Basisprincipes radiotherapy

W. De Neve

UNIVERSITEIT GENT

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

Basisprincipes

- Technologie- of biologievoordracht?
- Technologievoordracht omdat
  - Basisprincipes blijven overeind
  - Technologie is basis van meeste vooruitgang
- Biologievoordracht omdat
  - Nieuwe inzichten in kankerbiologie openen mogelijkheden voor radiotherapie
  - De oude basisprincipes zijn ontoereikend

Ionizerende straling in behandeling van kanker: basisprincipe

- Straling op gezonde en kankercellen
- Gezonde cellen herstellen schade beter dan kankercellen
- Repititief stralen – fractionatie
- Resistent -> meer fracties -> meer dosis
- Defecte DNA-repair mechanismen
  - Oorzaak van kanker
  - Kwetsbaarheid van kanker voor straling

België

- Kanker nieuwdiagnoses: ~67,000/jaar
- Radiotherapie
  - Bij initiële diagnose: 37-40%
  - Tijdens ziekteverloop: >50%
  - Bijna uitsluitend kankertherapie
  - Tertiaire verwijzing via MOC
- 25 centra, 12 satellieten
- 25,000 volwassenen/j; 100 kinderen/j

Basisprincipe kan niet verklaren

- Curatie van resistente tumoren met 1 fractie
- Inefficiëntie van langdurige bestralingen
- Curatie na partiële bestralingen (bystander)
- Effecten op niet-bestraalde tumoren (abscopal)
- Effecten van bestraling gezond weefsel op tumoren

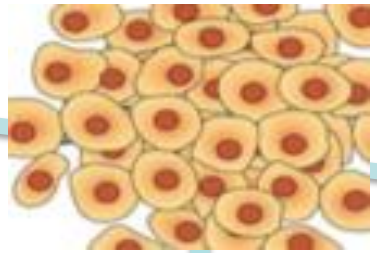
Cellen -> ecosystemen -> organisme

- Radiotherapie heeft zowel anti-kanker als kanker-beschermende effecten via
  - Ecosysteem
  - Het organisme
- Meest aandacht: vasculatuur en immuunsysteem
- Deze inzichten stellen de klassieke fractionatie en grote volume radiotherapie in vraag

Radiotherapie zelf-modulatie

- Pro-survival van kanker
  - Vele repetities
  - Kleine fractiedosissen
  - Langdurige behandelingen
- Anti-survival van kanker
  - Weinig fracties
  - Fractiedosis 5-15 Gy
  - Kleine volumes gezonde weefsels

Radiotherapy modulation of IMMUNOGENIC cell death



TIME

Many fractions in normal tissue
Long treatment duration
High dose in normal tissue
Large volume of normal tissue

Tumor protection

Large fraction dose in tumour
Few fractions
Low integral dose

Tumor eradication

Research questions
Type of radiation (photons, particles)
Margins, surgery, dose-painting, adaptation to shrinking tumours
Modifiers: anti-angiogenic, anti-inflammatory, immune checkpoint inhibitors, targeted agents, chemotherapy

Gelukkig toeval in de technologische evolutie

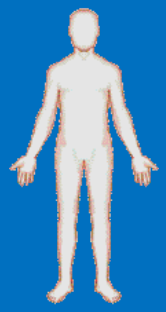
- Nieuwe technologie maakt radiotherapie geschikt voor +modulatie
- Verkleining bestraalde regio's
- Hypofractionatie (kort intense radiotherapie)
- Hoge precisie
- Combinatietherapie
  - Chirurgie
  - Systemische therapie

Illustratie van technologische evolutie

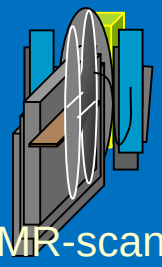
- MOC -> radiotherapie
- Secretariaat, administratie
- Poliklinisch contact met team
  - Indicatiestelling
  - Informatie, akkoord, afspraken
- Voorbereiding
  - CT-simulatie
  - Planning
- Behandelingsuitvoering
- Opvolging

Radiotherapie CT-simulatie = 3(+)-D-beeldacquisitie

Radiotherapie planning = in-silico simulatie

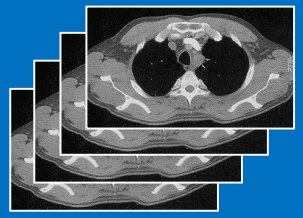


Patiënt

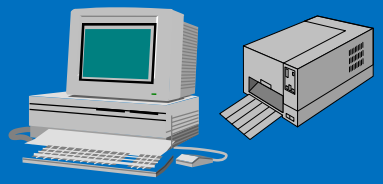


MR-scan

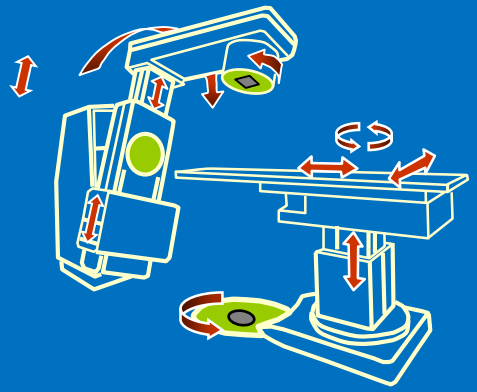
CT-scan



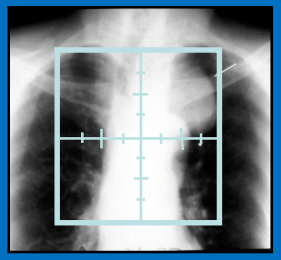
Beeldenset



Computer-planning

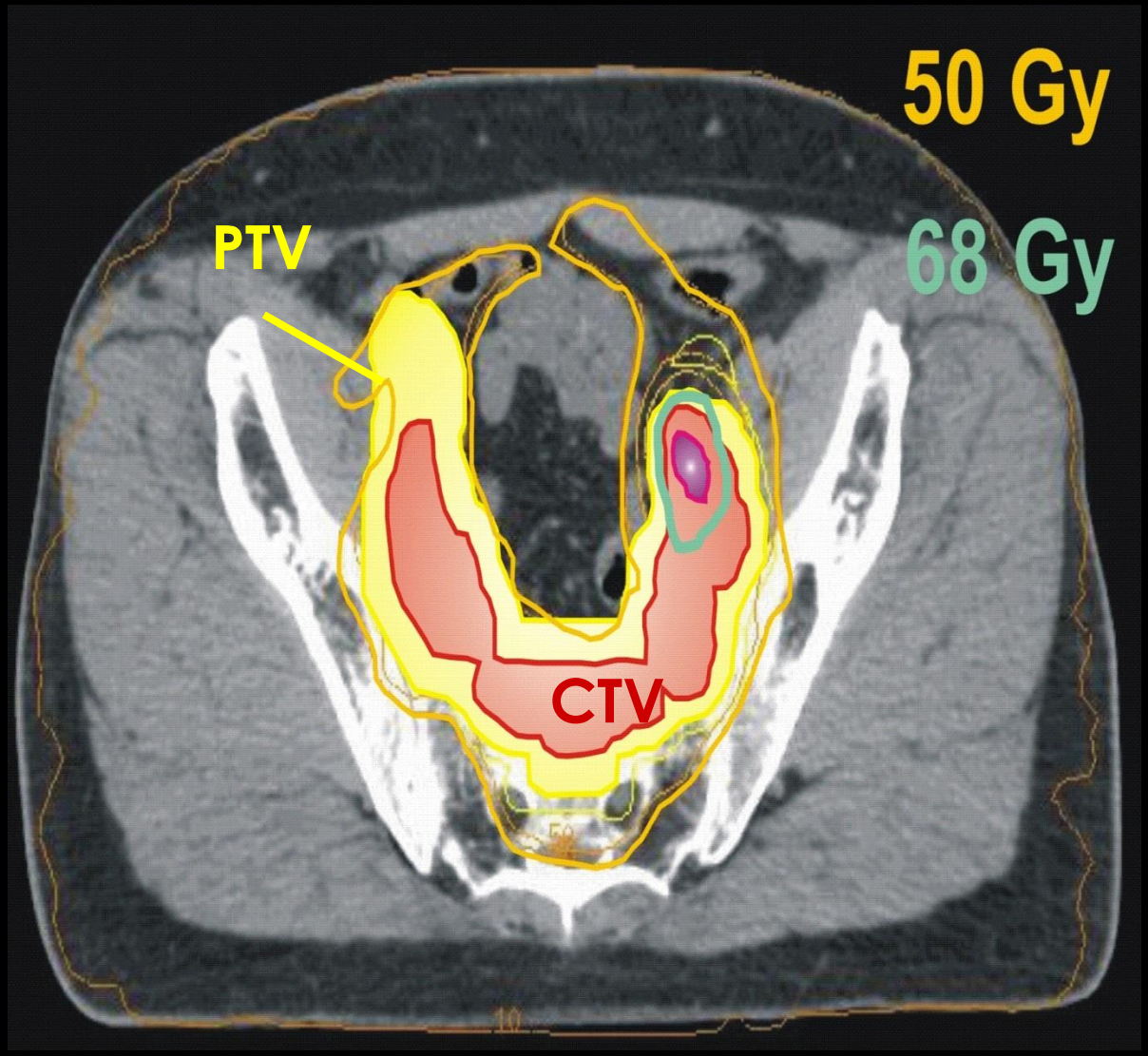


Simulator (verleden)



