Recommendations for no-compliance in (chemo)radiotherapy treatments

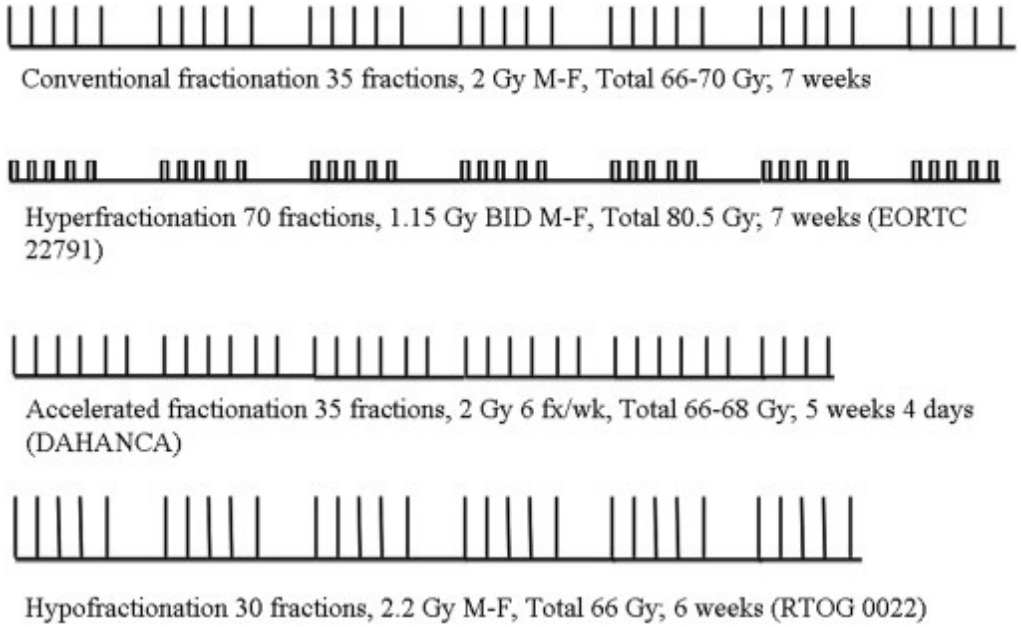
Session 3 – Actions: How to prevent and recover no-compliance

Karin Haustermans

Introduction

RT fractionation schedules

- Conventional fx: 1.8 – 2.0 Gy/fx
- Hyperfx: reduced dose/fx over a conventional OTT, multiple fx/day*
- Accelerated fx: reduced OTT with conventional dose/fx, multiple fx/day*
- Hypofx: higher dose/fx over a reduced conventional OTT



*as far apart as possible and certainly not closer than 6 hrs

Kamran A et al, Semin Oncol 2014

CRT in clinical practice

- CRT is successfully being applied in many solid tumors

Table 1 Overview of disease entities and indications in which concurrent chemoradiotherapy is used.[a]

Disease entity	Indication and treatment	Commonly used agents	Benefit
Upper aerodigestive tract cancers			
Head and neck cancer	Locally advanced HNC—primary or adjuvant treatment	Cisplatin, 5-FU, FHX, cetuximab	Improved organ preservation and survival compared with radiation alone
Non-small-cell lung cancer	Stage IIIB, nonoperable nonmetastatic disease	Cisplatin, carboplatin/paclitaxel, cisplatin/etoposide	Curative approach in poor surgical candidates or IIIB disease
Small-cell lung cancer	Limited stage disease	Cisplatin/etoposide	Curative in ~20% of patients
Esophageal cancer	Locally advanced disease	Cisplatin/5-FU	Survival benefit, increased cure rates, organ preservation
Gastrointestinal malignancies			
Rectal cancer	Neoadjuvant	5-FU	Improved sphincter preservation, decrease in local and distal failures
Anal cancer	Mainstay of curative treatment	5-FU, MMC	Improved organ preservation
Gastric cancer	Adjuvant	Cisplatin, 5-FU	Some data indicate a survival benefit
Pancreatic cancer	Adjuvant, unresectable locoregionally advanced tumors	5-FU	Improved locoregional control, possibly a survival benefit
Cholangiocarcinoma	Adjuvant, unresectable locoregionally advanced tumors	5-FU	Some data indicate a survival benefit
Gynecological and genitourinary cancers			
Cervical cancer	Primary modality	Cisplatin, 5-FU, hydroxyurea	Improved local and distal control, organ preservation
Bladder cancer	Primary modality	Cisplatin	Improved local control
Other cancers			
Glioblastoma	Adjuvant	Temozolomide	Survival benefit
Sarcoma	Neoadjuvant	Doxorubicin	Downstaging, improved organ preservation

[a]This is a limited overview, and concurrent chemoradiotherapy is used in most solid tumors either as a standard treatment or investigationally. For further details please refer to the organ-specific literature. Abbreviations: 5-FU, 5-fluorouracil; FHX, 5-FU, hydroxyurea and radiation; HNC, head and neck cancer; MMC, mitomycin C.

Seiwert, Nat Clin Pract Oncol 2007

Combined treatment schedules

- Combined treatment schedule
  - Sequential association
    - Induction or adjuvant
    - When target cell populations are different
    - To optimize the dose intensity of chemo and RT in both chemo- and radiosensitive disease
  - Concomitant association
    - When cellular and molecular interactions are used to improve loco-regional control
    - Increased early and late normal tissue toxicity
- Key benefit in clinical setting: inhibition of tumor cell proliferation by drugs during radiation inter-fraction interval

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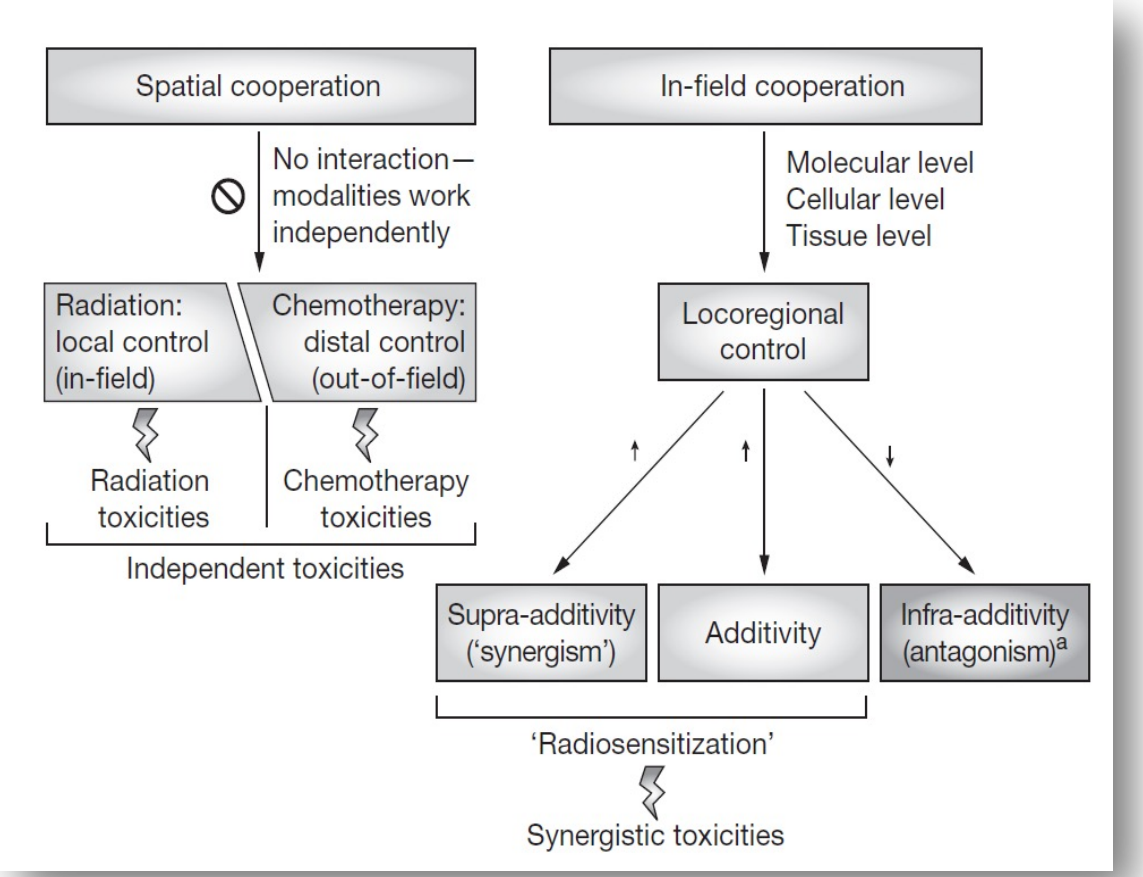
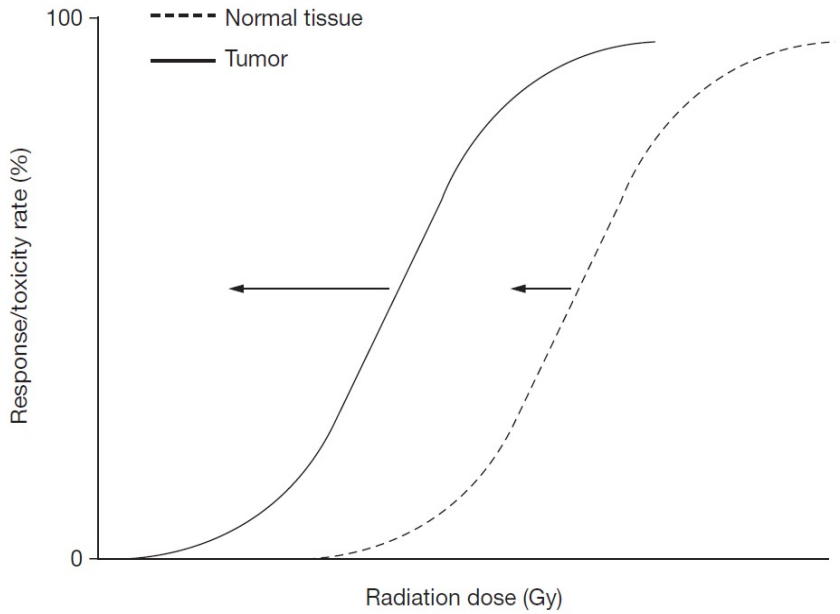
Rationale for adding chemo to RT

