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Practice changing data and emerging concepts from recent radiation therapy randomized clinical trials

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Abstract

Introduction: Oncology treatments are constantly and rapidly evolving . We aimed at highlighting the latest radiation therapy practice changing trials and emerging concepts, through an overview of recent randomized clinical trials (RCT).

Materials and methods: Requests were performed in the Medline database to identify all publications reporting radiation therapy RCT from 2018-2021.

Results: Recent RCT sustained the role of newer combinatorial strategies, through radioimmunotherapy for early stage or metastatic lung cancer, but also through newer pro-apoptotic agents (*e.g.* debio 1143 in locoregionally advanced head and neck squamous cell carcinoma) or nanoparticles (*e.g.* NBTXR3 in locally advanced soft-tissue sarcoma). High-tech radiotherapy allows intensifying treatments as shown by the FLAME trial in prostate cancer, and gaining ground in some indications through the development of stereotactic body radiotherapy for example. First randomized evidence on personalized radiation therapy through imaging based (¹⁸F-FDG PET-CT for lung cancer or early stage unfavorable Hodgkin lymphoma, PMSA PET-CT or MRI for high-risk prostate cancer) or biological biomarkers (PSA for prostate cancer, HPV for head and neck cancer, etc) surrogates were conducted to more tailored treatments, with more favorable outcomes. Patients' quality of life and satisfaction appeared to be increasing aims. RCT have validated (ultra)hypofractionated schemes in many indications as for breast, prostate or rectal cancer, resulting in equivalent outcomes and toxicities, more convenient for patients and favoring shared-decision making.

Conclusion: Radiation therapy is a dynamic field of research, and many RCT have greatly impacted therapeutic standards over the last years. Public investments in radiotherapy research should facilitate the transfer of innovation to clinic.

Key words: Radiotherapy; Practice changing data; Randomized; Hypofractionated; Quality of Life; Shared Decision Making.

Introduction

Cancer treatment represents a dynamic axis of medical research, with many practice changing data and new concepts emerging from randomized clinical trials (RCT) each year. In the field of radiation oncology, drug-radiotherapy combinations (e.g.: immunoradiotherapy) and technology developments (stereotactic body radiotherapy [SBRT], image-guided brachytherapy, and in few indications protontherapy) represent ways to improve the therapeutic index ratio [1].

New major endpoints are emerging, focusing on quality of life (QoL) and patient satisfaction. In this context, hypofractionated radiotherapy RCT have brought particularly interesting data, providing in many cases comparable outcomes to the standard treatment, with several advantages including shorter treatments, higher convenience for patients, and decreased costs. Patient preferences and shared decision making are increasingly studied and encouraged.

Considering that the important number of publications can dilute key messages, we aimed to highlight the main axes of radiation therapy development (**Figure 1**), through an overview of practice changing data and emerging concepts from recent radiation therapy RCT.

Search strategy and selection criteria

Requests were performed in the Medline database (*via* PubMed) to identify all adults publications reporting radiotherapy RCT since January 2018 (**Table S1**). The latest update was performed in December 2021, using the following MESH terms: "radiotherapy" AND "clinical trial" AND "randomized OR randomised", as keywords and "English" as language. A total of 1,347 results were found, including some protocols, some incomplete or prematurely closed trials, some supportive care trials, and some negative trials with no impact

on standard treatment. Titles and abstracts have been read, as well as manuscripts of the screened papers. Only radiotherapy practice-changing or emerging concepts of large randomized phase 2 or 3 clinical trials were selected (n=110). Primary endpoints included overall survival (OS), progression/disease-free survival (PFS/DFS), local control rate, pathological complete response (pCR) or adverse events rate and QoL. Some major RCT are cited to illustrate the main radiation oncology advances (manuscript, **Figure 1** and **Table 1**), whereas **Table S1** reported all publications matching with the research criteria.

Radiosensitization

Radiosensitization represents a major way to enhance the local therapeutic index and could prevent from distant metastasis. Conventional DNA-targeting chemotherapies have been the standard of care (SoC) in the last 20 years. Within the 2000s, several molecularly targeted therapies have been assessed in association, mostly resulting in higher toxicities and no increased outcomes [1]. Newer radiotherapy combinations with DNA-interfering agents or immune checkpoint blockers are assessed.

Chemotherapy and targeted therapies

HPV-associated oropharyngeal carcinoma displays increased outcomes and better response to treatments, suggesting a possible therapeutic de-escalation. Concurrent cetuximab *versus* (vs) cisplatin was tested in three RCT, De-ESCALaTE HPV, NRG Oncology RTOG 1016 and TROG 12.01 [2–4]. The association of radiotherapy plus cetuximab showed no benefit in terms of reduced toxicity, tumor control, progression-free survival (PFS) and overall survival (5-year OS: 77.9% vs 84.6%; non-inferiority p=0.51), platinum-based radiotherapy remaining the SoC in this setting.