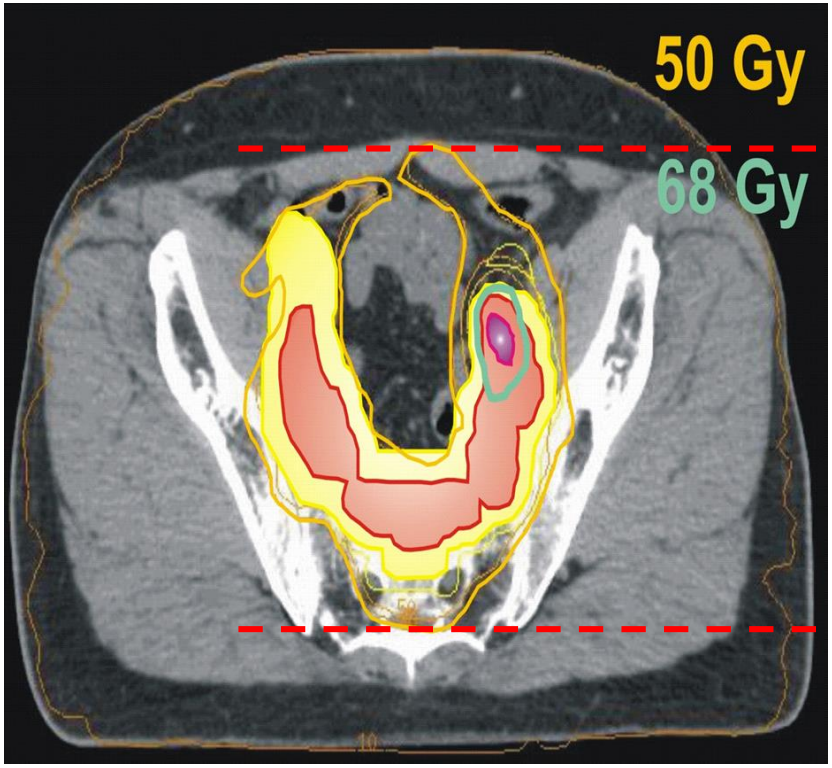
bestraling

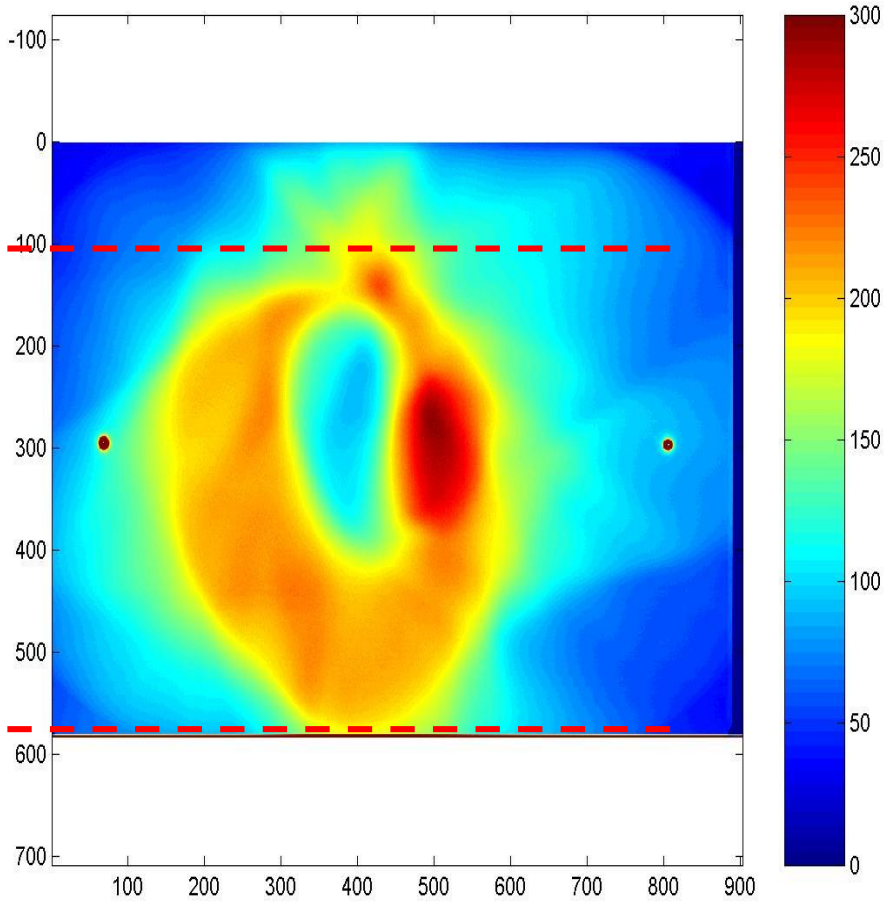
Transverse dose distribution through presacral and internal iliac nodes