- Spatial and in-field cooperation

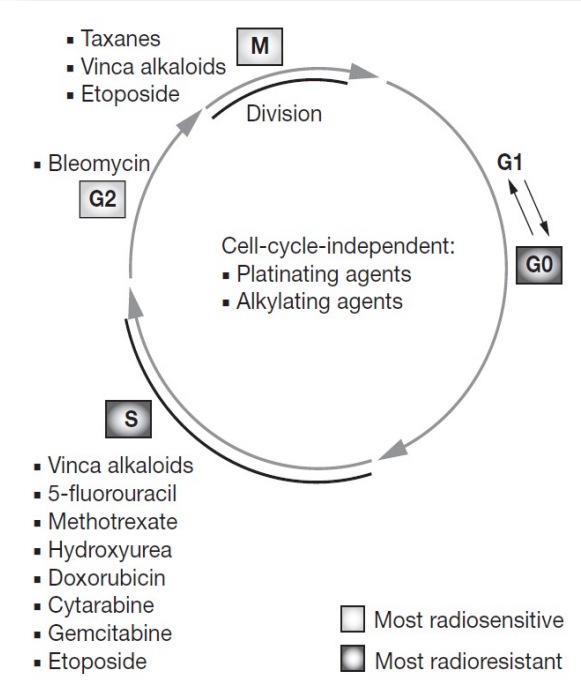


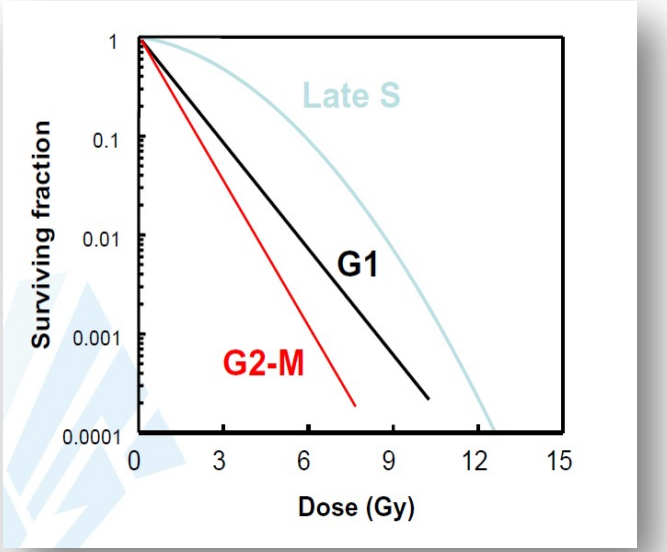


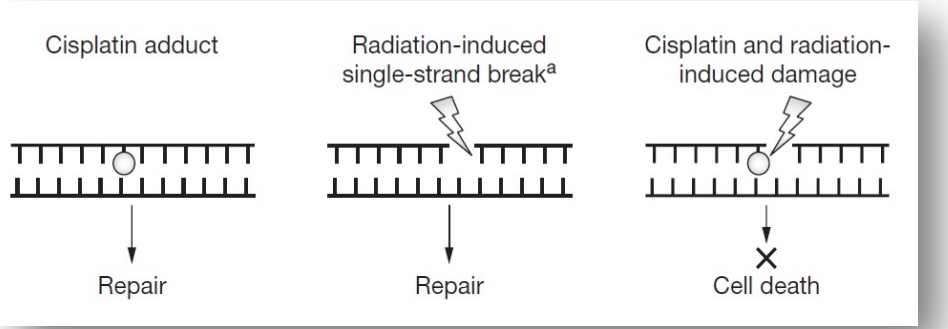
Seiwert, Nat Clin Pract Oncol 2007

Rationale for adding chemo to RT

- Cytokinetic cooperation/synchronization
- Interference with RT-induced DNA damage and repair







Seiwert, Nat Clin Pract Oncol 2007

Rationale for adding chemo to RT

Table 19.4 Summary of the pre-clinical data regarding the mechanisms of interaction between ionizing radiation and chemotherapeutic agents

	DNA damage induction repair		Chromosome aberrations	Cell cycle	Apoptosis	Reoxygenation
Anti-metabolites						
5-Fluorouracil	–	±	–	+	?	?
Methotrexate	?	?	?	?	?	?
Hydroxyurea	?	±	+	+	?	?
Gemcitabine	–	–	+	+	–	+
Fludarabine	–	–	+	+	–	?
Alkylating agents						
Cisplatin	+?	+	?	–	?	?
BCNU	?	+	–	?	?	?
Cyclophosphamide	?	?	–	?	?	?
Topoisomerase inhibitors						
Etoposide	?	+	–	+	+	?
Camptothecin	?	?	–	±	±	±
Adriamycin	–	±	±	+	?	?
Anti-microtubule agents						
Vinca-alkaloids	?	–	?	+	?	?
Taxanes	?	–	+	+	+	+
Antibiotics						
Mitomycin-C	?	?	–	?	?	?
Bleomycin	?	–	±	+	?	?
Actinomycin-D	?	+?	?	?	–	–

Note: '–': not demonstrated; '+': demonstrated; '±': conflicting data; '?': unknown.

Abbreviation: BCNU: β-chloro-nitrosourea.