The best schedule of concurrent chemotherapy remains an open question in locally advanced head and neck squamous cell carcinoma (HNSCC). Once-a-week 30 mg/m² cisplatin chemoradiation has been compared with once-every-3-weeks 100mg/m² [5]. High dose bolus cisplatin resulted in superior locoregional control (73.1% vs 58.5%, p=0.01), particularly in the adjuvant setting, without survival improvement. This gain in locoregional control must be balanced with increased severe acute toxicities (84.6% vs 71.6%, p=0.01). However, the weekly dosing was considered suboptimal compared to the more commonly used 40 mg/m² dose.

Long-term survival effects of additional chemotherapy over radiotherapy alone continue to be reported. As an example, in high-risk endometrial cancers, the updated analysis of the PORTEC-3 clinical trial has shown improved 5-year OS (81.4% vs 76.1%, p=0.03) and failure-free survival (76.5% vs 69.1%, p=0.02) with adjuvant and concurrent chemoradiotherapy vs radiotherapy alone [6,7]. At 5 years, grade ≥ 2 adverse events were reported in 38% of women in the chemoradiotherapy group, vs 23% in the radiotherapy-alone group (p<0.01). The adjunction of chemotherapy was particularly relevant for patients with FIGO stages III and/or serous cancers. However, for stages III or IVA endometrial carcinoma, adjuvant and concurrent chemoradiotherapy was not shown to enhance 5-year relapse-free survival (59% vs 58%) compared to an exclusive chemotherapy consisting of six cycles of chemotherapy doublet (carboplatin and paclitaxel) [8]. Chemoradiotherapy was on the other hand associated with a lower 5-year incidence of vaginal recurrence (2% vs 7%; HR=0.36; 95% CI=0.16-0.82) and pelvic and paraaortic lymph-node recurrence (11% vs 20%; HR=0.43; 95% CI=0.28-0.66) than chemotherapy alone, but distant recurrence was more common (27% vs 21%; HR=1.36; 95% CI=1.00-1.86). The benefit of radiotherapy and brachytherapy regarding locoregional control should probably be combined with an intensification of systemic treatment.

Finally, newer and possibly less toxic chemotherapy could be of interest in frail patients. In the ZJCH-E-E trial, Ji *et al.* reported that concurrent S-1 (a novel oral fluoropyrimidine derivative) could be effective and tolerable in elder esophageal cancer patients. The 2-year OS was increased with radiotherapy and S-1 over irradiation alone (53.2% vs 35.8%, respectively), without increased severe toxicities, except leukopenia [9]. For patients with locoregionally advanced nasopharyngeal carcinoma, nedaplatin-based concurrent chemoradiotherapy has been compared to cisplatin-based concurrent chemoradiotherapy [10]. The 2-year PFS was 89.9% in the cisplatin group and 88.0% in the nedaplatin group (non-inferiority $p < 0.05$), with different toxicity profiles (lower frequency of grade 3-4 anorexia, nausea, vomiting, and late auditory toxicities with nedaplatin, but more thrombocytopenia during the treatment). Thus, nedaplatin-based concurrent chemoradiotherapy represents an alternative doublet treatment strategy to cisplatin-based concurrent chemoradiotherapy for patients with locoregional advanced nasopharyngeal carcinoma.

Newer radiosensitizers

In high-risk locoregionally advanced HNSCC, a randomized phase II trial, Debio 1143-201, has highlighted the efficacy of xevinapan (debio 1143), a pro-apoptotic agent (inhibitor of apoptosis proteins antagonist) used for the first time in association with a standard high-dose cisplatin chemoradiotherapy (n=96) [11]. Locoregional control at 18 months was achieved in 54% of patients of the experimental arm, vs 33% of the standard arm ($p = 0.03$), with similar toxicity profiles. A phase III trial is ongoing to confirm these results.

Different type of nanoparticles are currently evaluated with irradiation. A phase II-III clinical trial, Act.In.Sarc, has assessed the safety and efficacy of neoadjuvant intratumoral injection of the high Z hafnium oxide (HfO₂) nanoparticle NBTXR3 with radiotherapy (50

Gy/25 fractions) vs radiotherapy alone in patients with locally advanced soft-tissue sarcoma (n=180 patients) [12]. The main objective was the pathological complete response and was reached in 16% of patients in the NBTXR3 group vs 8% of patients in the radiotherapy alone group (p=0.04).

Radioimmunotherapy

Radiotherapy enhances the antitumor immune response, inducing antigens release and tumor antigen presentation. In the preoperative setting, a first randomized phase II trial showed that concurrent SBRT (24 Gy in 8 fractions) and the anti PD-L1 durvalumab increased major pCR rates (16 [53.3%] vs 2 [6.7%]; p<0.01) as compared to durvalumab alone for early stage lung cancer patients [13].