From G. De Meerleer

From virtual to real world: QA
Transverse dose filmdosimetry

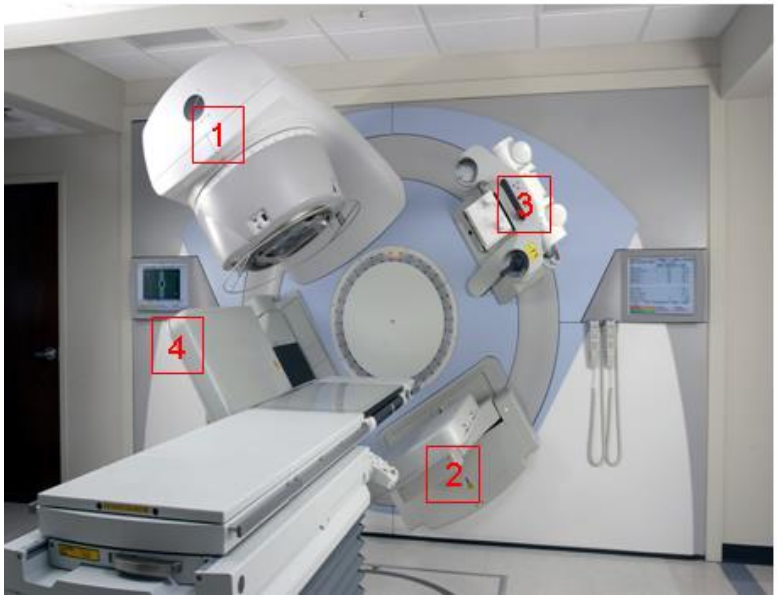




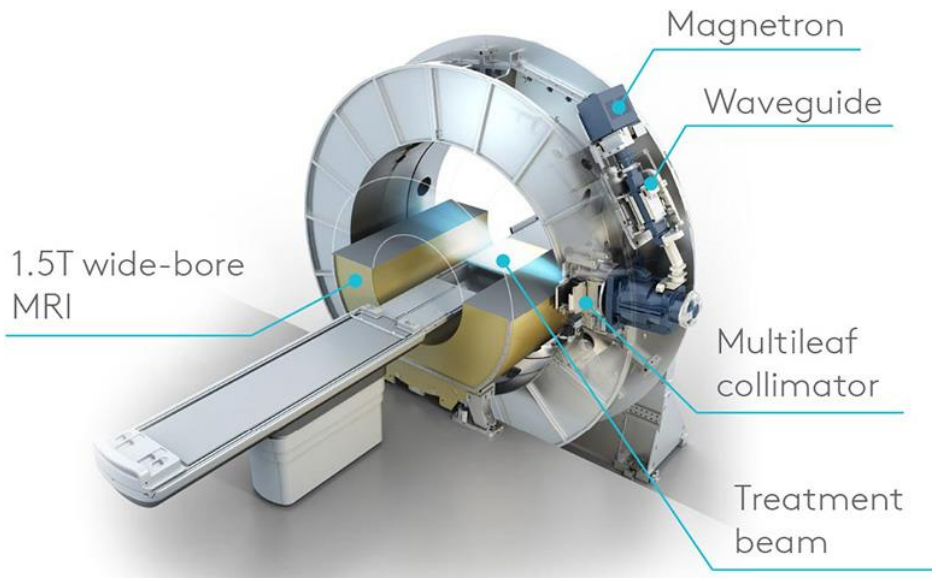
From G. De Meerleer

Bestralingsmachines hebben 3(+)D-imaging aan boord

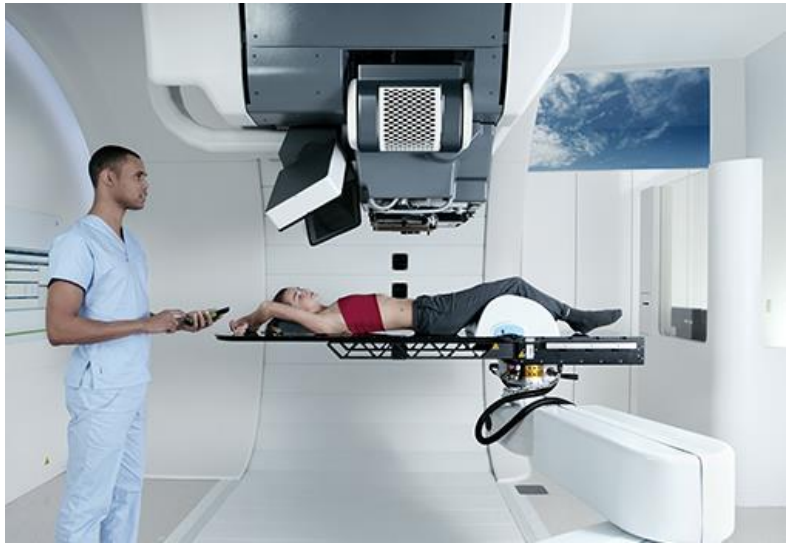
A: Elekta Synergy



B: Tomotherapy Hi-ART

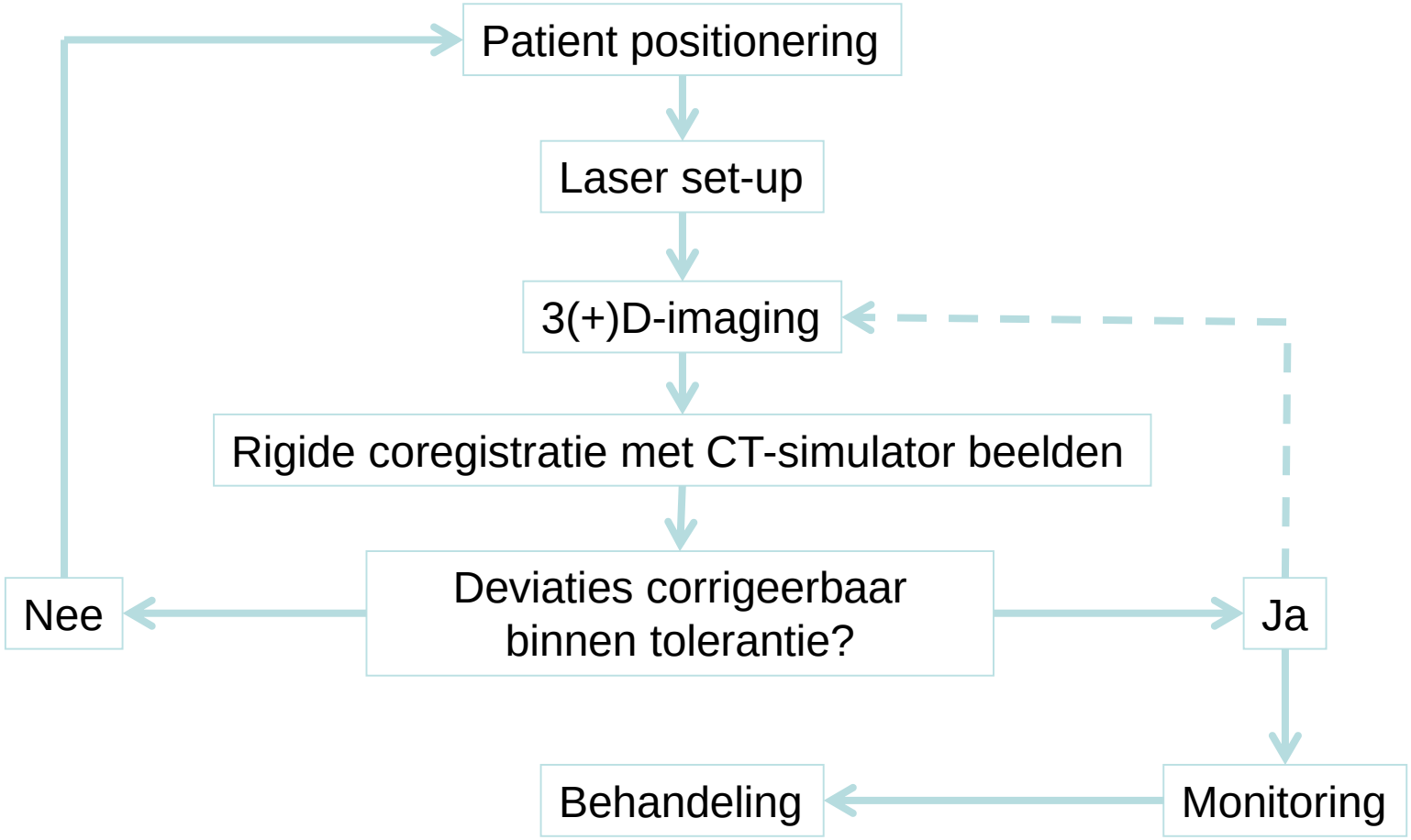


C. Elekta Unity

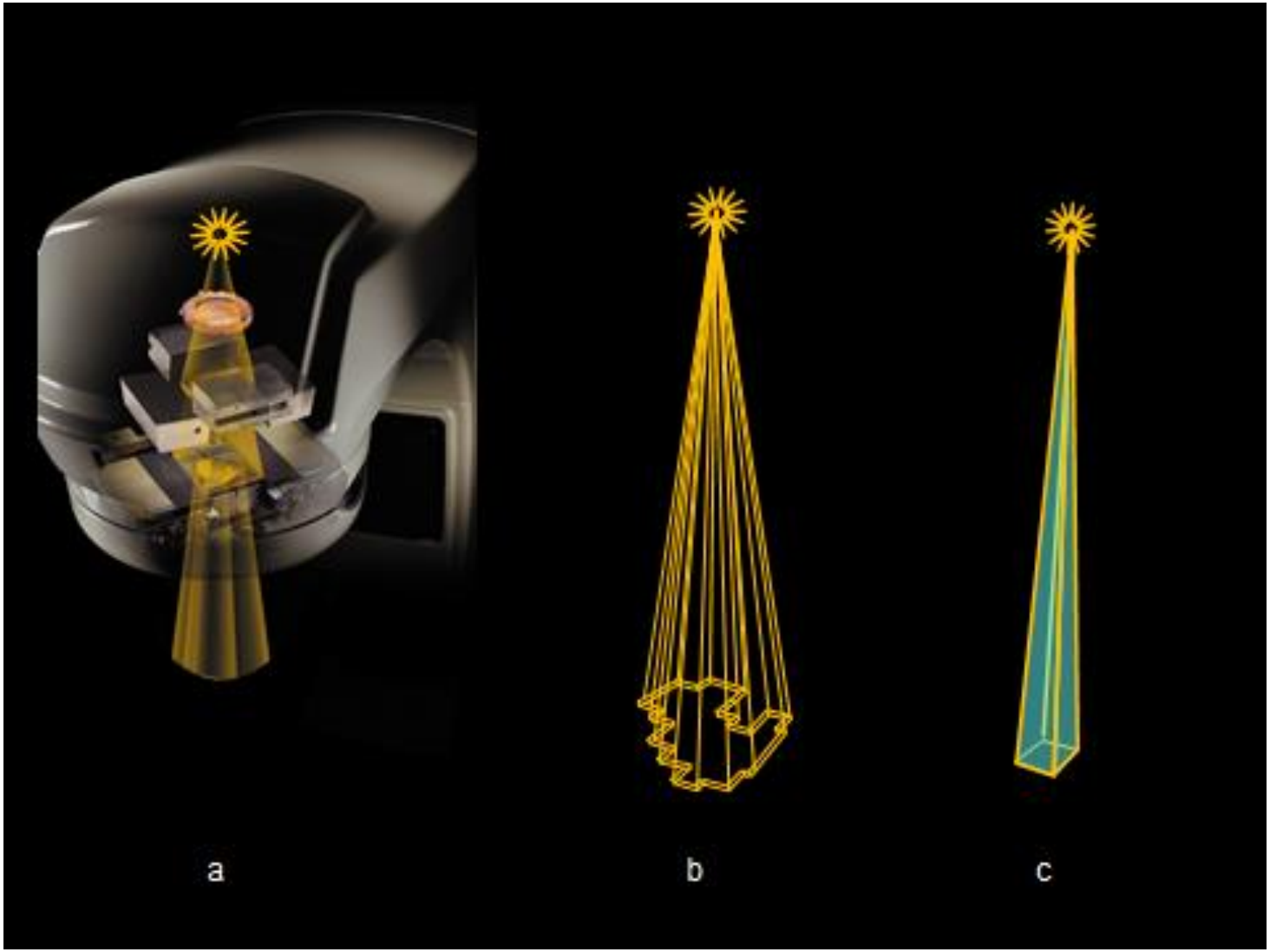


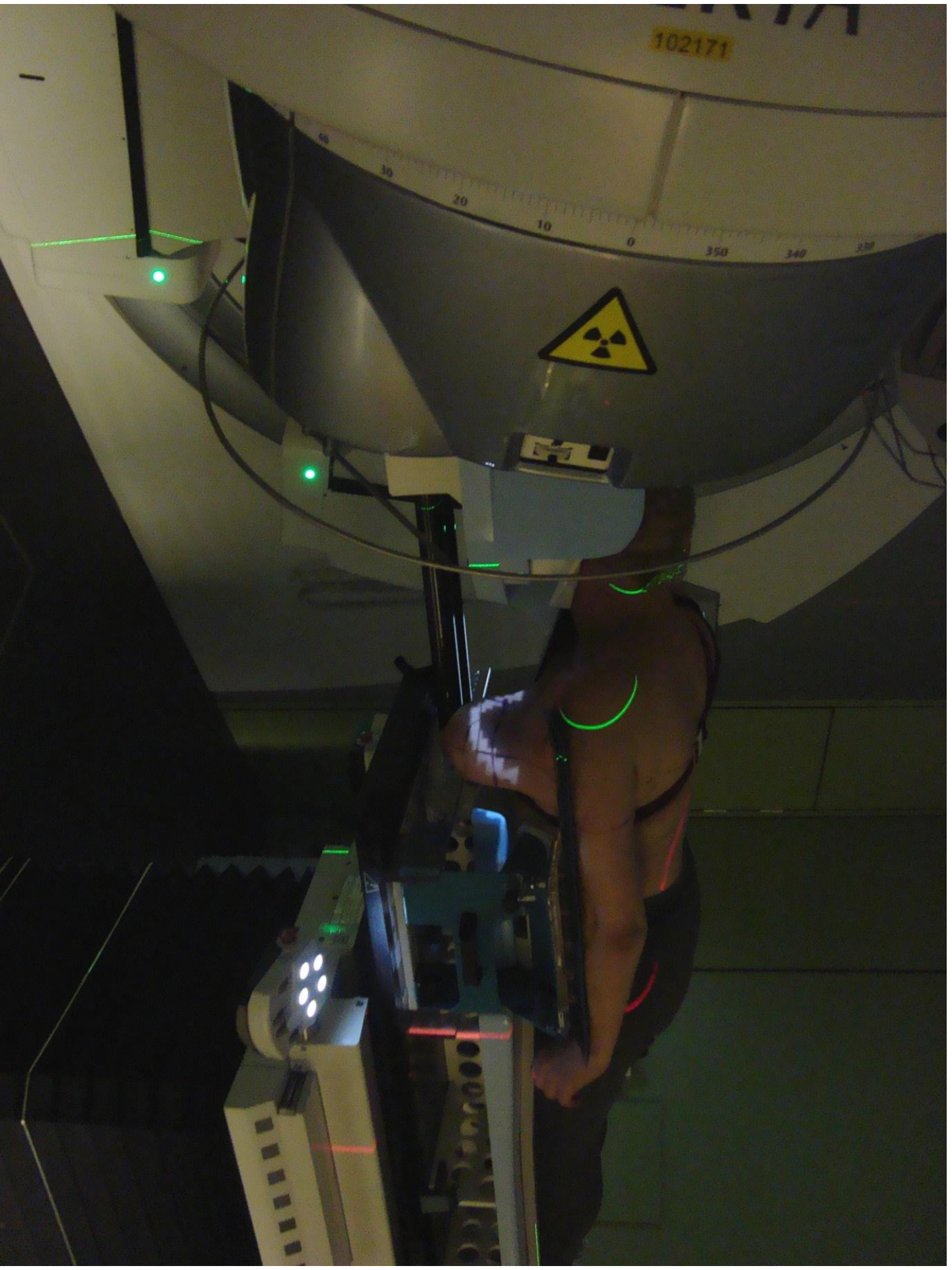
D. IBA Proteus One: UZ-Leuven

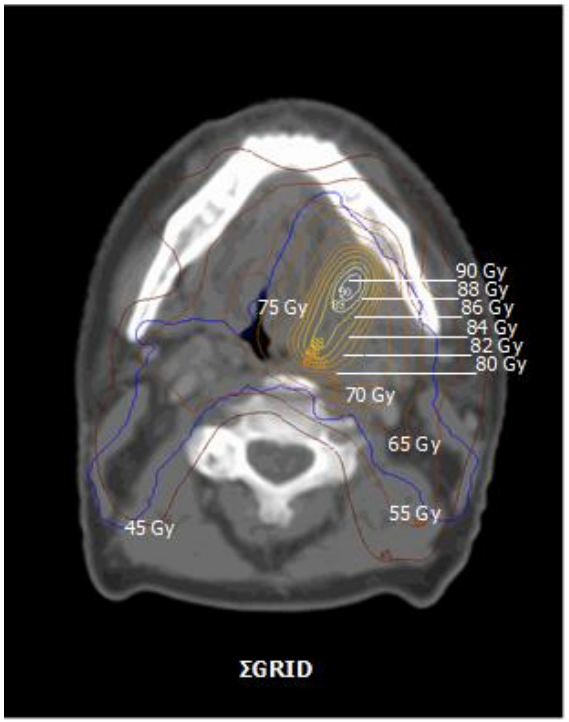