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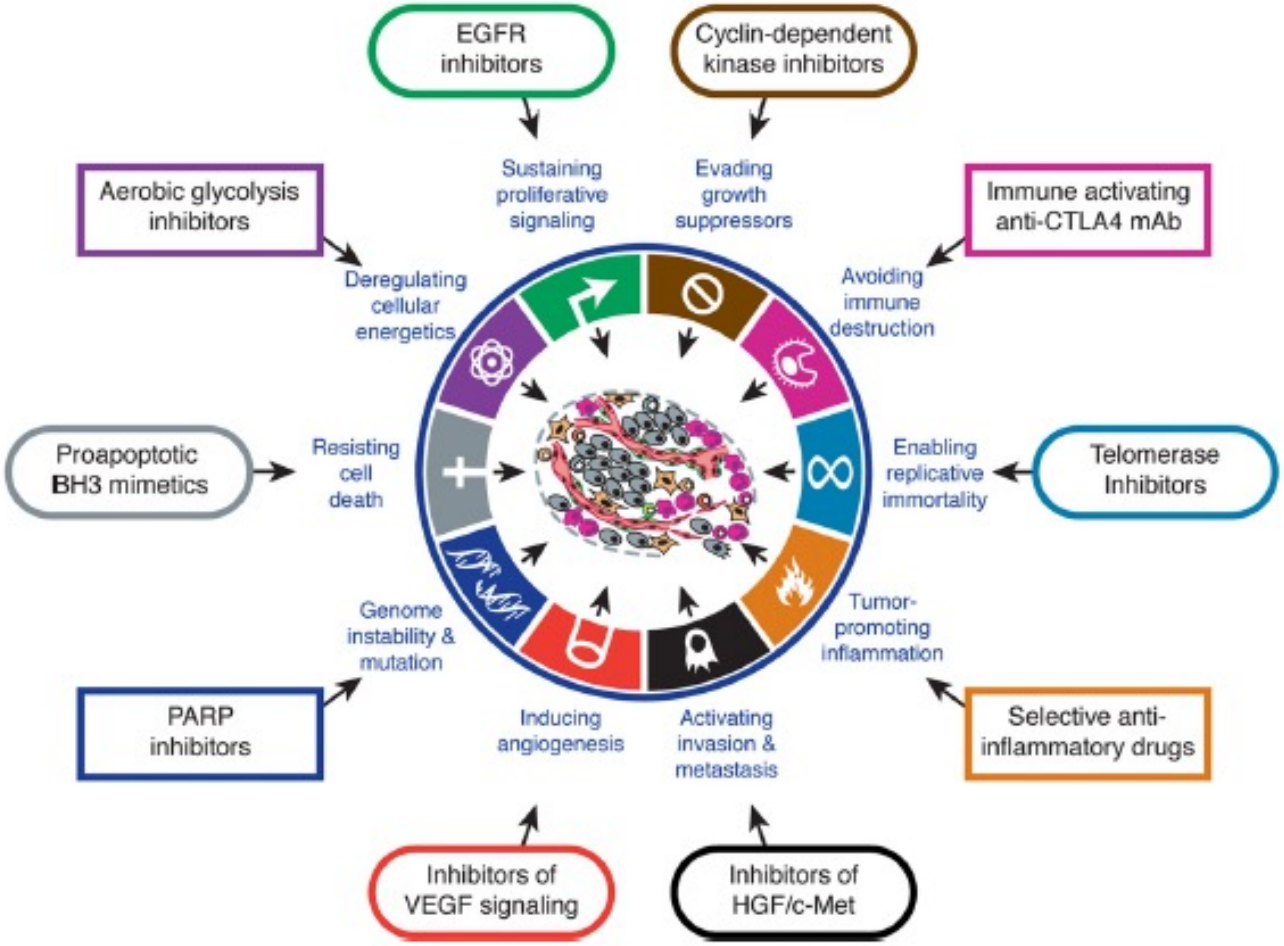
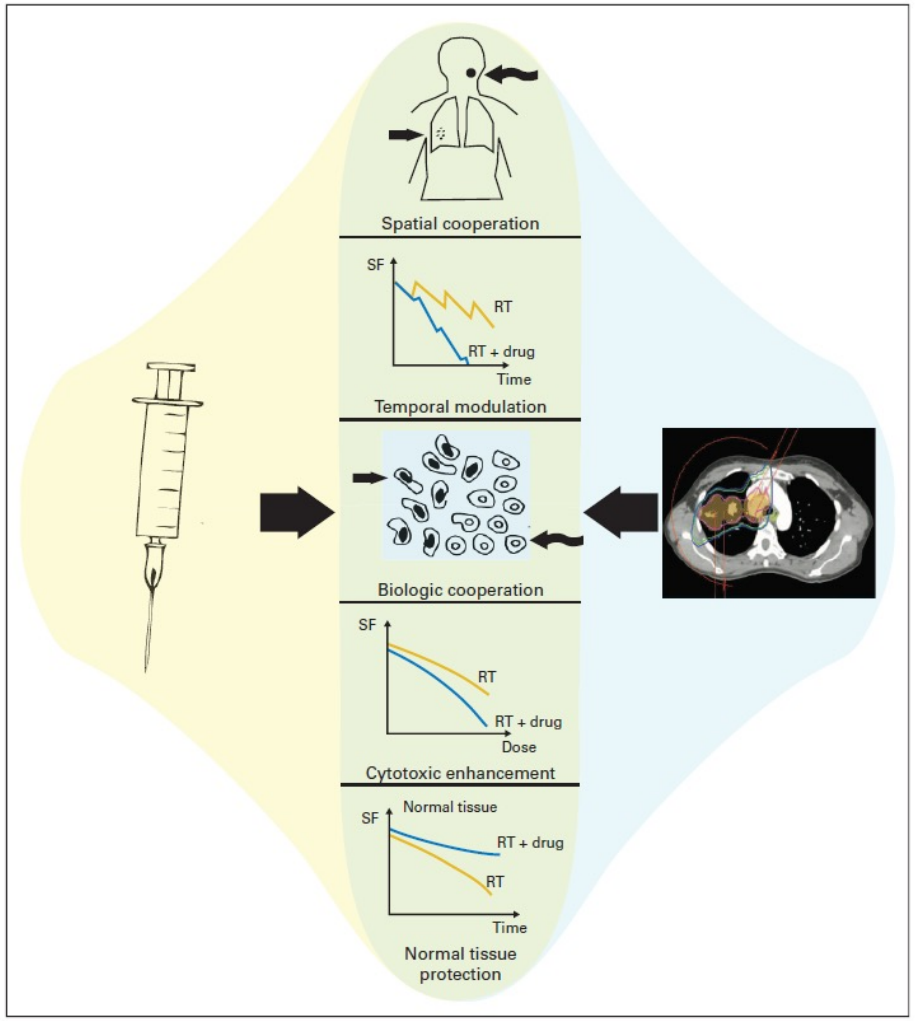
Molecular targeted agents



Molecular targeted agents & RT



Morris et al, JCO 2014

No-compliance: what is the problem?

- Delivery of (C)RT not according to standard is known to lead to
  - A reduced tumor control
    - Geographic misses (GTV-CTV)
    - Underdosage of PTV
    - Underdosage of systemic treatment
  - An increase in serious adverse events
    - Exceeding tolerance levels of organs at risk

→ Negative therapeutic effect

No-compliance: what is the problem?

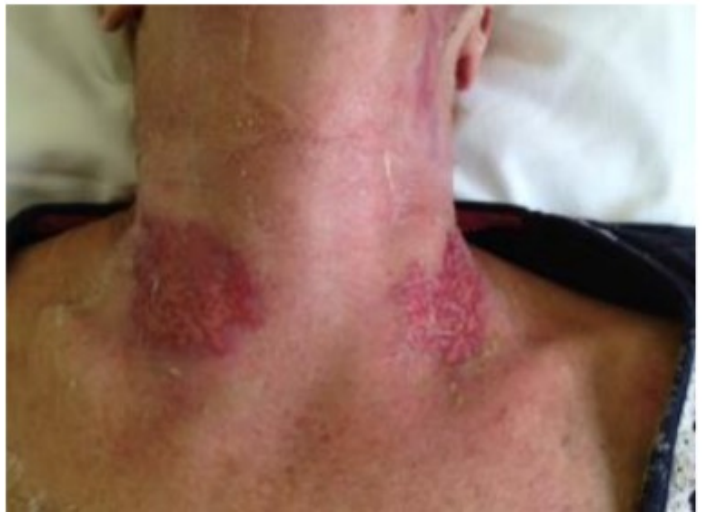
- Delays or interruptions in (C)RT cause an increase in overall treatment time and are known to lead to
  - The development of (C)RT resistance
    - Multiple mechanisms: mutated p53, DNA repair gene amplification, increased levels of ROS scavengers, activation of prosurvival or poor prognostic oncogenes (EGFR, c-MET)
  - Allow resistant cells to repopulate
    - Regrowth of tumor cells between doses of RT or CT
    - Accelerated repopulation: treatment failure and emergence of true radioresistance

→ Negative therapeutic effect

How to prevent no-compliance in (C)RT?

Due to patient-related factors

- Severe radiation reactions
  → Importance of correct patient information & education: establish good communication and gain patient's trust, explain accurately about disease, treatment and potential side-effects, answer questions
  →Importance of good side effects care



- Intercurrent disease
  → Discuss with your colleagues from other departments involved what needs to be prioritized

Due to logistic factors

- Transport difficulties
  - Involve social work or a case manager to look into possible solutions for transport difficulties, e.g. taxi service, accommodation close to the hospital…
  - Consider hypofractionated treatment schedules to limit the number of trips
- Public holidays
  - Take these into account when designing the treatment plan
- Treatment machine downtime due to preventive maintenance
  - Try to plan preventive maintenance after hours or during weekends as much as possible

How to recover no-compliance in (C)RT?

Implementation of RTQA

Crucial to ensure compliance with current standards to safely and effectively administer RT!

