IMRT is inherently an inexact art

Potential negatives of IMRT

IMRT may increase:

High dose irradiated volume (dose escalation)

↓

↑ toxicity ?

Int J Radiat On Biol Phys 2008

BEAM PATH TOXICITIES TO NON-TARGET STRUCTURES DURING INTENSITY-MODULATED RADIATION THERAPY FOR HEAD AND NECK CANCER

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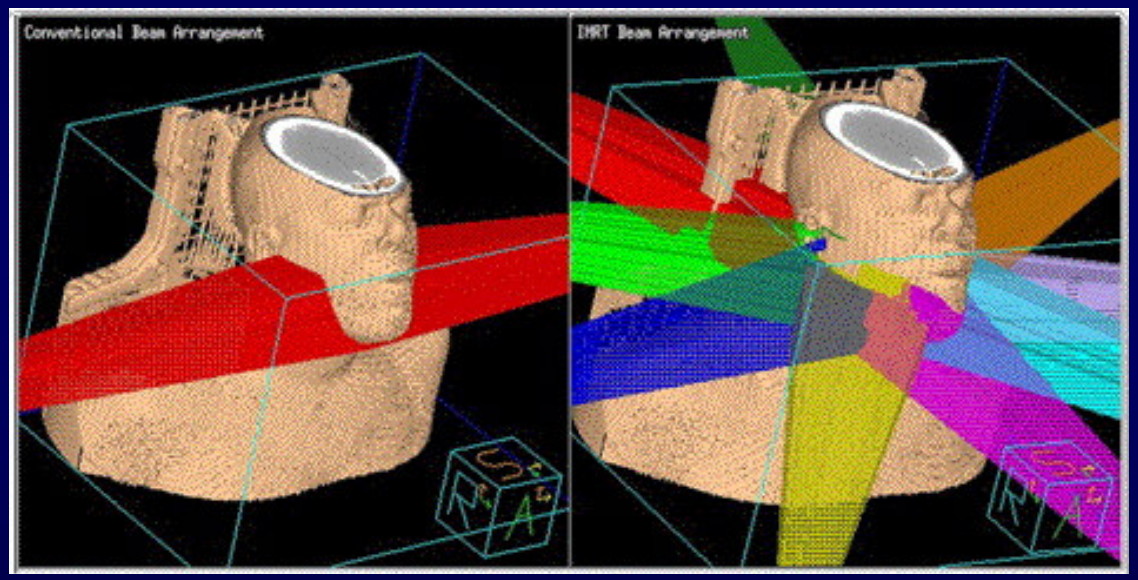
WILLIAM H. MORRISON, M.D.,* K. KIAN ANG, M.D., PH.D.,* AND ADAM S. GARDEN, M.D.*