Behandelingsprocedure

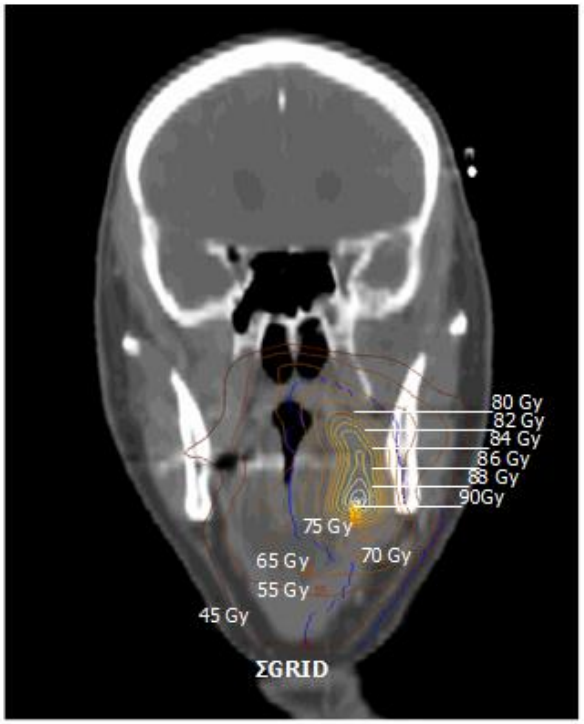


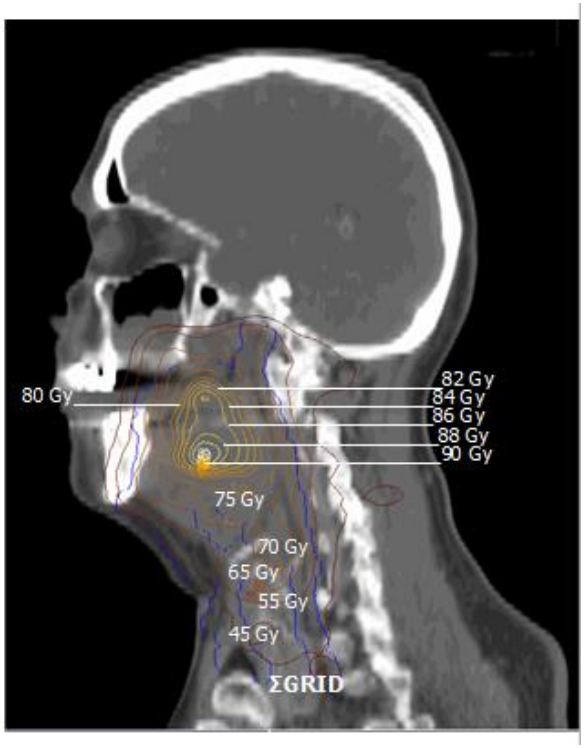
Dose-painting = 3D-printing van dosis

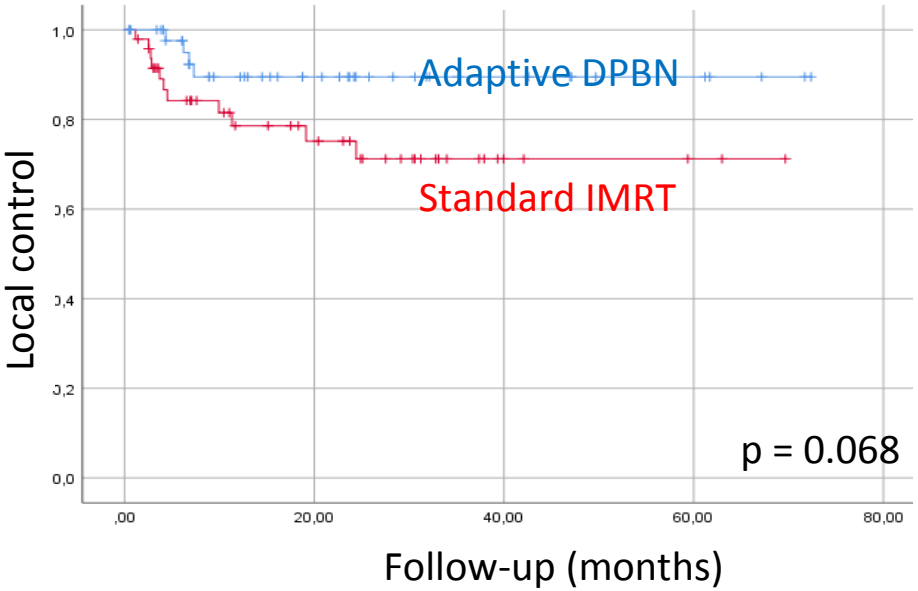



102171
40
30
20
10
0
350
340


90 Gy
88 Gy
86 Gy
84 Gy
82 Gy
80 Gy
75 Gy
70 Gy
65 Gy
55 Gy
45 Gy
ΣGRID


80 Gy
82 Gy
84 Gy
86 Gy
88 Gy
90Gy
75 Gy
70 Gy
65 Gy
55 Gy
45 Gy
ΣGRID


80 Gy
82 Gy
84 Gy
86 Gy
88 Gy
90 Gy
75 Gy
70 Gy
65 Gy
55 Gy
45 Gy
ΣGRID


Adaptive DPBN
Standard IMRT
Local control
1,0
0,8
0,6
0,4
0,2
0,0
,00
20,00
40,00
60,00
80,00
p = 0.068
Follow-up (months)