Impact of RT protocol-deviations on patient's outcome in prospective phase II-III trials

No-compliance to protocol-specified RT requirements is associated with reduced survival, local control and potentially increased toxicity

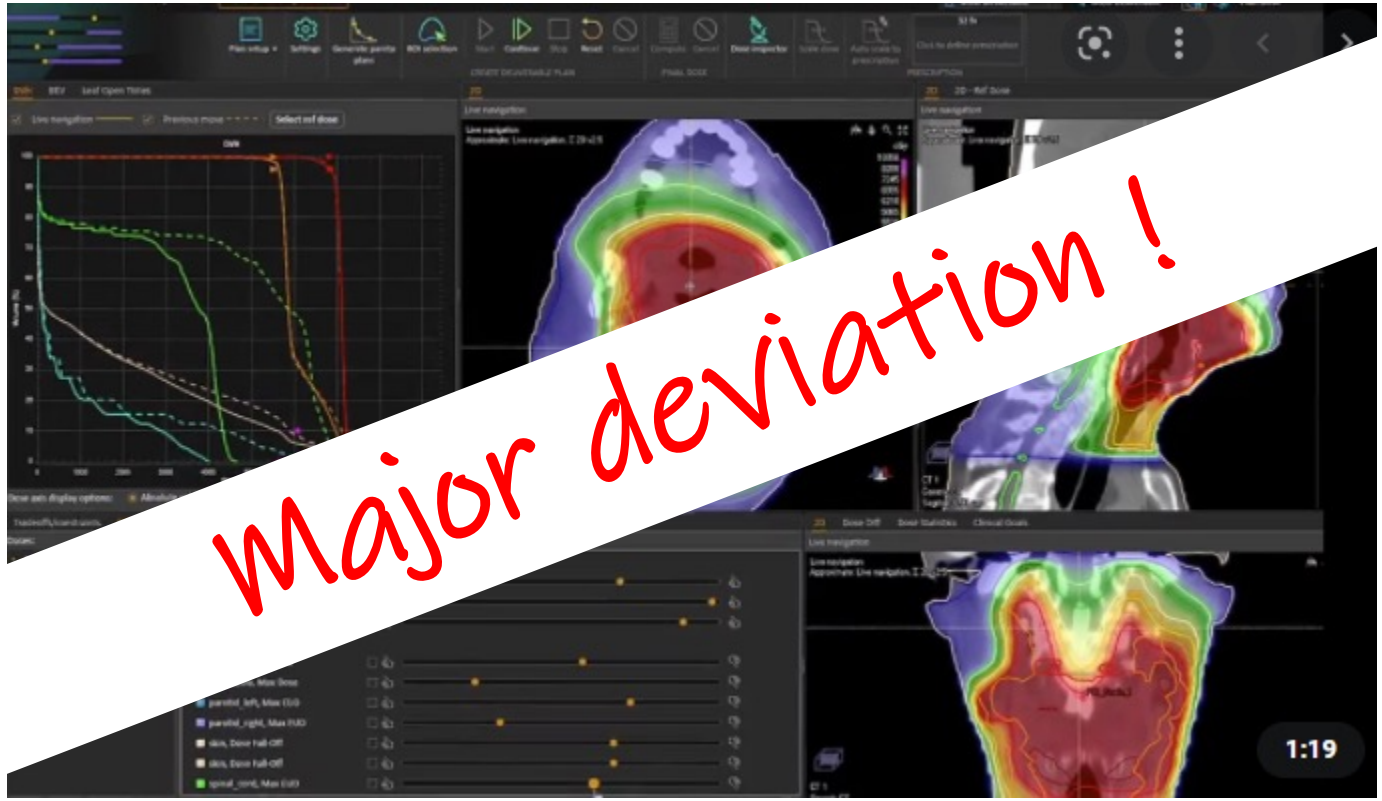
Table 2
Results of QART assessment with patient outcome in prospective clinical trials.

Study [ref]	Type of QA	Number of cases evaluated *n* (%)	Minor deviations *n* (%)	Major deviations *n* (%)	Technical issues with QA review *n* (%)	Impact on clinical outcome	*p* Value
HD 4 [5]	R	368 (98.0)	–	141 (37.5)*	8 (2.1)	7-year RFS with D: 72% *vs.* 7-year RFS with no D: 84%	0.004
EORTC 20884 [2]	R	135 (88.8)	–	63 (46.7)	46 (30.3)	5-year RFS with D: 90% *vs.* 5-year RFS without D: 84%	0.31
RTOG 0411 [4]	R	NS	–	13 (13.4)	NS	Grade GI ⩾ 3 toxicity with D:45%‡ *vs.* Grade GI ⩾ 3 toxicity without D:18%‡	0.05
RTOG 9704 [1]	R	416 (92.2)	–	200 (48.0)**	14/35 (40.0)†	mOS with D: 1.46 yo *vs.* mOS without D: 1.74 yo	0.008
RTOG 0022 [8]	R	67 (97.0)	47 (89.0)	6(11.0)	14/67 (21.0)	LRF with major D: 50% *vs.* LRF with no major D: 6%	0.04
TROG 0202 [15]	P & R††	687 (80.5)‡‡	–	97 (11.8)	33/820 (4.0)	OS with major D: 70% *vs.* OS without major D: 50%	<0.001

Abbreviations: R, retrospective; P, prospective; LRF, local-regional failures; D, deviations; mOS, median overall survival; RFS, relapse-free survival; GI, gastro-intestinal; NS, not specified.

Weber D et al Radiat Oncol 2012

Scenario 1
RTQA

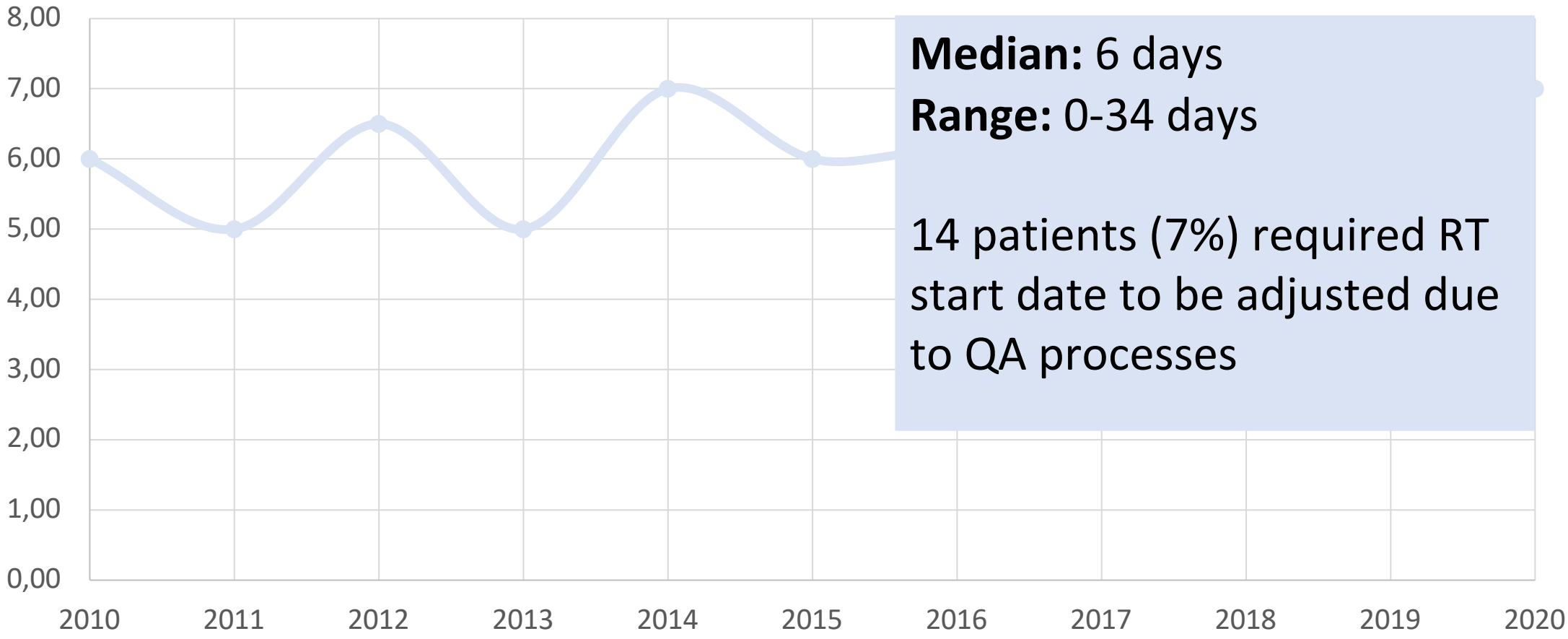


Potential solutions: RTQA

- RTQA undertaken in 'real time' prior to treatment for the first 5 pts randomized to CRT from each center
  - If major violations identified, an additional two cases were submitted for RTQA
  - Once acceptable quality was achieved, RTQA was completed for one third of subsequent cases (randomly selected)

- Review included:
  - *Pre-treatment review:* to ensure appropriate CTV coverage
  - *Post-treatment review:* to assess compliance of RT delivery with protocol guidelines after completion of RT

Median time from QA to treatment start date (days) over time



Median: 6 days
Range: 0-34 days

14 patients (7%) required RT start date to be adjusted due to QA processes

Scenario 2

Chemo not prepared in due time

Consider treatment interactions

- Consider mechanism(s) of treatment interaction of the particular chemotherapeutic drug(s) and RT
- Concomitant?
  - Still possible to deliver chemo on the same day?
- Sequential?
  - Still possible to deliver chemo according to schedule?

