



Reirradiation of head and neck tumors

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Clinical importance of reirradiation

- Tumors with acquired radioresistance / hypoxia
- Patients die of locoregional progression rather than metastases (2year incidence of progression or death 60%)
- Tumor dose > 60 Gy in previously irradiated tissues (usually received 50-70 Gy; organ dose constraints already reached)

Clinical importance of reirradiation

■ Increasing situation and practice (Nieder C)

-Technological advances in X RT

-Increased locoregional control

-Last potentially « curative » option

Clinical importance of reirradiation

- Improved X techniques

- not favoring IMRT over hypofractionated stereotactic RT (SBRT) or vice versa (Tao GORTEC 2018 (French Head and neck clinical research group) in head and neck cancers

- although study with limits

- In terms of locoregional control and toxicities

Clinical importance of reirradiation

Low quality data :

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-Retrospective studies (missing clinical and DICOM RT data, unstandardized reporting)

-Small non comparative prospective studies

-Competitive risks (locoregional progression and death)

-Limited follow up



Clinical importance of reirradiation

■ Risk for late toxicities

(carotid blowout, osteoradionecrosis, esophageal stricture / feeding tube, fistula, aspiration...) : 20-40%, median 9 months

■ Spinal cord recovery increasing with time lapse between 2 RT courses ; BED_{Gy2} 135 Gy, <98 Gy at each course

Clinical importance of reirradiation

- Yet, 20% of patients alive, disease free and without late toxicities at 2 years
- Intermediate prognosis but worth proton therapy
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- Excellent locoregional rates with proton therapy in 4 retrospective studies (up to 80% 2y local control rate)
- Likely selection biases, true benefit ?

Clinical importance of reirradiation

- Equipoise ?
 - High dose gradients with all techniques
 - Intermediate / low dose spread with IMRT/Stereotactic X RT
- Cost utility ?
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- Case mix of many proton centers > 10%
 - Difficult to treat tumors
 - Unrandomized

Uncertainties in reirradiation and challenges

- Baseline assessment of dysfunction
- Definition of target volumes (CT +/- TEP, MRI) : fibrotic tissues versus tumor, tumor volumes,
- Small PTV margins

- Alpha beta of surrounding tissues low
- Alpha beta of tumor tissues variable
- Both to be better characterized, especially in the reirradiation context

Uncertainties in reirradiation and requirements

- Critical dose to received normal tissues ; requires accurate registration
- Inconclusive data with hyperfractionation and between X-IMRT vs X-Stereotactic RT, tumor size selection effect
- Aim with protons : Tumor coverage (relative dose escalation) + tissue sparing (from intermediate doses)
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Reirradiation trial project

- Randomized phase II for recurring head and neck tumors
 - squamous carcinomas (alpha/beta 10) stratified
 - against various rare HN cancers of lower alpha/beta values of 3-5 for adenoid cystic carcinomas, sarcomas etc
- Best X technique against PBS proton therapy
- Endpoint of randomized phase II: composite endpoint of locoregional progression and quality of life by EORTC HN35 score at one year
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Reirradiation trial project

■ N patients : 90

- to be extended into phase III if accrual fulfills expectations; not unlikely; hard to treat tumors

■ Trial design (based on practice for X RT)

- Stratified on size:

- Normofractionated X IMRT vs IMPT for tumors $> 3\text{cm}$ or

- Hypofractionated Stereotactic X RT / hypofractionated proton therapy for tumors $\leq 3\text{cm}$

- Stratified on concomitant systemic treatment

Reirradiation trial project

- Systematic QA (dummy run of first 2 patients at each center + retrospective QA of later patients)
- Secondary objectives
 - Prognostic factors
 - Locoregional control
 - Survival
 - Toxicities
 - Quality of life
 - Quality of life adjusted years QALY
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Reirradiation trial project

■ Ancillary studies

- Circulating inflammatory and immune biomarkers
- Circulating DNA
- Radiomics (CT, MIR, +/- PET CT) of tumor at reirradiation and radiomics of response
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- Comparative dosimetries (with conservative RBE provided that tumor coverage is at least similar to X with protons)
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Reirradiation trial project

■ Ancillary studies

- Modelling of tumor / normal tissue response by RBE, dose / fraction, alpha beta, time interval
- limited by number of patients, extend?
- toward adapted PBS reirradiation ?
- Medico-economic issues.
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- *First CNS (head) patients will be treated in Caen in July 2018, head and neck patients 4 months later*