Technological progress since 1970s

First Linac

Cerrobend blocks

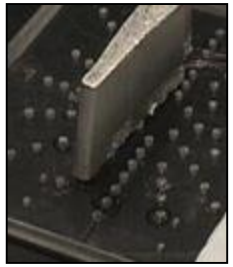
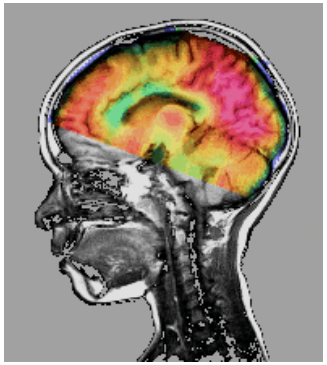
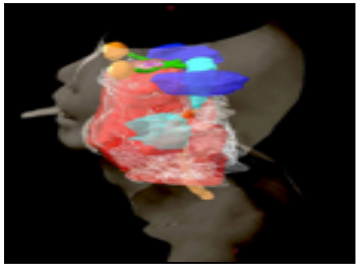


Image Fusion



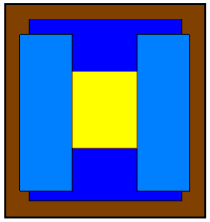
Multileaf collimator

IMXT dose-painting



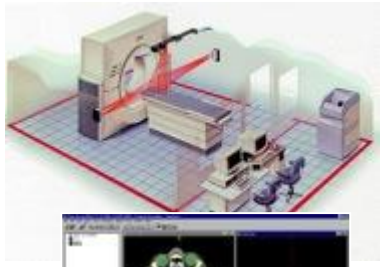
MRI-linac

1960 1970 1980 1990 2000 2010 2015

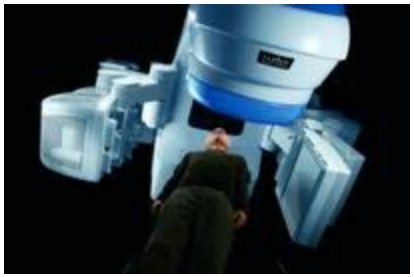


Standard collimator

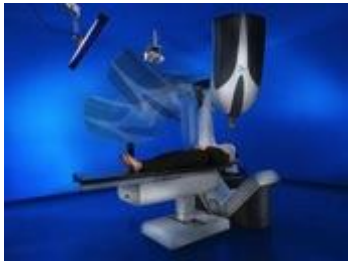
Shaped electron fields



Computerized 3D CT treatment planning



High resolution IGXT/gating

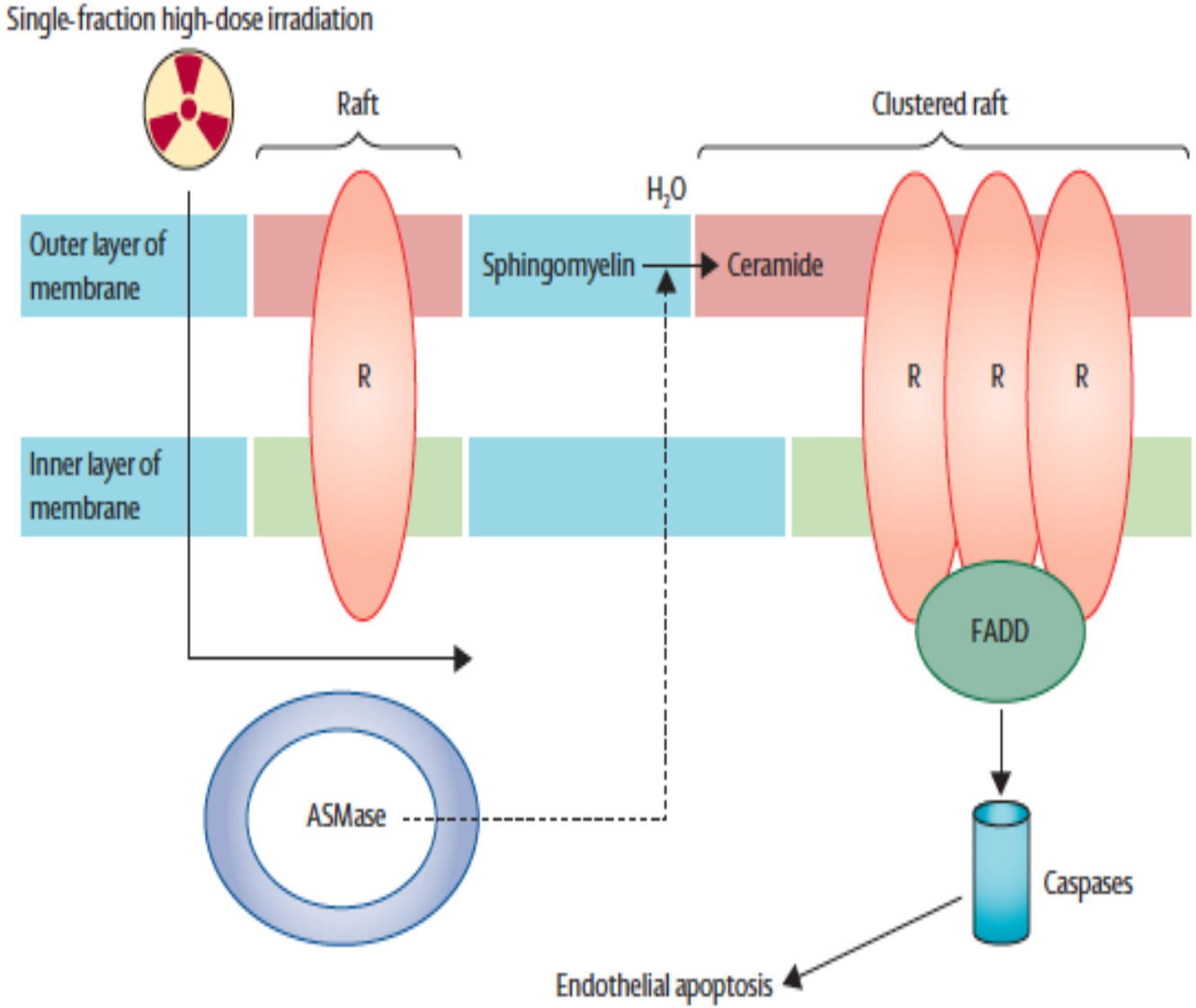


Robotic XT/tracking

Conclusies

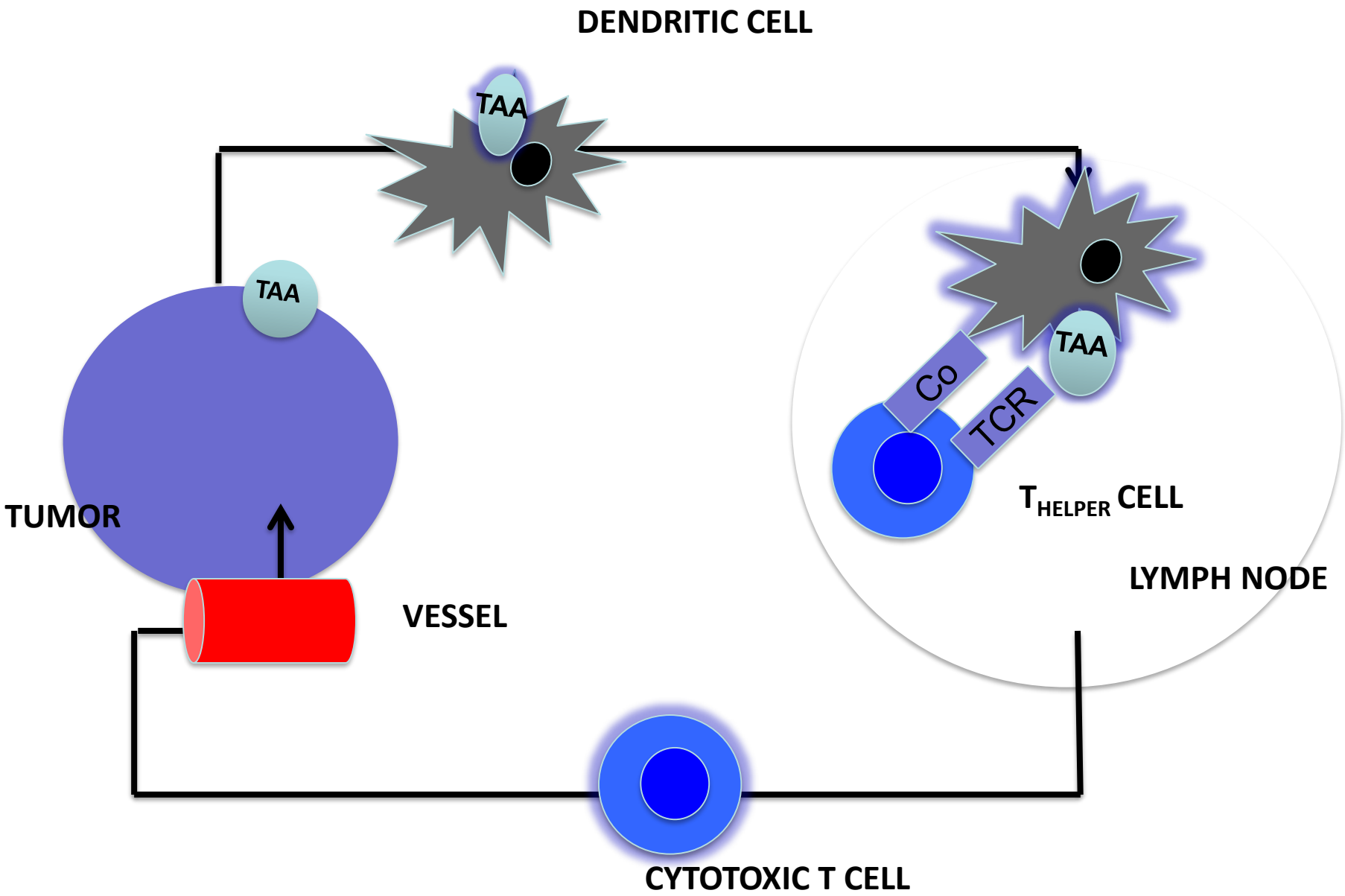
- Technologie en Biologie in harmonie
- Top 3 implementies van korte atoxische flexibele efficiënte behandelingen
  - Long, borst, rectum, prostaat?
  - Oligo-metastatische ziekte
  - Radio-immunotherapy
- Relevant eindpunt: toxiciteit-vrije overleving