Table 3 Mechanisms of chemotherapy and radiotherapy interaction.

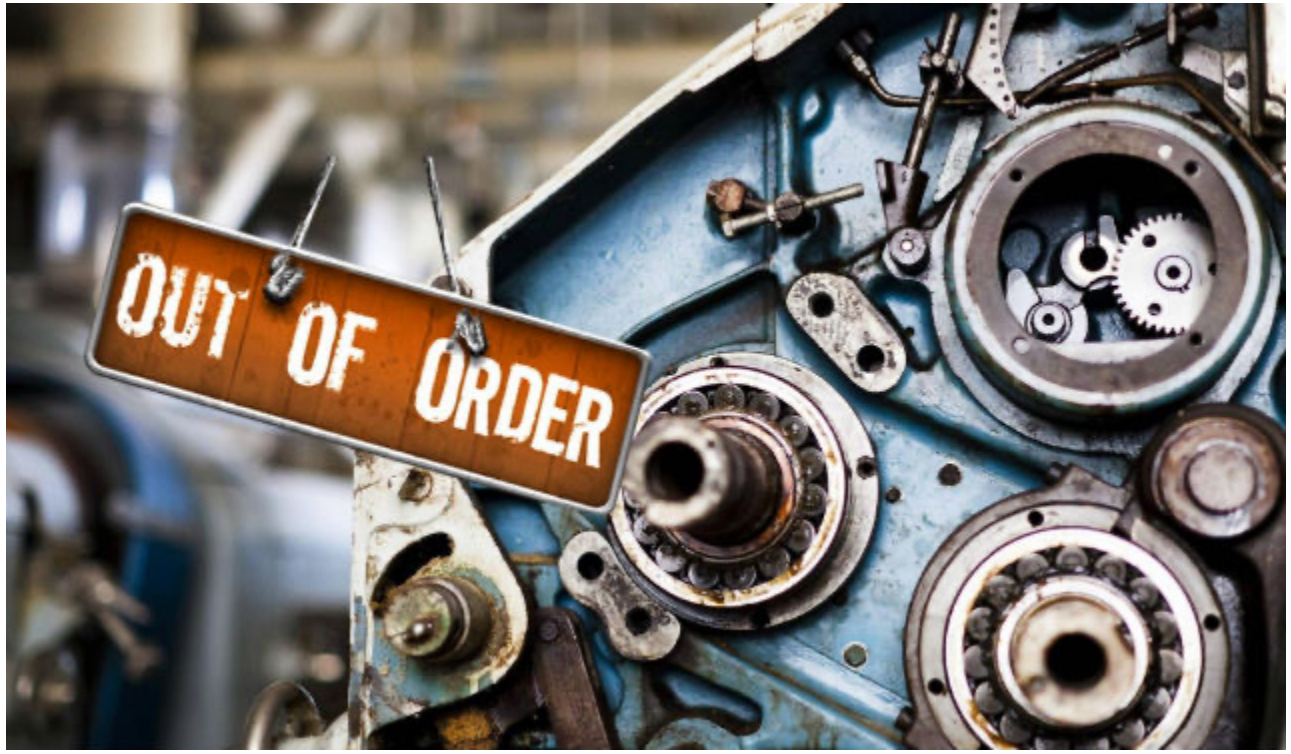
Process affected	Mechanism[a]	Drug examples
Increased radiation damage[a]	Incorporation of chemotherapy drug into DNA/RNA	5-FU: incorporation into DNA, increasing susceptibility to RT damage Cisplatin: cross-links with DNA or RNA (intrastrand and interstrand); works for both hypoxic and oxygenated cells[51]
Inhibition of DNA repair process[a]	Interference with the DNA repair process after radiation	Halogenated pyrimidines (e.g. 5-FU, bromodeoxyuridine, iododeoxyuridine) Nucleoside analogs (e.g. gemcitabine, fludarabine) Cisplatin Methotrexate Camptothecins and doxorubicin Etoposide Hydroxyurea Carmustine, lomustine
Cell-cycle interference (cytokinetic cooperation and synchronization)[a]	Most cytotoxic chemotherapies as well as radiation are cell-cycle-specific, and proliferating cells are most susceptible Accumulation of cells in the G2 and M phases (the most radiosensitive phases) Elimination of radioresistant cells in the S phase	Taxanes lead to cell-cycle arrest via tubulin stabilization Nucleoside analogs (e.g. gemcitabine, fludarabine), etoposide, methotrexate, hydroxyurea
Enhanced activity against hypoxic cells[a]	Reoxygenation second to tumor shrinkage. Hypoxic cells are 2.5–3.0 times less radiation-sensitive than normoxic cells[18,44] Chemotherapy can help to eliminate hypoxic cells	Most chemotherapeutic agents; described in particular for paclitaxel[45] Tirapazamine, mitomycin (selective killing of hypoxic cells); nitroimidazoles (resensitize hypoxic cells to radiation)
Radiotherapy enhancement by preventing repopulation[a]	Systemic therapy can slow or stop rapid proliferation, which could otherwise be the basis for repopulation phenomenon	Most chemotherapeutic agents, in particular: Antimetabolites with activity in the S phase inhibit repopulation (e.g. 5-FU, hydroxyurea) EGFR inhibitors, which impede cell proliferation between RT fractions[100]
Inhibition of prosurvival and 'poor prognosis' markers[a]	Targeted therapies (best demonstrated for EGFR inhibition) block signaling pathways that might be responsible for radioresistance and poor prognosis	EGFR inhibitors—shown for anti-EGFR antibody, PKI-166 (small-molecule TKI), and EGFR antisense,[129–131] but on the basis of clinical experience likely to be a class effect[49,132]
Hyperradiation sensitivity[b]	HNSCC cells resistant to standard-fraction CRT can be resensitized to CRT by using smaller fraction sizes (<1 Gy) more frequently	Effect demonstrated for taxane-based CRT including paclitaxel as well as docetaxel[29,50] Low-dose fraction radiation

[a]Chemoradiotherapy potentiation through drug addition. [b]Chemoradiotherapy potentiation through alteration in radiation administration. Abbreviations: 5-FU, 5-fluorouracil; CRT, chemoradiotherapy; HNSCC, head and neck squamous cell carcinoma; RT, radiotherapy; TKI, tyrosine kinase inhibitor.

Seiwert, Nat Clin Pract Oncol 2007

Scenario 3

Machine breakdown



Potential solutions

- Consider tumor type
  - Prolongation of OTT is mainly problematic for HNSCC, NSCLC, cancer of the uterine cervix
  - It occurs in all tumors even in prostate cancer

Potential solutions

- Adapt treatment schedule after the gap
  - Accelerated radiation schemes
    - For planned schedule delivering 1 fx per day, 5 days per week, this can be accomplished by giving more than 5 fx per week by
      - Giving 2 fx per day or
      - By treating on Saturday and/or Sunday
    - Aim to deliver planned total dose, with prescribed dose per fraction, in as near the planned OTT as possible

Potential solutions

- Adapt treatment schedule after the gap
  - Hypofractionated radiation schedule
    - Risk of increased late sequelae or decreased tumor control?
    - Depends on the exact values of α/β values for the relevant late normal tissue endpoints and the tumor type in question.

Potential solutions

- Adapt treatment schedule after the gap
  - Hypofractionated radiation schedule
    - An example…

A patient with colorectal cancer is planned to receive pre-operative RT with 5 x 5 Gy from Monday to Friday. The first 2 fx are given as planned on Mon and Tue, but due to a machine breakdown, no treatment could be given on Wedn.

It is assumed to deliver the isoeffective tumor dose by increasing the size of the 2 fx to be given on Thu and Fri in order to finish as planned on Fri. We assume that the α/β = 10 Gy for colorectal cancer.

What is the required dose per fx for the last 2 fx? What is the accompanying change in risk of rectal complications for this modified fractionation schedule?

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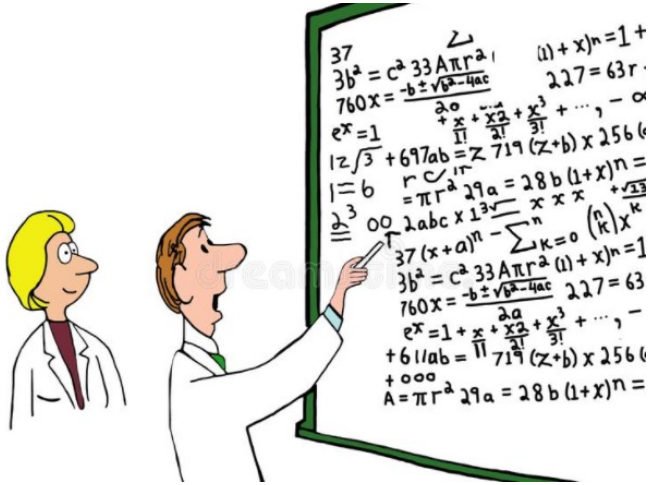
Potential solutions

- Adapt treatment schedule after the gap
  - Hypofractionated radiation schedule
    - An example…



What is the required dose per fx for the last 2 fx?