In locally advanced stages, many concurrent chemoradiotherapy-immunotherapy trials are ongoing [1]. In HNSCC, a large (n=697 patients) phase III trial, JAVELIN head and neck 100, however showed disappointing results with the addition of the anti-PDL1 avelumab to concurrent chemoradiotherapy (median PFS not reached, stratified Hazard Ratio [HR]=1.21 [95% CI 0.93–1.57] favoring the placebo group; one-sided p=0.92) [14].

In the metastatic setting, radioimmunotherapy trials produced conflicting results in trials evaluating the abscopal effect of radiotherapy when given with immunotherapy. The abscopal effect describes the shrinking or disappearance of the tumor in parts of the body that were not the direct target of local therapy, but were destroyed by the immune system. The phase 3 trial CA184-043 has assessed radiotherapy (8 Gy in a single fraction to the bone) + the anti-CTLA4 ipilimumab or placebo in metastatic castrate-resistant prostate cancer patients [15]. The primary endpoint (OS) was not improved, even if a PFS improvement (HR=0.70, 95% CI 0.61–0.82; p<0.01) was observed with ipilimumab. In a phase II randomized trial testing the abscopal effect on 62 metastatic HNSCC patients, the addition of SBRT to one

metastatic lesion to the anti-PD1 nivolumab did not lead to an objective response rate (ORR) or outcome improvements over nivolumab alone [16]. On the contrary, a pooled analyze of two randomized phase II trials (n=148) reported improved median PFS (HR=0.67, p=0.04) and median OS (HR=0.67, p<0.01) in metastatic NSCLC patients receiving SBRT to a single tumor site (PEMBRO-RT)/lung or liver lesions amenable to RT (MDACC trials) and the anti-PD1 pembrolizumab over pembrolizumab alone [17–19]. Only unirradiated lesions were measured for response. Best abscopal response rate was 19.7% with pembrolizumab vs 41.7% with pembrolizumab plus radiotherapy (odds ratio [OR] 2.96, 95% CI=1.42-6.20; p<0.01). Confirming phase III (e.g. NCT03774732) are ongoing in this setting.

Treatment intensification

Newer radiotherapy indication or treatment intensification may lead to an increased proportion of cured patients, but at the risk of increased toxicity.

Radiotherapy gaining ground

In hepatocellular carcinoma showing macroscopic vascular invasion, transarterial cisplatin-based-chemoembolization (TACE) and normofractionated irradiation was compared to the SoC sorafenib in the AMC IRB 2013-0627 trial [20]. The experimental treatment was well tolerated, and resulted in an improved OS (13.8 vs 10.8 months, p=0.04), PFS, ORR, and time to progression.

In patients with clinically resectable, locally advanced cancer of the esophagus or of the esophagogastric junction, neoadjuvant chemoradiotherapy (consisting of carboplatin plus paclitaxel with concurrent 41.4 Gy radiotherapy) followed by surgery was compared to surgery alone in the CROSS trial [21,22]. At a long-term follow up, the absolute 10-year OS

benefit was 13% (38% vs 25%) in favor of the neoadjuvant arm [22], as confirmed by the NEOCRTEC5010 trial [23,24].

There is ongoing debate on indications for whole-pelvis rather than prostate only radiation therapy in cN0 prostate cancer men at high risk of nodal involvement. The POP-RT RCT showed that lymph node irradiation improved biochemical control and metastasis-free survival over prostate only radiotherapy, in a population at high risk of lymph node involvement ($\geq 20\%$) [25]. The GETUG-AFU 23 / PEACE 2 trial (NCT01952223) and RTOG 0524 (NCT01368588) which asked the same question have since closed accrual with around 800 and 2500 patients respectively. In the metastatic setting, local therapy of the primary tumor is considered with the intent of reducing primary tumor burden, relieving symptoms, or propagation of metastases. For patients with *de novo* metastatic nasopharyngeal carcinoma who had a complete or partial response following three cycles of cisplatin and fluorouracil chemotherapy, the efficacy and safety of chemoradiation (60 to 70 Gy to GTV, 50 to 66 Gy to the different PTV/33 fractions) have been compared to exclusive chemotherapy in the SYSUCC5010 trial [26]. Radiotherapy added to chemotherapy significantly improved the 24-month OS in this population (76.4% vs 54.5%, $p < 0.01$). The frequency of late severe (grade ≥ 3) hearing loss and trismus was 5.2% and 3.4% respectively in the chemotherapy plus radiotherapy group. Another study, STAMPEDE, demonstrated that prostate radiotherapy improved OS (0.68, $p < 0.01$) for men with low volume metastatic prostate cancer, but not in an unselected population or in patients with high volume metastatic disease [27].