Additional slides


Single-fraction high-dose irradiation
Raft
Clustered raft
H_2O
Outer layer of membrane
Sphingomyelin
Ceramide
R
R
R
R
Inner layer of membrane
FADD
ASMase
Caspases
Endothelial apoptosis

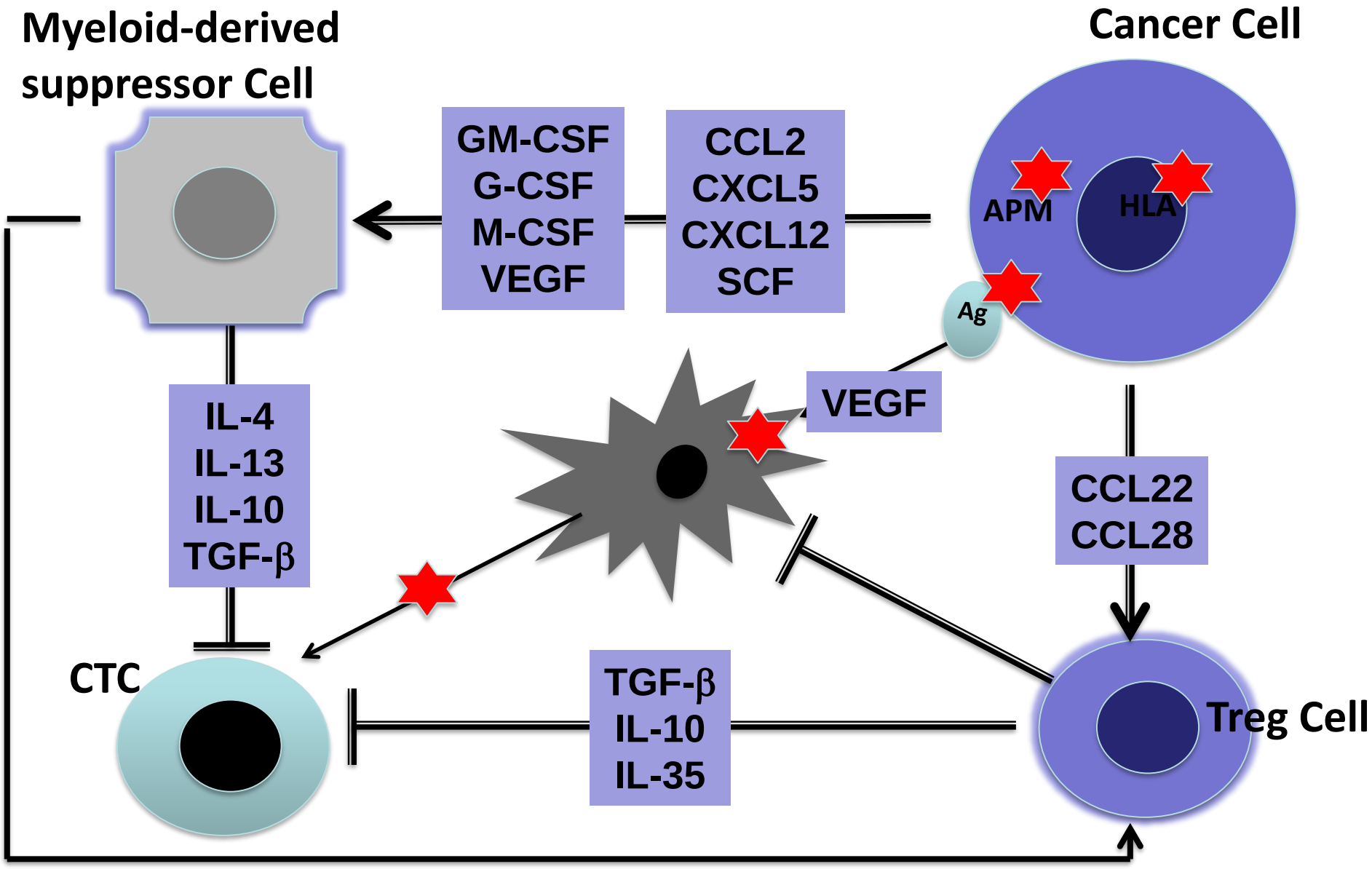
Indirect cancer cell death
Immunogenic

MALIGNANT TUMORS ARE IMMUNOGENIC



Contributed by M. Mareel

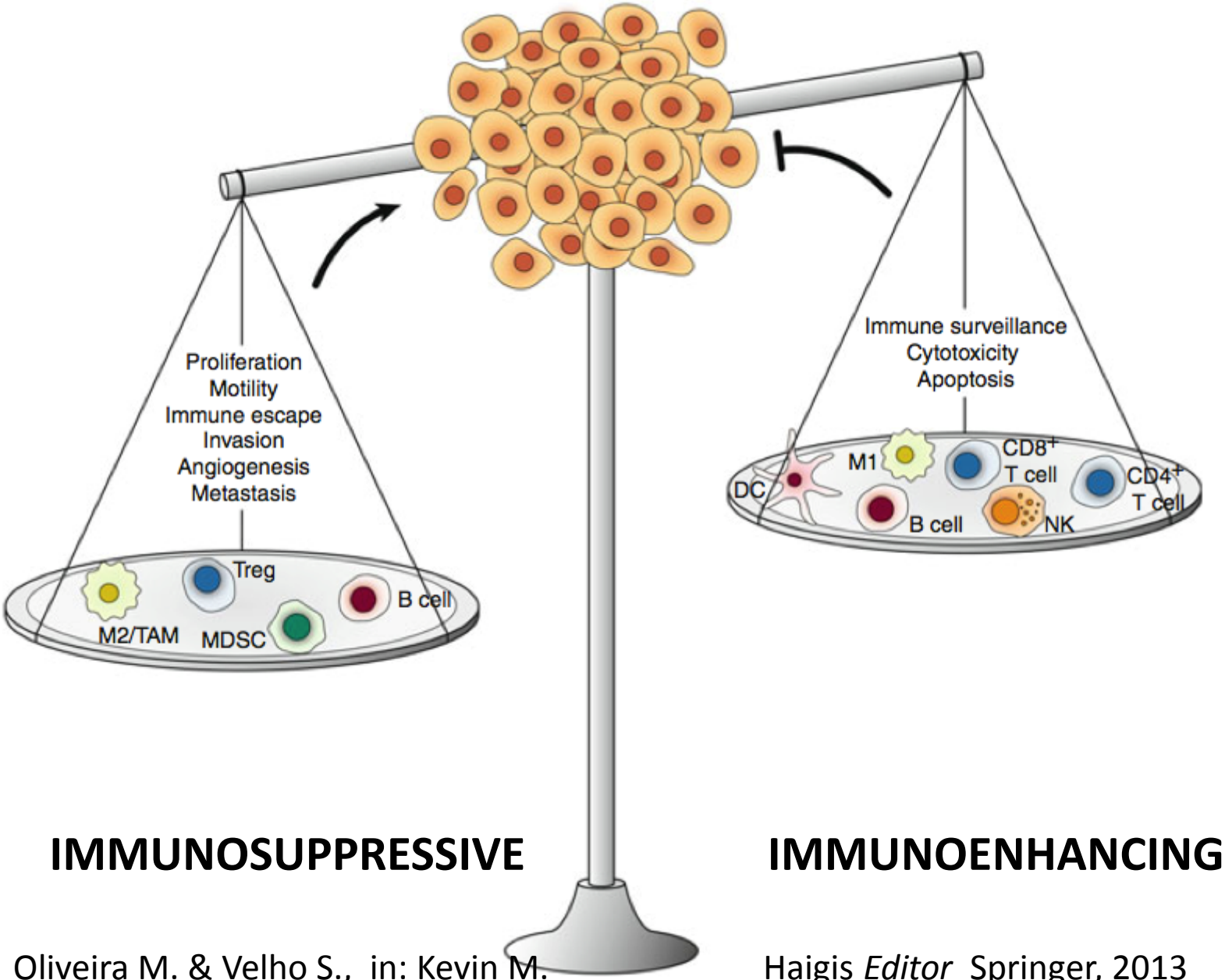
MALIGNANT TUMORS INHIBIT IMMUNE RESPONSES



Adapted from Elinav et al. 2013, Nature Reviews Cancer 13: 759.