Anterior mucositis

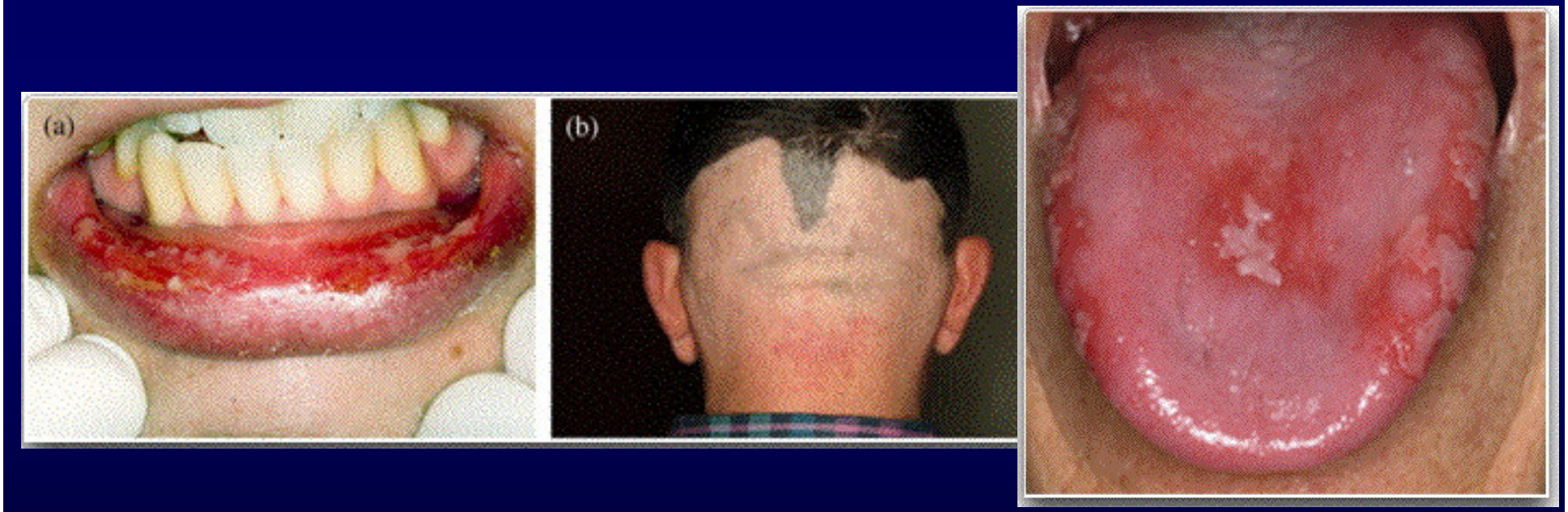
Occipital scalp alopecia

Headache

Nausea and vomiting

IMRT has solved some HNc treatment planning problems but has created others

If a structure subject to potential toxicity is not contoured and given appropriate hierarchical dose-goal rank in IMRT plans, then the dose to such normal structures and the clinical consequences may not be appreciated until toxicities develop



Rosenthal 2008

Potential negatives of IMRT

IMRT may increase:

Low dose irradiated volume (IGRT can further increase the low dose irradiation volume…)

↓

↑second cancers?

IMRT - Risk of radio-induced cancers

There are two reasons why the switch from 3DCRT to IMRT may result in an increased rate of secondary malignancies:

1. Greater # fields
2. Leakage radiation increase as consequence of the MU increase

Table 3. Estimated risk of fatal radiation-induced malignancies after RT for prostate cancer (%/Sv)

Hall and Wuu	
Conventional 6 MV	1.5
IMRT 6 MV	3.0
Kry *et al.*	
Conventional 18-MV Varian	1.7
IMRT 6-MV Varian	2.9
Siemens	3.7
IMRT 10-MV Varian	2.1
IMRT 15-MV Varian	3.4
Siemens	4.0
IMRT 18-MV Varian	5.1

x 2

Hall 2006

Evidence for IMRT

The most frequent sites studied:

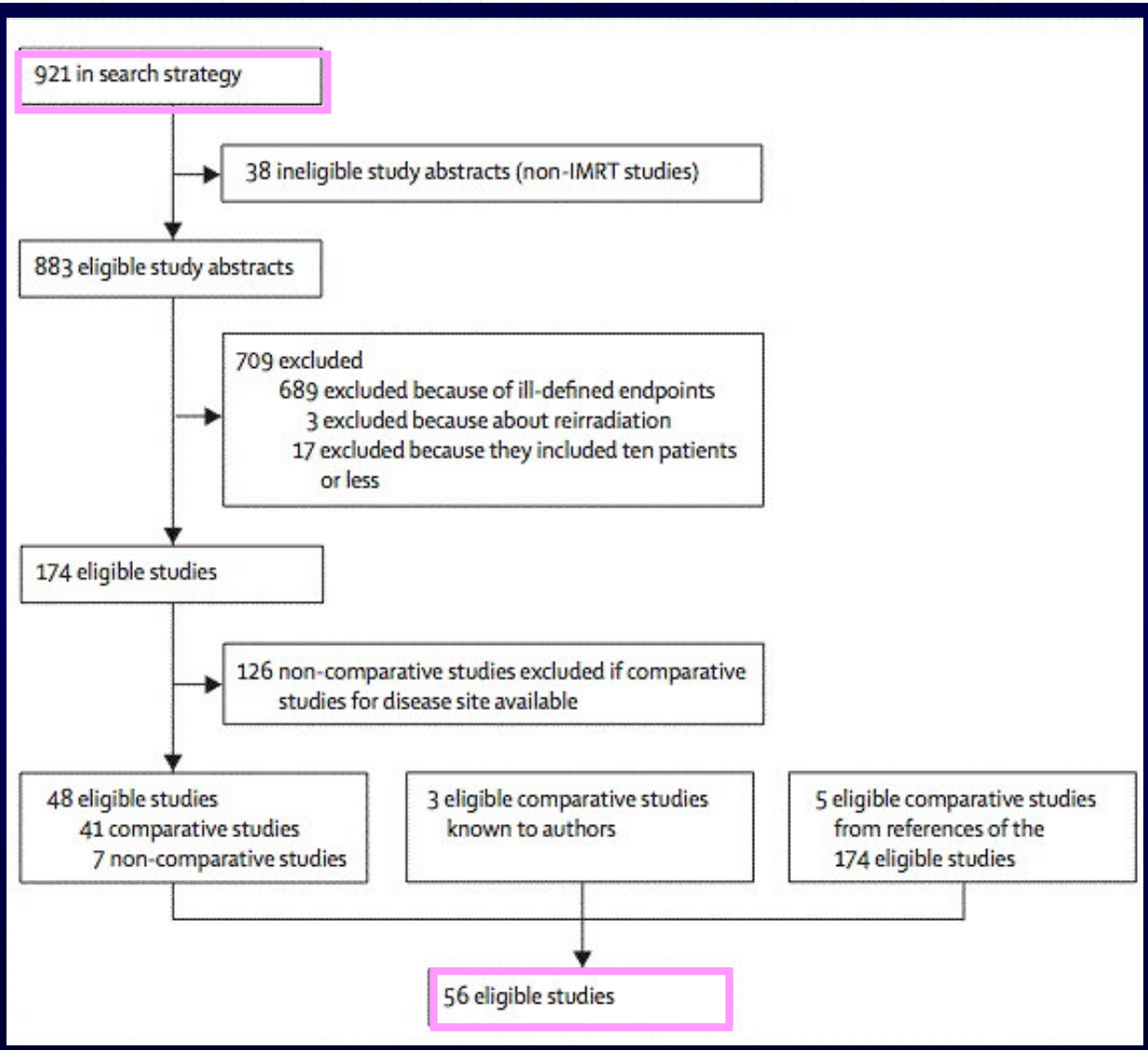
- *prostate*
- *head and neck*

- gynecologic cancers, breast, lung
- others…

Lancet Oncol 2008

Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies

Liv Veldeman, Indira Madani, Frank Hulstaert, Gert De Meerleer, Marc Mareel, Wilfried De Neve



Lancet Oncol 2008

Head and neck

Nasopharyngeal cancer - 5 studies (2 RCT)

- Better acute and late salivary function
- Improved dry mouth QoL
- Overall QoL similar
- Not significantly higher local control

Pow 2006, Wolden 2006, Hsiung 2006, Fang 2007, Kam 2007

Lancet Oncol 2008

Head and neck

Sinonasal cancer - 3 studies

- Dry-eye syndrome and optic neuropathy can be substantially decreased by IMRT
- No significant differences in OS and local control after IMRT were noted

Duthoy 2005, Hoppe 2007, Chen 2007

Lancet Oncol 2008

Head and neck

Cancer of the oropharynx, hypopharynx, larynx and oral cavity - 13 studies

- Similar survival and locoregional control after IMRT and non-IMRT have been noted
- Grade 2 and 3 xerostomia was significantly less frequent after IMRT

Chao 2001, Jabbari 2005, Braam 2006, Lee 2006, Milano 2006, Rades 2007, Studer 2007, Rothschild 2007, Pacholke 2005, Daly 2007, Munter 2007, Graff 2007, Yao 2007

Lancet Oncol 2008

Prostate cancer – 16 studies

- Significantly decreased GI or GU toxic effects were reported for the IMRT groups at equal or even increased physical or biological prescription doses compared with the non-IMRT groups
- Sexual function was also significantly better after IMRT

Zelefsky 2000, Shu 2001, Zelefsky 2001, Kupelian 2002, D'Amico 2002, Kupelian 2005, Ashman 2005, Sanguineti 2006, Jani 2006, Namiki 2006, Yoshimura 2006, Vora 2007, Jani 2007, Jani 2007, Su 2007, Lips 2007

Lancet Oncol 2008

Gynecological malignancies – 5 studies

IMRT has the potential to decrease acute and late GI and GU toxic effects, but longer follow-up is needed to assess its effect on locoregional control