Radiotherapy dose escalation or hyperfractionation

With modern radiotherapy technologies (intensity-modulated radiotherapy [IMRT], image-guided radiotherapy...), some trials hypothesized that additional ionizing irradiation doses

could be safely delivered. However, several recent RCT failed to show an advantage of dose-escalation. The RTOG 0617 trial compared definitive standard-dose (60 Gy) vs high-dose (74 Gy) radiation with concurrent chemotherapy in locally advanced NSCLC. Higher dose resulted in more severe dysphagia and reduced OS as compared to 60 Gy, but it should be highlighted that only 47% patients received IMRT in this trial [28]. The ARTDECO trial compared concurrent chemoradiotherapy with a 50.4 Gy standard dose to 61.6 Gy in locally advanced esophageal cancer. No differences were observed in terms of outcome and toxicity in this trial [29]. On the other hand, the FLAME trial compared a focal “isotoxic” external-beam radiation therapy boost to the prostate based on MRI (up to 95 Gy vs 77 Gy). The addition of the boost resulted in higher biochemical DFS, without observed OS or toxicity differences [30].

Hyperfractionated accelerated (e.g. twice daily) radiotherapy with concomitant chemotherapy (HFCRT) offers the theoretical advantage of reduction of late radiation injury and prevention of tumor repopulation in treatment intervals, often at a cost of increased acute side effects. Twice-daily concurrent chemoradiotherapy is still considered the SoC in localized small cell lung cancer. A recent randomized phase II trial, THORA, suggested that higher HFCRT dose (60 Gy in 40 fractions vs 45 Gy in 30 fractions) could be achievable and improve 2-year OS (odds ratio 3.1; $p < 0.01$) [31]. In locally advanced HNSCC, a network meta-analysis (MACH-NC) included individual patient data from 28,978 patients in 115 trials showed that HFCRT could offer the best OS as compared to conventional chemoradiotherapy [32]. However, the added cost and logistical challenges of multiple fractions per day have limited the widespread utilization of these techniques. Induction chemotherapy followed by chemoradiotherapy was the second better intensifying option in this analysis [32].

Reinforcing induction/consolidation systemic treatments

Metastatic relapse is the main pattern of failure in many patients receiving curative-intent radiotherapy, justifying the incorporation of newer and more effective systemic treatments.

Induction chemotherapy prior to radiotherapy has become SoC in several tumor type including HNSCC (MACH-NC) [32], nasopharyngeal [33], and rectal cancers (PRODIGE 23) [34]. A Chinese trial reported an improved 3-years DFS (85.3% in the induction chemotherapy group vs 76.5% in the standard-therapy group, $p < 0.01$) and 3-years OS (94.6% vs 90.3%) after induction chemotherapy (gemcitabine + cisplatin) before cisplatin-radiotherapy among patients with locoregionally advanced nasopharyngeal carcinoma [33]. In two locally advanced rectal cancers phase III trials (PRODIGE23 and RAPIDO), total neoadjuvant oxaliplatin-based chemotherapy before chemoradiotherapy (PRODIGE 23) or after short course radiotherapy (RAPIDO) showed increased response rates and PFS as compared to the standard (long-course chemoradiotherapy + adjuvant chemotherapy) groups [34,35].

For many tumor sites, consolidation systemic treatment in patients who do not progress after frontline chemoradiotherapy was assessed as well to decrease subsequent distant relapse and possibly increase OS. According to the CAN phase III trial, including high-risk nasopharyngeal carcinoma (stage III–IVA, excluding T3–4N0 and T3N1 disease, $n=406$) without locoregional disease or distant metastasis after definitive chemoradiotherapy, the addition of oral metronomic capecitabine for a year improved failure-free survival at 3 years (85.3% vs 75.7% in the observation arm; HR=0.50; $p < 0.01$) [36]. For patients with high-risk non-metastatic prostate cancer receiving androgen suppression and radiotherapy, the addition of a chemotherapy with docetaxel was shown to be associated with an improved OS (93% vs 89% at 4 years, $p=0.03$), an improved DFS and a reduction of distant metastasis, according to the RG Oncology RTOG 0521 trial [37]. In this population, the addition of abiraterone and prednisolone alone or with enzalutamide to androgen-deprivation therapy

(ADT) was also shown to significantly increase the rate of metastasis-free survival compared with ADT alone (HR=0.53, 95% CI=0.44–0.64, $p<0.01$), and the rate of OS (HR=0.60, 95% CI=0.48–0.73, $p<0.01$) (STAMPEDE trial) [38]. Toxicity profiles were more favorable than reported with docetaxel [37]. There was no evidence of a difference in metastasis-free survival when enzalutamide and abiraterone acetate were administered concurrently, compared with abiraterone acetate alone (interaction HR=1.02, CI=0.70–1.50, $p=0.91$). Abiraterone acetate with prednisolone should therefore be considered as a new standard treatment for this population.