Solution: 6,7 Gy / fx on Thu and Fri, a total of 13,4 Gy to achieve the same tumor effect

→ less than the 3 x 5 Gy originally planned for Wedn-Fri

→ reason: larger effect per Gy deriving from the increased dose per fx

How will this affect risk of bowel damage (α/β = 4 Gy)?

EQD2 modified schedule = 38,9 Gy vs 37,5 Gy for 5 x 5 Gy schedule

→increased risk of late bowel morbidity

→Consider to stick to 5 Gy / fx and give the 5th fx on Sat or simply accept a 3 day protraction (finishing on Mon)

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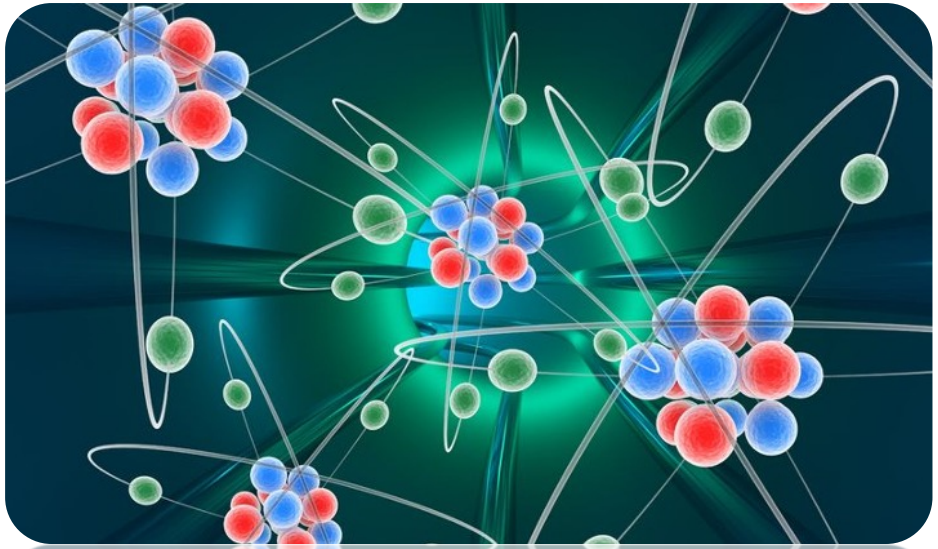
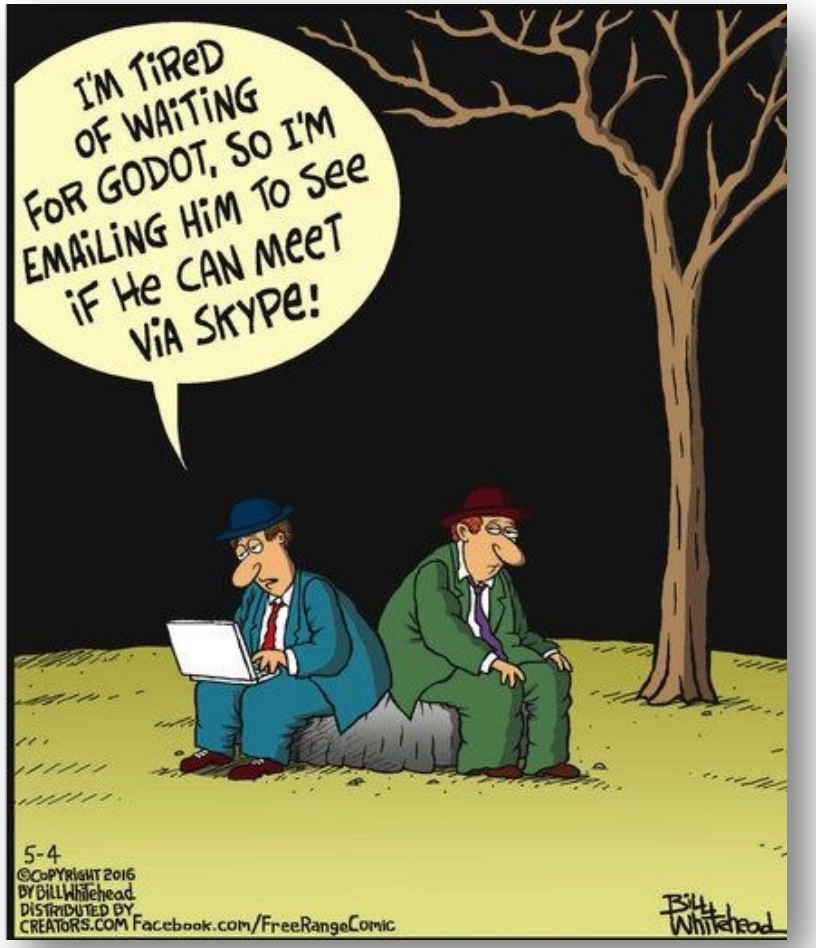
Potential solutions

- Change linac or treatment modality in order to avoid a gap or delay in treatment
  - Compatible Linacs (back-up plans)
  - Consider back-up treatment with photons in case of downtime of proton therapy machine



Scenario 4

Patient does not show up for (C)RT



Potential solutions

- Impact depends on timing: before or during treatment
- Try to reach the patient asap to understand the problem (patient-related, logistic)
- Try to find a solution / convince the patient (or his/her family)

Scenario 5
Pandemic

Impact of the COVID-19 Pandemic on Patients and Staff in Radiation Oncology Departments in Belgium: A National Survey

- Covid-19 reached Belgium in Feb 2020
- Weekly survey March-June 2020
- Sent to all 26 RT depts (RTD)
  - 73% completed first survey
  - 57% responded to all weekly surveys
- COVID-19 status of patients and staff
  - 24 members COVID-positive, of which 67% RTTs

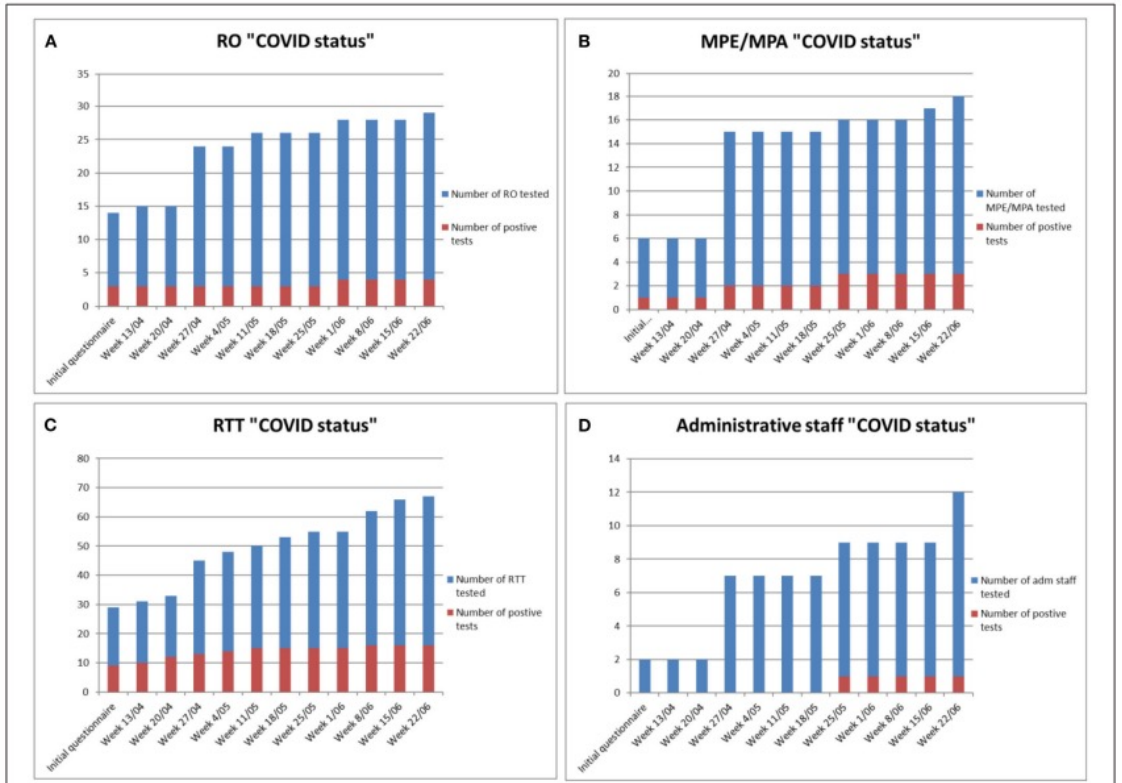


FIGURE 1 | Cumulative number of RTD staff members tested and number of staff tested positive for COVID-19: for **(A)** Radiation Oncologists (RO); **(B)** Medical Physics Experts (MPE) and Medical Physics Assistants (MPA); **(C)** Radiation therapists (RTTs) and **(D)** Administrative staff.