Contributed by M. Mareel

THE IMMUNE BALANCE IN UNTREATED MALIGNANT TUMORS

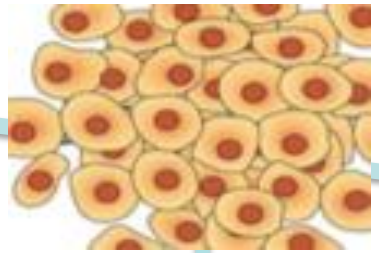


IMMUNOSUPPRESSIVE **IMMUNOENHANCING**

Oliveira M. & Velho S., in: Kevin M. Haigis *Editor* Springer, 2013

Contributed by M. Mareel

IONIZING RADIATION REVERSES THE IMMUNOSUPPRESSION



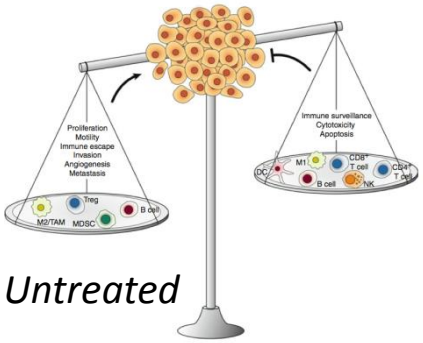
TIME

VEGF
IL-6
TGF-β
IL-10
Others

IMMUNOSUPPRESSIVE

GM-CSF
IFN-γ
IL-1
Others

IMMUNOENHANCING



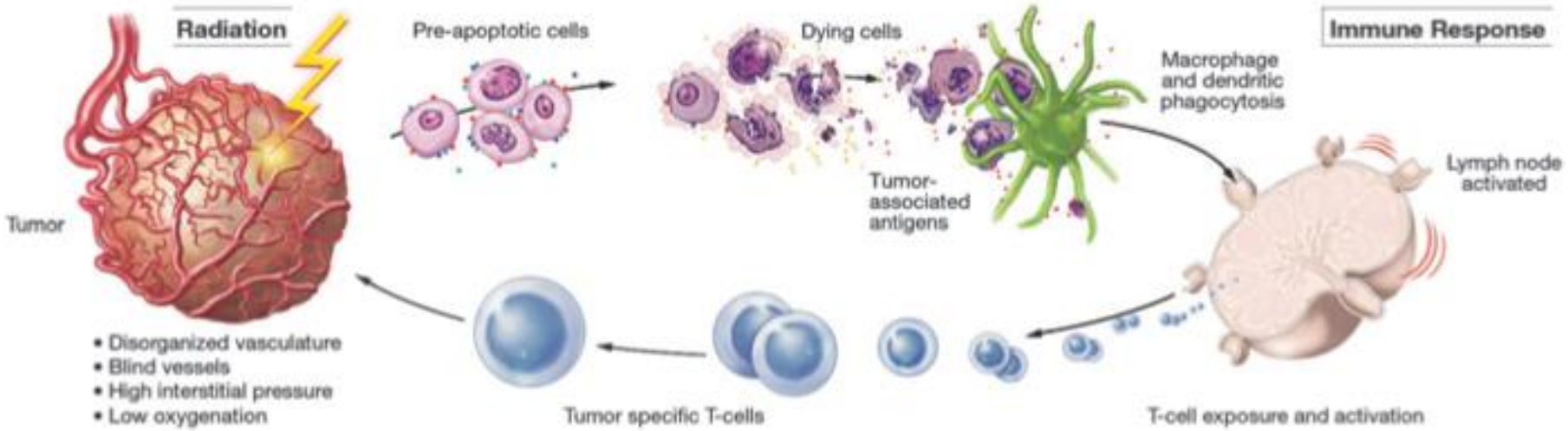
Untreated

Adapted from Durante et al. Trends Mol. Med. 19: 565, 2013

Adapted from Kroemer et al. Annu Rev Immunol 31: 51, 2013

Contributed by M. Mareel

IRRADIATED TUMORS ELICIT CANCER-SPECIFIC IMMUNE RESPONSES



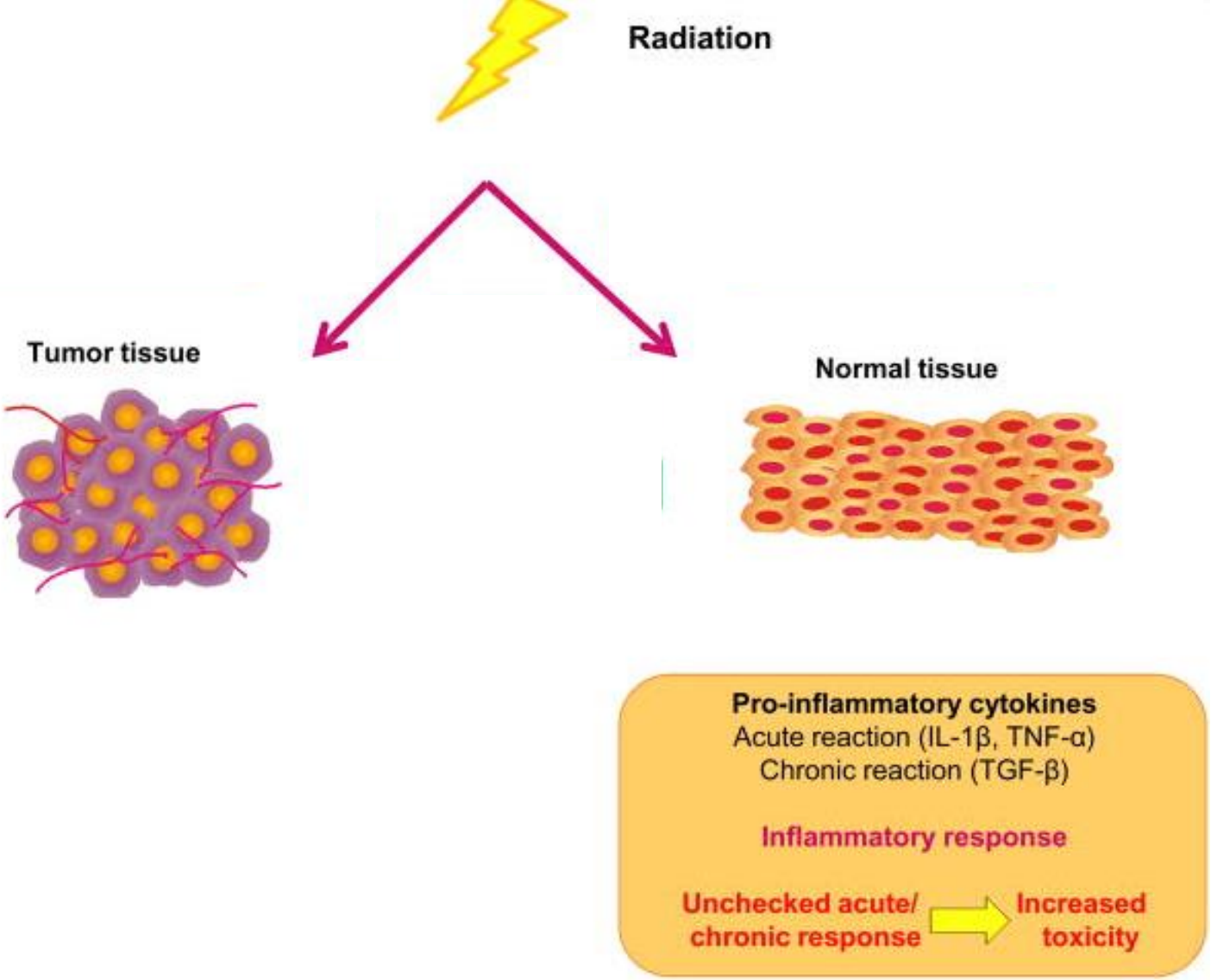
Kamrava M., Mol. Biosyst. 5: 1262, 2009

RADIATION-INDUCED IMMUNOGENIC CANCER CELL DEATH

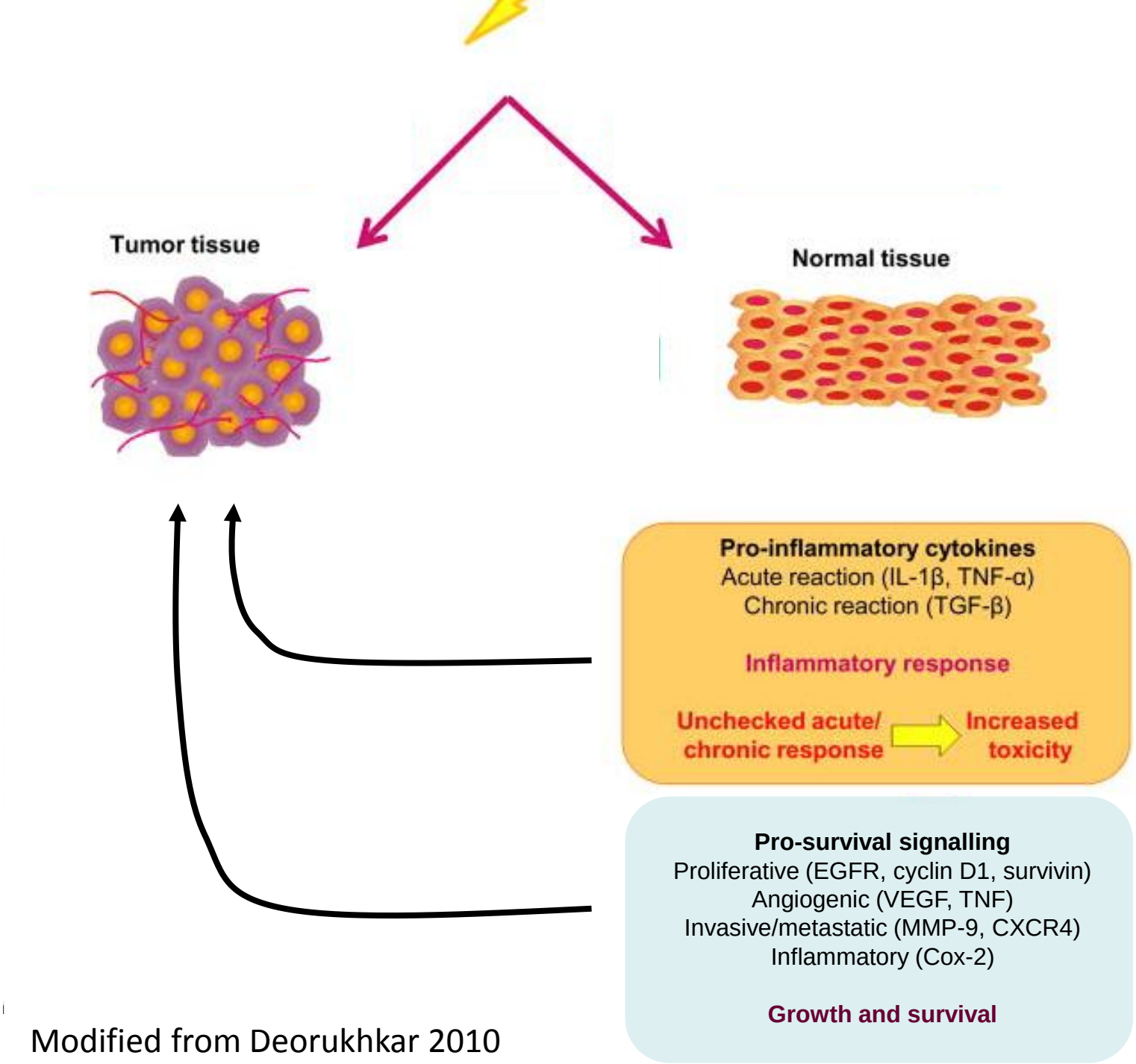
-Strongest induction at large dose/fraction

-A few fractions may be more efficient than single fraction

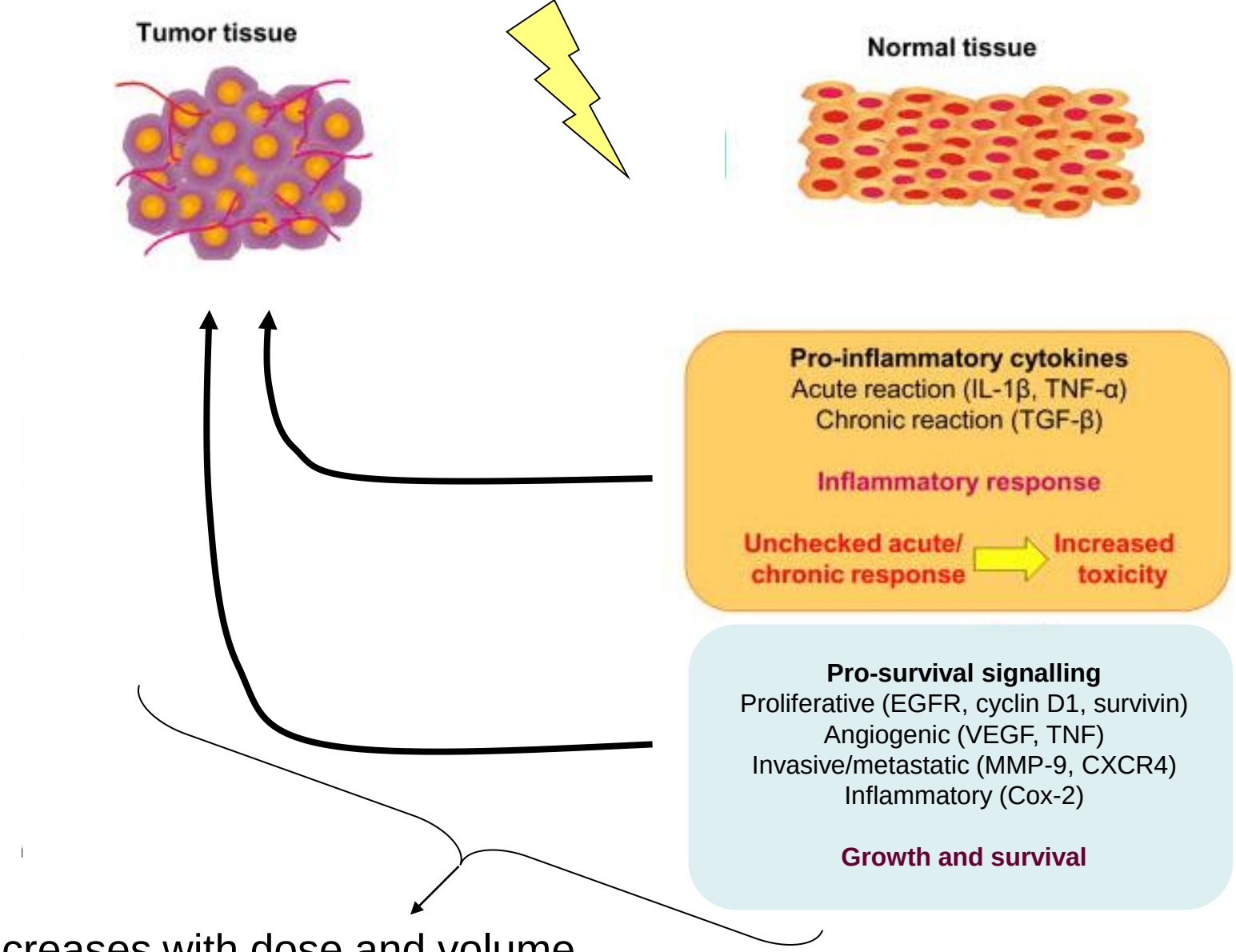
Demaria & Formenti. Frontiers in Oncology, Oct. 2012



Deorukhkar 2010



Modified from Deorukhkar 2010



Increases with dose and volume

Fractionation triggers waves of signalling

Time on radiation treatment: decreases factors of immunogenic cell death
increases pro-survival factors

Modified from Deorukhkar 2010

Journal of Clinical Oncology, 2013 ASCO Annual Meeting Abstracts.
Vol 31, No 15_suppl (May 20 Supplement), 2013: RTOG 0617
Bradley et al.

Background: The first objective of RTOG 0617 was to compare the overall survival(OS) of patients(pts) treated with standard-dose(SD)(60Gy) versus high-dose(HD)(74Gy) radiotherapy with concurrent chemotherapy(CT).

Methods: This Phase III Intergroup trial randomized 464 pts with Stage III NSCLC to the SD(60Gy) vs. HD(74Gy) arms prior to closure of the HD arm. Concurrent CT included weekly paclitaxel(45 mg/m2) and carboplatin(AUC=2). Pts randomized to cetuximab received a 400 mg/m2 loading dose on Day 1 followed by weekly doses of 250 mg/m2. All pts were to receive consolidation CT. We are reporting the final results on radiation dose.