Newer compounds are also tested as a consolidation strategy. The LUX-Head & Neck 2 trial reported that EGFR inhibitor afatinib did not show benefit after concurrent chemoradiotherapy in HNSCC [39]. Adjuvant immunotherapies are showing promising results in some locations. In the PACIFIC trial, the anti-PD-L1 durvalumab delivered after thoracic chemoradiotherapy in locally advanced unresectable NSCLC enhanced OS (at 24-month, 66.3% vs 55.6, $p<0.01$) as compared to placebo, becoming a SoC in this setting [40,41]. Adjuvant nivolumab (an anti PD1) as compared to placebo (CheckMate 577) also showed increased DFS (HR=0.69; $p<0.01$) among patients with resected esophageal or gastroesophageal junction cancer who had received neoadjuvant chemoradiotherapy followed by surgery [42]. It should be emphasized that initial ^{18}F FDG Positron Emission Tomography - Computed Tomography (PET-CT) was not mandatory in these trials, possibly enriching the dataset in advanced patients.

Local ablative treatments in oligometastatic patients

The oligometastatic paradigm suggests that some patients with a limited number of metastasis might have a better prognosis, especially after local ablative treatment adjunction. Few RCT (SABR-COMET, ORIOLE) support the interest of SBRT in oligometastatic case outcomes,

or its ability to delay systemic treatment [43,44]. Palma *et al* have reported a 13-month increase in OS and a doubling of PFS in patients with a controlled primary tumor and 1-5 metachronous oligometastases, but with 4.5% of patients presenting grade 5 toxicities (radiation pneumonitis, pulmonary abscess and perforated gastric ulcer) [43]. Phillips *et al* have shown an improved PFS after SBRT for oligometastatic prostate cancer in a randomized phase II trial, without \geq grade 3 adverse events [44]. Ost *et al*, through a randomized phase II trial, reported an increased androgen deprivation therapy-free survival for prostate cancer patients receiving metastasis-directed therapy (13 months *vs* 21 months, $p=0.11$), with no grade 2-5 toxicity [45]. Efforts in homogenizing oligometastatic definitions/patients selection and generating phase III evidence should be particularly prioritized in this context.

Personalized radiation therapy

Precision medicine is rapidly moving forward and has demonstrated that molecular or imaging-based subgroups may be deciphered, and could avoid the traditional “one size fits all” strategy.

Nuclear medicine and MRI integration

Development of imaging based biomarkers leads to upgrade cancer staging, prognostic description and predictive data. ^{18}F FDG PET-CT leads to better selection of target volume, allowing chemoradiotherapy volume reduction (involved-fields *vs* historical elective nodes) in locally advanced NSCLC, without jeopardizing outcomes (PET-Plan) [46].

In the proPSMA trial, Hofman *et al*. have shown that Prostate-Specific Membrane Antigen (PSMA) PET-CT as a first-line investigation was superior to conventional CT and bone scan in terms of staging accuracy, but also less costly and led to less radiation exposure

before curative-intent therapy in men with high-risk prostate cancer [47]. PSMA PET-CT has since become the standard of care for prostate cancer staging.

¹⁸F-FDG PET-CT could also help deciphering best responders to treatments, as highlighted by the GITIL/FIL HD0607 trial [48]. In the non-inferiority GHSG HD17 trial, consolidation radiotherapy was avoided in PET-negative patients after chemotherapy for newly diagnosed early-stage unfavorable Hodgkin lymphoma. The difference between-group PFS was 2.2%, demonstrating that omission of consolidation radiotherapy is possible without loss of efficacy [49].

The FLAME trial has assessed the benefit of a simultaneous integrated focal boost to the macroscopic prostatic tumor (up to 95 Gy), through a delineation based on a multiparametric MRI, using T2-weighted, diffusion-weighted imaging and dynamic contrast-enhanced sequences [30]. With a median follow-up of 72 months, significantly improved 5-year biochemical DFS (from 85% to 92%, $p < 0.01$) was reported, without significant differences in toxicity. This trial illustrates the concept of dose-painting, using inhomogeneous dose targeted to anatomical, molecular and/or functional imaging, with the aim of focally increasing dose to high risk volumes, without increasing toxicity rates. This concept is already being used in cervix cancer brachytherapy for more than 15 years, thanks to MRI guided treatment [50]. In the last few years, some EBRT RCT are investigating upcoming trials, for example using metabolic data and hypoxia-based dose escalation in head and neck cancer (NCT02352792, NCT03865277), or using MRI findings for prostate cancer (NCT01411345, NCT02307058).

Surrogate biomarkers

In patients with increasing PSA concentration after radical prostatectomy (from 0.1 ng/mL to between 0.2 ng/mL and 2.0 ng/mL), the 120-month data from the GETUG-AFU 16 trial have

shown that salvage radiotherapy (66 Gy/33 fractions) combined with short-term androgen suppression improved outcomes (reduced risks of biochemical or clinical progression and death) as compared with salvage radiotherapy alone [51]. The 120-month PFS was 64% for patients treated with radiotherapy plus short-term androgen suppression, and 49% for others ($p < 0.01$).