Vaandering A et al, Front Oncol 2021

Impact of the COVID-19 Pandemic on Patients and Staff in Radiation Oncology Departments in Belgium: A National Survey

- Impact of Covid-19 on RTD activities

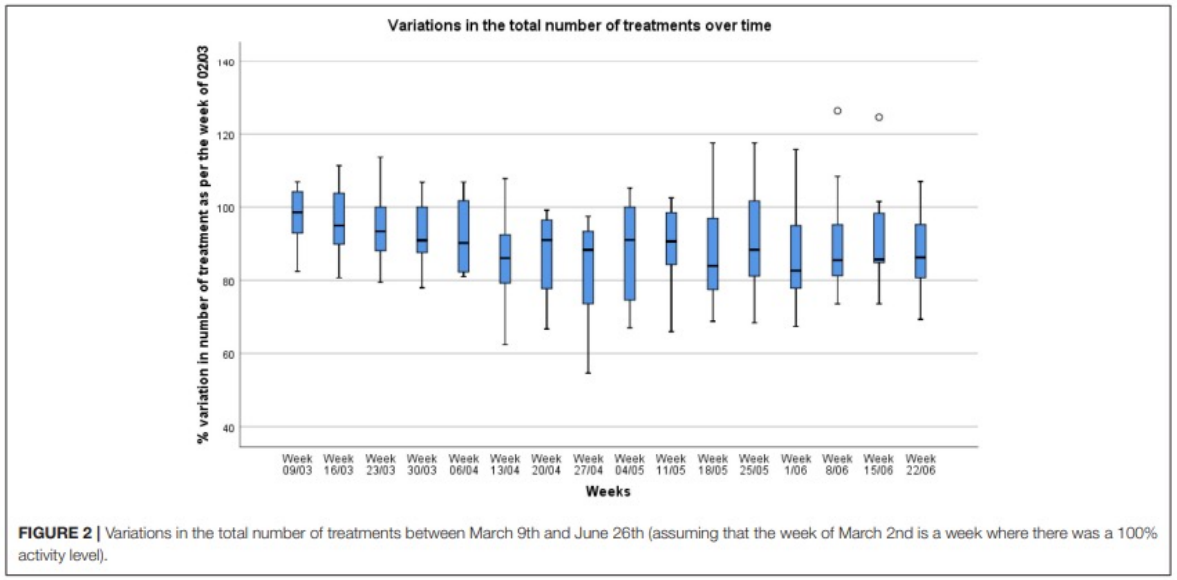
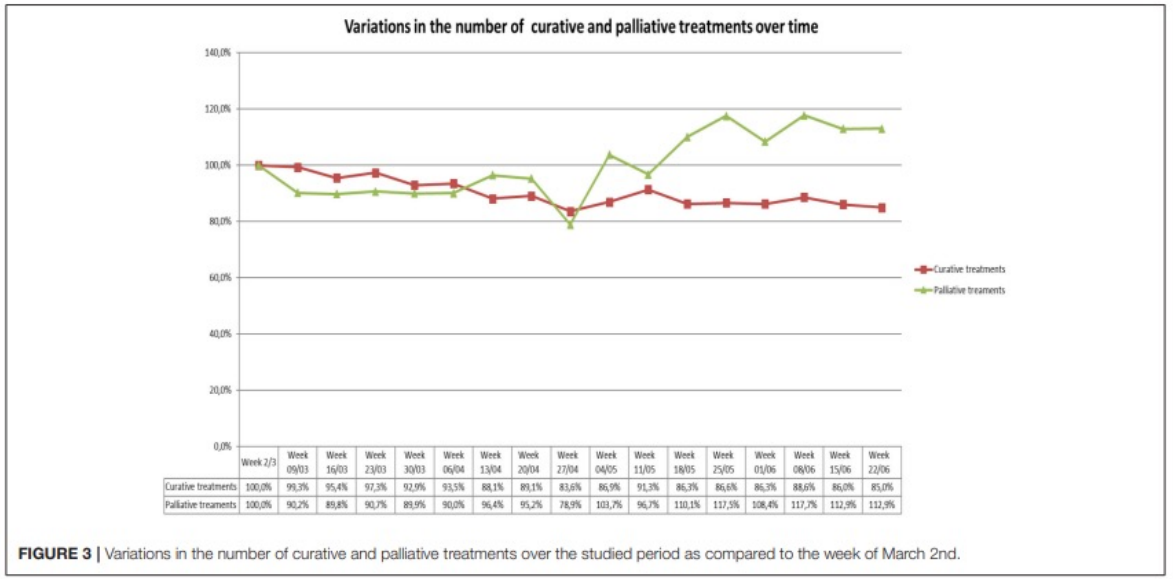


FIGURE 2 | Variations in the total number of treatments between March 9th and June 26th (assuming that the week of March 2nd is a week where there was a 100% activity level).

The number of patients treated dropped by a maximum of 18.8% when compared to March 2nd, 2020

Decrease in the number of both curative and palliative treatments until the end of April 2020—at which time there is a sudden increase in the number of palliative treatments up to 18.2% as compared to the baseline week



	Week 2/3	Week 09/03	Week 16/03	Week 23/03	Week 30/03	Week 06/04	Week 13/04	Week 20/04	Week 27/04	Week 04/05	Week 11/05	Week 18/05	Week 25/05	Week 01/06	Week 08/06	Week 15/06	Week 22/06
Curative treatments	100,0%	99,3%	95,4%	97,3%	92,9%	93,5%	88,1%	89,1%	83,6%	86,9%	91,3%	86,3%	86,6%	86,3%	88,6%	86,0%	85,0%
Palliative treaments	100,0%	90,2%	89,8%	90,7%	89,9%	90,0%	96,4%	95,2%	78,9%	103,7%	96,7%	110,1%	117,5%	108,4%	117,7%	112,9%	112,9%

FIGURE 3 | Variations in the number of curative and palliative treatments over the studied period as compared to the week of March 2nd.

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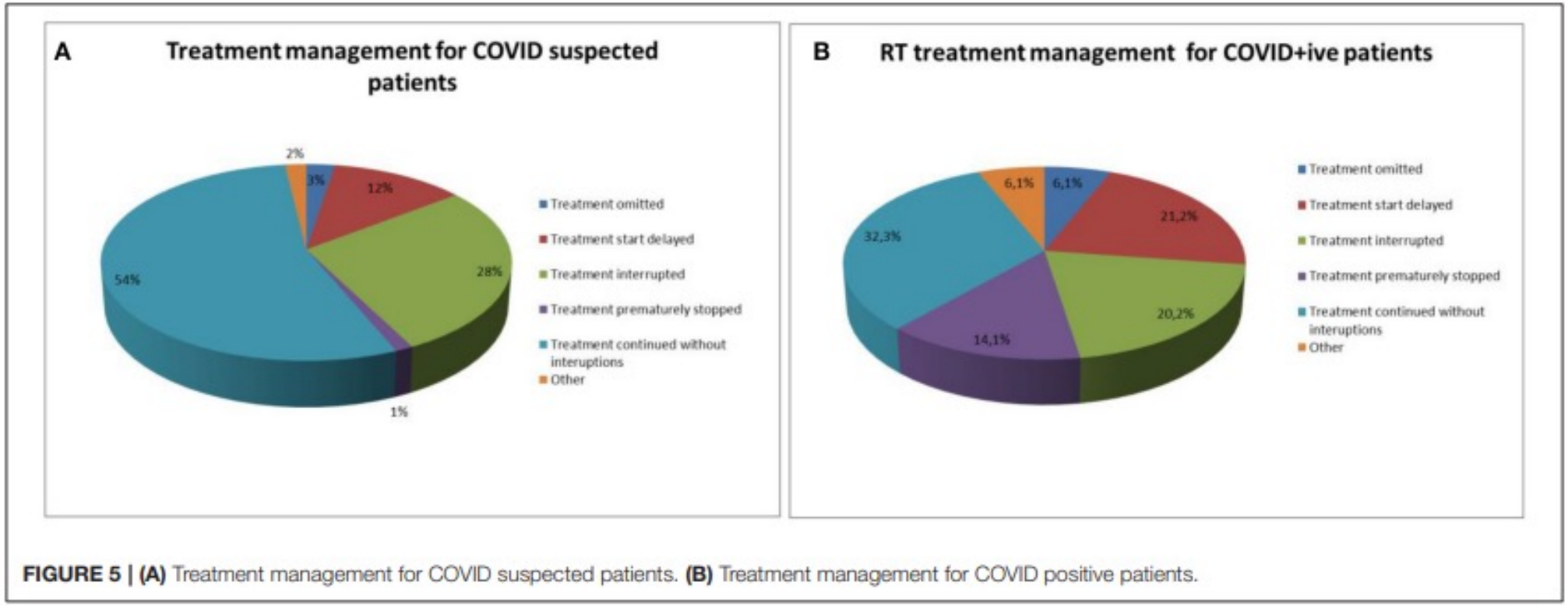

FIGURE 5 | (A) Treatment management for COVID suspected patients. **(B)** Treatment management for COVID positive patients.