Mundt 2001, Brizey 2001, Mundt 2002, Mundt 2003, Chen 2007

Lancet Oncol 2008

CNS tumors - 3 studies

- Glioblastoma : similar survival and toxic effects
- Astrocytoma (hypo IMRT) : better 1- and 2-year PFS and OS
- Pediatric medulloblastoma : lower ototoxicity

Fuller 2007, Iuchi 2006, Huang 2002

Lancet Oncol 2008

Breast cancer - 4 studies (2 RCT)

- IMRT reduces acute and late effects
- Beneficial effects on cosmesis

Pignol 2006, *Freedman 2006*, ***Donovan 2007***, *Harsolia 2007*

Lancet Oncol 2008

Lung cancer and pleural mesothelioma – 3 studies

- Lung

  A significantly lower incidence of gr. ≥3 radiation pneumonitis was detected

- Mesothelioma

  Small non-comparative study reporting fatal radiation pneumonitis created controversy about the use of IMRT in this setting. In another study, that used strict treatment planning objectives and no chemo, there were no gr. ≥ 3 acute toxic effects, except for 7% of cases of acute gr. 3 oesophagitis

Ahamad 2003, Yom 2007, Allen 2006

Lancet Oncol 2008

Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies

Liv Veldeman, Indira Madani, Frank Hulstaert, Gert De Meerleer, Marc Mareel, Wilfried De Neve

- This review shows evidence of reduced toxicity for various tumour sites by use of IMRT
- There is no indication that IMRT has led to adverse effects on locoregional control or survival
- The findings regarding local control and overall survival are generally inconclusive.

Lancet Oncol 2008

Almost all studies are mono-institutional and compares IMRT with a historical control group

Many form of bias: stage migration, improvements in histological diagnosis, improvements in RT techniques and other treatment modalities implemented simultaneously

In some studies, the non-IMRT group was treated by use of two-dimensional techniques. In these situations, the question remains whether the improvement noted in the IMRT group could also have been obtained by non-modulated three-dimensional-conformal techniques

Radiation oncologists have implemented various IMRT techniques, for which effects on clinical efficacy and safety have not been analyzed separately

Generating Evidence for IMRT

Randomized trials can not be simplistic considered as the one and only "gold standard" for all situations

Alternative to Randomized Trial?

Reproduce (validate) single institution's data preferably in multi-institutional setting

The IMRT cost-benefit ratio

Definitions

Cost Effectiveness

- Cost of intervention is related to its impact on a clinically relevant endpoint ("effectiveness")
- Years of life saved (survival) is most commonly used endpoint

Cost Benefit

- The benefit of intervention (improved survival, less toxicity, longer DFS) is converted to dollars
- Cost of intervention is in dollars
- The cost-benefit of NEW and STANDARD treatments is calculated as benefit (dollars) minus cost (dollars)

IJROBP, 2006

USING DECISION ANALYSIS TO DETERMINE THE COST-EFFECTIVENESS OF INTENSITY-MODULATED RADIATION THERAPY IN THE TREATMENT OF INTERMEDIATE RISK PROSTATE CANCER

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STEVEN FEIGENBERG, M.D.,* ALEXANDRA HANLON, PH.D.,* SACHIN KULKARNI, M.S.,†
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IMRT was found to be cost-effective, however, at the upper limits of acceptability.

The results, however, are dependent on the assumptions of improved biochemical disease-free survival with fewer patients undergoing subsequent salvage therapy and improved quality of life after the treatment

The cost-benefit ratio:

level 1 - individual patient

level 2 - cohort of patients

level 3 - population

Conclusions

Should IMRT be standard treatment?

NO

(Can IMRT be standard when there is no standard IMRT?)

Should each patient receive optimal radiotherapy?

YES

The seduction of technology

A major attraction of the radiation therapy specialty has become the technology. Increasingly, clinical care has been abdicated to other specialties and radiation oncologists are becoming the image-guided delivers of a single physical therapy

The "radiation ONCOLOGIST" has become a
"RADIATION oncologist"

No one would deny the potential of the news technologies, but their application has begun to race ahead of any proven utility at least in rigorous evidence-based terms

Zelefsky, Semin Radiat Oncol 2007

ISTITUTO SUPERIORE DI SANITÀ

Indicazioni per l'assicurazione di qualità nella radioterapia ad intensità modulata

A cura di
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