Many biomarkers are currently being tested in clinical trials to guide treatment modalities. Plasma Epstein-Barr Virus (EBV) DNA in nasopharyngeal cancers (NCT02135042, NCT02363400, NCT02874651, and NCT03544099), HPV DNA in HNSCC [52] or cervical cancers (NCT03739775, NCT02554565), molecular profile (POLE, MSI, NSMP, p53) in endometrial cancers (NCT00411138, NCT03469674), 1p/19q co-deletion in glioblastoma (CeTeG/NOA-09 and trials) [53,54] or EGFR mutations in lung cancers (NCT03521154) are promising markers to personalize radiation-based treatments. In the phase II trial NRG Oncology HN002 including HPV-associated oropharyngeal cancer patients, the 2-year PFS after de-escalation (60 Gy IMRT over 6 weeks with concurrent weekly cisplatin) was superior to historical controls, justifying advancement to a phase III study [55].

Another way to facilitate a personalized approach to locoregional treatment decisions is to develop biomarkers of toxicities. Grossberg *et al.* have conducted a cohort study, which was nested in a RCT comparing hypofractionated (42.56 Gy/16 fractions) with conventionally fractionated whole breast irradiation (50 Gy/25 fractions) after breast-conserving surgery [56]. The C-509T allele in TGFB1 was shown to be a candidate genomic marker of radiation breast fibrosis risk. If confirmed, this could possibly facilitate a more personalized approach to locoregional treatment decisions in breast cancer.

Reducing treatment burden, enhancing patients quality of life and satisfaction with similar survival outcomes

With longer-term survivors, more attention has been given to sequelae of treatments. Technological improvements allowed to better spare critical organs and possibly reduce overall treatment time.

(Ultra)hypofractionated radiotherapy

Hypofractionation (increasing dose per fraction above 2 Gy, leading possibly to acceleration i.e. decrease total duration of treatment) is one of the main ways to enhance value-based health care in radiotherapy, if non-inferiority of survival outcomes is proven, without increased toxicities. Hypofractionation and acceleration are relevant for the health care systems (e.g. more patients treated in a shorter period), particularly in the context of an ageing/frail population [57], with limited health care resources and with the emergence of pandemics.

In early stage breast cancer patients, the DBCG HYPO trial confirmed that adjuvant whole breast radiotherapy schedule delivering 40 Gy/15 fractions offers locoregional tumor control and rates of late toxicities at least as good as the accepted international standard of 50 Gy/25 fractions [58,59]. According to a recent randomized trial, hypofractionated adjuvant radiotherapy delivered to the breast and lymph nodes seems to be similarly relevant for higher risk breast cancer (tumor stage T3-T4 and/or positive lymph nodes) [60]. Further trials comparing moderate hypofractionated to conventional lymph node radiotherapy are ongoing (NCT03127995, NCT02690636, NCT03829553, NCT04025164, NCT02912312, and NCT04228991).

More hypofractionated whole breast or accelerated partial breast irradiation (APBI) schedules have been reported, with or without acceleration. The FAST-Forward trial has

shown that a more hypofractionated adjuvant whole breast scheme, with 26 Gy/5 fractions over one week, is as effective and safe as the 40 Gy/15 fractions regimen [61]. With a median follow-up of 71.5 months and 4,110 enrolled patients with invasive carcinoma of the breast (pT1–3, pN0–1, M0), the 5-year incidence of ipsilateral breast tumor relapse was non inferior after 26 Gy (1.4%) than after 40 Gy (2.1%; $p < 0.01$), without increased toxicities. Incidence of locoregional relapses, but also distant relapses, DFS, and OS were not different. The FAST trial has also assessed highly hypofractionated adjuvant whole breast treatment (30 or 28.5 Gy/5 fractions), delivered with once-weekly fraction, for women ≥ 50 years of age with low-risk invasive breast carcinoma (pT1-2 pN0) [62]. At 10 years, normal tissue effects were not different after 28.5 Gy/5 once weekly fractions than after 50 Gy/25 fractions, as well as breast cancer-related events or deaths, offering a particularly interesting scheme for frail patients with a low-risk breast cancer. Regarding APBI, the APBI-IMRT-Florence trial showed that APBI (30 Gy/5 daily-fractions over one week) resulted in similar 10-year ipsilateral breast tumor recurrence (3.7% vs 2.5% respectively, $p = 0.40$), OS (91.9% vs 91.9%) and breast cancer-specific survival (97.8% vs 96.7%, $p = 0.45$) than conventionally fractionated whole breast irradiation (50 Gy/25 fractions) [63]. APBI was associated with less acute ($p < 0.01$) and late adverse events ($p < 0.01$), and improved late cosmetic outcomes as evaluated by both physicians ($p < 0.01$) and patients ($p < 0.01$). At the contrary, twice-daily APBI resulted in higher late side effects [64] and possibly higher ipsilateral breast-tumor recurrence [65] as compared to whole-breast irradiation according to two large phase III trials, the RAPID and the NSABP B-39/RTOG 0413.