Results: 464 pts were accrued prior to closure of the HD arm in 6/11, of which 419 were eligible for analysis. Median follow up was 17.2 months. There were 2 and 10 grade 5 treatment-related adverse events(AEs) on the SD and HD arms, respectively. Grade 3+AEs were 74.2% and 78.2% on SD and HD arms, respectively (p=0.34). The median survival times and 18-month OS rates for the SD and HD arms were 28.7 vs 19.5 months, and 66.9% vs 53.9% respectively (p=0.0007). The primary cause of death was lung cancer (72.2% vs 73.5%)(p=0.84). Local failure rates at 18 months were 25.1% vs 34.3% for SD and HD patients, respectively(p=0.03). Local-regional and distant failures at 18 months were 35.3% vs 44%(p=0.04) and 42.4% vs 47.8%(p=0.16) for SD and HD arms, respectively. Factors predictive of less favorable OS on multivariate analysis were higher radiation dose, higher esophagitis/dysphagia grade, greater gross tumor volume, and heart volume >5 Gy.

Conclusions: In this setting of chemoradiation for locally-advanced Stage III NSCLC, 60 Gy is superior to 74 Gy in terms of OS and local-regional control. The effect of the anti-EGFR antibody (cetuximab) awaits further follow up. This project was supported by RTOG grant U10 CA21661, CCOP grant U10 CA37422, and ATC U24 CA 81647 from the National

Conclusions

- Dose painting
  - IMXT vs. IMPT
    - Equal in tumor
    - OARs
      - Sparing IMPT > IMXT
      - Difference increases with distance from PTV
    - Integral dose: over 3-fold lower for IMPT in H&N cancer
- Indirect cancer cell death
  - Particle therapy >> photon therapy
    - Healthy tissue dose
  - NIRS protocols tuned for vasculogenic and immunogenic cell death
    - High fraction size
    - Few fractions (few waves of pro-survival triggers)
    - Short (favourable) overall time
    - Combination with modulating substances
  - Proton protocols not so well tuned
    - Normofractionation
    - Large margins
  - Role of dose-painting and adaptive measures