For clinically suspected COVID-positive patients treatment was interrupted in 28% of patient and delayed in 12% of patients.

For COVID positive patients, the treatment was either delayed or interrupted In 20% of the positive cases. In 14% the treatment was prematurely stopped and in 6% of patients another element impacted the treatment.

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Changes of RT indications

Changes of RT fractionation schemes

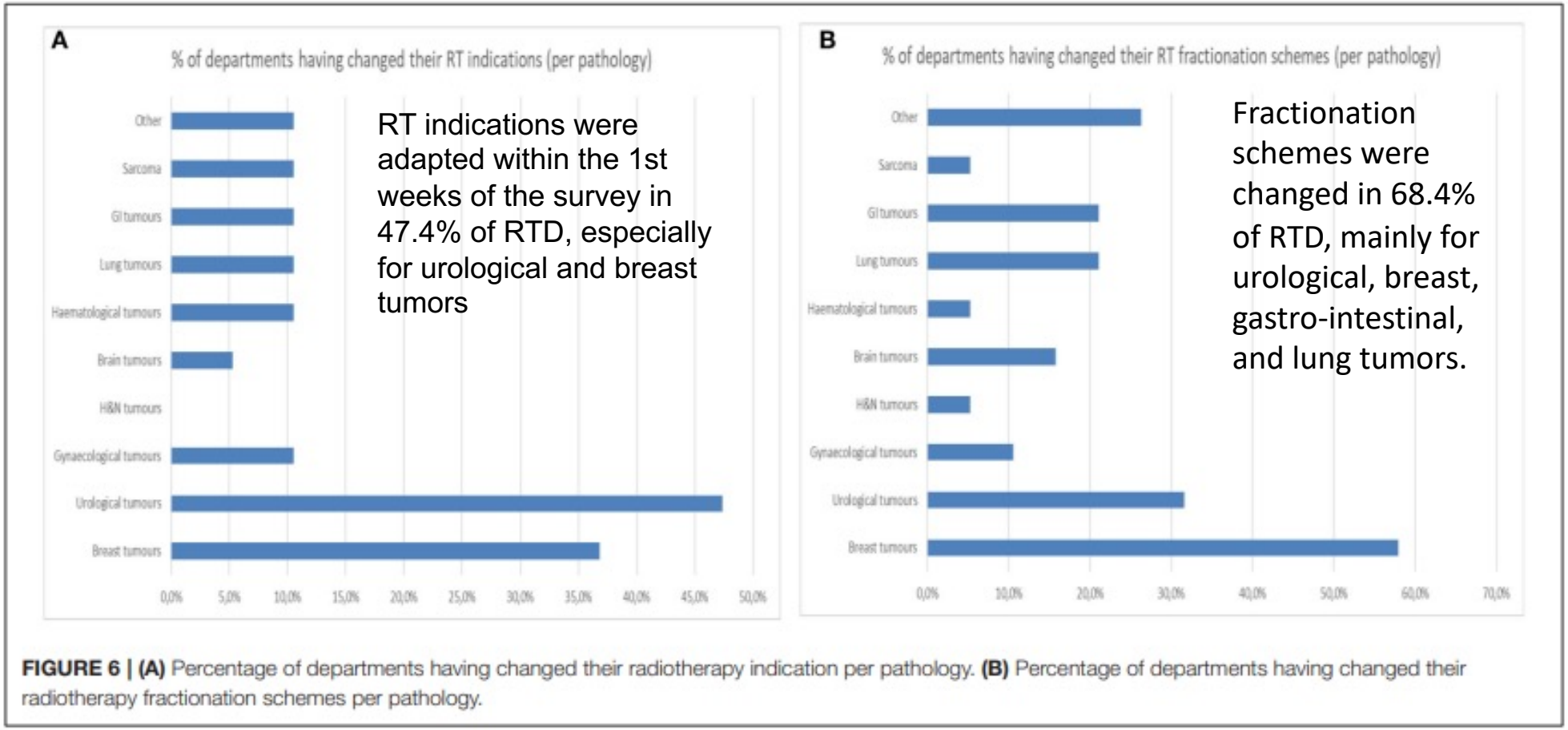

FIGURE 6 | (A) Percentage of departments having changed their radiotherapy indication per pathology. **(B)** Percentage of departments having changed their radiotherapy fractionation schemes per pathology.

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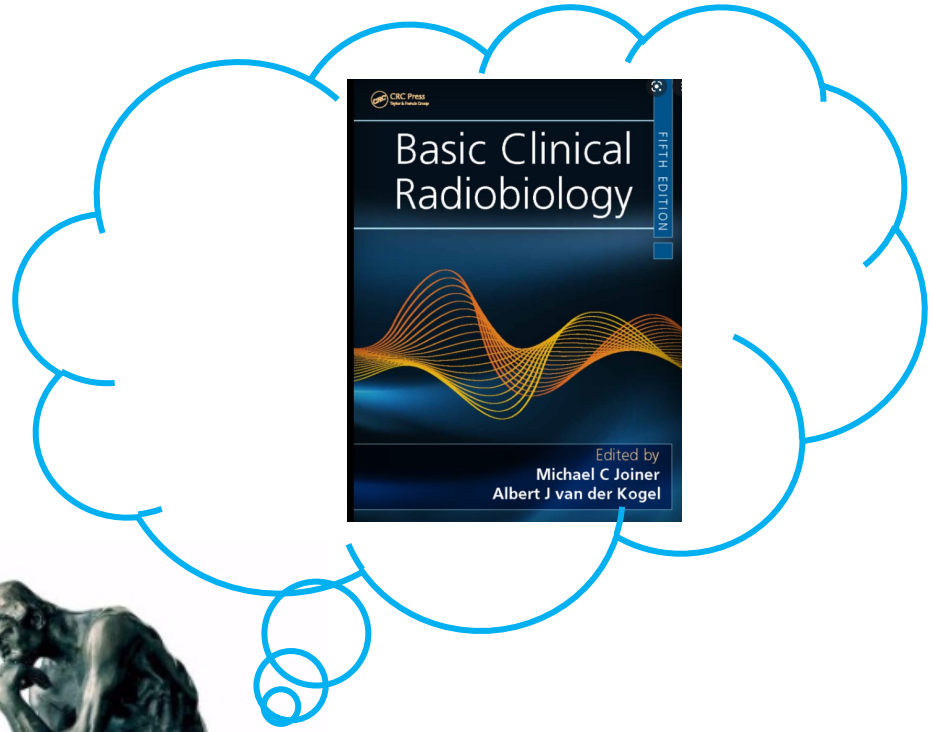
Recommendations

Tip #1 – Remember radiobiology*

- Think about what you've learned about the R's of radiobiology, working mechanisms and interactions of chemo, MTA, immuno,…



*Seems to be useful knowledge after all ;)

Tip #2 – Communicate

- With your team (RTTs, MDs, residents, dosimetrists, medical physicists…)
- With your colleagues from other departments (medical oncology, pediatric oncology…)

Tip #3 – Document

- Any no-compliance
- The adjustments/changes made
- As soon as possible
- In the (electronic) patient file

Tip #4 – Be prepared

- Try to anticipate what you can and implement RTQA

Conclusions

- To prevent a negative therapeutic effect of no-compliance in (C)RT
  - Avoid treatment gaps as much as possible
  - Actively modify treatment after a gap
  - Mainly in HNSCC, NSCLC, cancer of the uterine cervix
  - Also some support for importance of OTT in SCC of the skin and vagina, and in medulloblastoma
- Communication and documentation is key!
- The RT community is flexible: change of practice (RT indications and fractionation schedules) was rapidly incorporated in the different RT depts due to covid-19.