Moderate hypofractionation has also become SoC in localized prostate cancer [66]. The interest of ultrahypofractionation SBRT, defined as fraction sizes of at least 5 Gy, has also been assessed. The HYPO-RT-PC trial has compared conventionally fractionated radiotherapy (78 Gy/39 fractions) with ultrahypofractionated treatment (42.7 Gy/7 fractions)

in intermediate or high risk prostate cancer [67]. The 5-year PFS rates were 84% in both arms. Late toxicities were similar, except for an increase in urinary toxicity at 1-year follow-up in the ultrahypofractionation group (6% vs 2%). The recently published clinical trial PACE-B suggests that substantially shortening treatment courses with SBRT does not increase either gastrointestinal or genitourinary acute toxicity [68]. Late side effects also seem to be comparable after ultrahypofractionated, as compared to conventionally fractionated radiation therapy [67,69,70].

Refining radiotherapy indications, timing and dose

Timing, dose and indications of radiotherapy are continuously challenged. The interest of a radiotherapy dose reduction (24 Gy in 12 fractions vs 4 Gy in 2 fractions) was assessed in indolent follicular and marginal zone lymphoma, in the FoRT trial. The 2- and 5-year local progression-free rates were decreased in the lower dose group, showing that 24 Gy in 12 fractions remains the optimal schedule [71]. Considering that many recurrences occur in vaginal cuff or distant sites, Randall *et al* have addressed the question of the superiority of vaginal cuff brachytherapy and chemotherapy compared with pelvic EBRT alone, in a population of patients with stage I endometrioid histology with high-intermediate-risk, stage II disease, or stage I to II serous or clear cell tumors (GOG-0249) [72]. No difference was shown in terms of 5-year recurrences-free survival, OS or late toxicity rate, but acute toxicities were increased. In prostate cancer, the question of early salvage radiotherapy role has been addressed. The GETUG-AFU 17 and the RTOG 08.03/ANZUP RAVES trials have compared adjuvant radiotherapy (66Gy) vs early salvage radiotherapy (64Gy) following radical prostatectomy, with or without concomitant short-term hormonotherapy respectively [73,74]. Patients had pathologically-staged pT3a-pT4a (bladder), positive surgical margins, pNx or pN0 disease, and PSA \leq 0.1 ng/mL. No benefit was retrieved for event-free survival in

patients assigned to adjuvant compared to salvage radiotherapy, and the risk of genitourinary toxicity and erectile dysfunction was increased. The RADICALS-RT trial and a meta-analysis have also reported consistent data [75,76]. Thus, delaying salvage radiotherapy could spare men from overtreatment.

Some trials failed to show a benefit of radiotherapy. For patients with resectable, locally recurrent nasopharyngeal carcinoma who have previously received radiotherapy, endoscopic surgery significantly improved OS compared with IMRT (20% of grade 5 toxicities in the radiotherapy arm), according to the ChiCTR-TRC-11001573 trial [77]. In retroperitoneal sarcoma, preoperative radiotherapy (50.4 Gy/28 fractions) did not reduce the median abdominal recurrence-free survival, and increased toxicity rates, as compared to observation (EORTC-62092, STRASS) [78]. In two phase III trials (Lung ART and PORT-C) assessing the role of postoperative radiotherapy for resected pIIIA N2 NSCLC who received (neo)adjuvant chemotherapy, DFS was not different as compared to the observation arm [79,80]. Subsequent analyses will evaluate the role of adjuvant radiotherapy in high-risk subgroups. For patients with locally advanced NSCLC, prophylactic cranial irradiation (PCI, mainly with 30 Gy/15 fractions, 30 Gy/12 fractions or 30 Gy/10 fractions) has been compared to observation in two phase III RCT, the NRG Oncology/RTOG 0214 and NVALT-11/DLCRG-02 [81,82]. PCI decreased the 5- and 10-year rate of brain metastasis and improved the 5- and 10-year DFS, but did not improve OS (the primary endpoint of the NRG Oncology/RTOG 0214 trial). Grade 3 and 4 acute toxic events occurred in 4% and 1% of cases in the PCI arm. Grade 3 late toxicities were reported in 3% of cases in the PCI arm, and grade 1-2 memory impairment and cognitive disturbance were increased.

Shared decision making

Some clinical trials with different treatment modalities highlighted equivalent outcomes and different toxicity profiles. They offer other therapeutic options that should be proposed to patients, and permit favoring patients choices and preferences. It can also be a way to enhance patients compliance with the planned treatment, which is an important parameter, as compliance correlated with important oncologic outcomes (e.g. locoregional failure-free survival, PFS and OS) in rectal and anal cancers (CAO/ARO/AIO-04 and ACT II trials) [83,84]. Thus, shared decision-making is possible in many cases that are increasingly frequent, and could results in more relevant treatment decisions.

For early breast cancers, the GEC-ESTRO APBI trial has shown that APBI using multicatheter brachytherapy after breast-conserving surgery was non-inferior to whole-breast irradiation (50 Gy/25 fractions followed by a boost) in terms of local control and OS, and was not associated with worse QoL compared with whole-breast irradiation [85]. The total treatment time for patients in the APBI group was 4–5 days. These findings support APBI using brachytherapy as an alternative treatment after breast-conserving surgery for patients with early breast cancer, which could be safely offer in this population.

Concerning good-risk ductal carcinoma *in situ*, EBRT was shown to significantly reduce the 15-year cumulative incidence of ipsilateral breast recurrence (7.1%vs 15.1%; $p<0.01$), compared to observation (NRG Oncology/RTOG 9804) [86]. However, it was associated to 1% of reported late grade 3 toxicities. The authors concluded that these results are not an absolute indication for RT, but rather should inform shared patient-physician treatment decisions.

Reducing side effects with high-tech radiotherapy

Technologic development could upgrade oncologic outcomes, but also patient-reported adverse events and QoL.

The implementation of IMRT had reduced the volumes receiving high doses while creating a low dose bath, and was shown to improve radiotherapy tolerance in many indications, mainly head, neck and pelvic areas (NRG Oncology-RTOG 1203, PARCER) [87–89]. The role of hippocampal-avoidance brain radiotherapy is currently assessed. Some reports, as the PREMER and the NRG Oncology CC001 trials, suggest a benefit in terms of neurocognitive preservation [90,91], but not all (NCT01780675) [92]. No difference in intracranial PFS and OS is reported in these trials.

Local relapse after brain metastases surgery may be reduced with adjuvant stereotactic radiosurgery (SRS). The JCOG0504 trial has compared, after brain surgery, adjuvant whole-brain radiation therapy (standard arm) vs adjuvant SRS in patients with 1-4 brain metastases [93]. The median OS was 15.6 months in both arms, with a longer median intracranial PFS in the standard arm (10.4 months, vs 4.0 months in the experimental arm). However, 16.4% of patients in the whole brain radiotherapy arm and 7.7% in the SBRT arm experienced grade 2-4 cognitive dysfunction.

The 15-year analysis of the EORTC 22922/10925 trial has reported a non-improved OS (73.1% in the experimental group vs 70.9%, $p=0.36$) after internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancers (50 Gy/25 fractions) [94]. However, it could be balanced with a significant reduction of breast cancer mortality, of any breast cancer recurrences, and it should be interpreted taking into account the technical advances of radiotherapy and staging from the beginning of the study (1996). The implementation of IMRT in this situation could modify the therapeutic ratio of this treatment.

The dosimetric advantages of proton beam therapy (PBT) results in a highly accurate treatment. However, PBT is less accessible and more expensive than photon beam therapy, and dosimetric advantages are insufficient to justify its use. Some clinical trials have assessed if PBT could translate into improved clinical outcomes, as compared with IMRT. Lin *et al*

have shown that for locally advanced esophageal cancer, PBT can reduce the risk and severity of adverse events measured using the total toxicity burden compared with IMRT, while maintaining similar PFS (NRG-GI006 trial) [95]. Concerning locally advanced NSCLC, a first clinical trial did not show local failure or severer radiation pneumonitis decrease with passive scattering PBT, as compared with IMRT [96]. A newer trial comparing concurrent chemotherapy and intensity-modulated PBT vs IMRT is ongoing (NCT01993810).

Palliative radiotherapy

With higher access, SBRT could also be used to relief pain in metastatic patients, and to improve local control. High-dose single-fraction SBRT (12 or 16 Gy, respectively for ≥ 4 cm or < 4 cm lesions) was shown to improve pain response rates as compared with conventional multifraction radiotherapy (30 Gy/10 fractions) for non-spinal metastases (NCI-2014-01482 trial) [97]. For spinal metastases, SBRT (24 Gy/2 fractions) was compared to conventional external beam radiotherapy (20 Gy/5 fractions) in the CCTG SC.24/TROG 17.06 trial [98]. Among 229 included patients, complete response for pain at 3 months was higher in the SBRT vs conventional group (35% vs 14%, respectively; risk ratio 1.33, 95%CI=1.14-1.55; $p<0.01$). No toxicity difference, including vertebral fracture or myelopathy, was observed.

Discussion

The abovementioned data demonstrates a great dynamism of radiation oncology research in most primary tumor types (**Figure 1 & 2**). A permanent update is needed, as suggested by the important number of high-level publications available each year. New major endpoints are emerging, focusing on QoL, patient satisfaction and shared decision making. Most of enrolled patients reported the perception that trial participation would result in better treatment, and more medical attention than off trials [99]. Despite these elements, and

although most cancer patients receive radiotherapy, the worldwide budget for radiotherapy research is limited. Compared to medical oncologic research, which is often supported by pharmaceutical companies, radiation oncology clinical trials receive mostly public funding. Thus, academic research centers have a key role in assessing innovative treatments or new treatment strategies, to develop and promote effective, QoL preserving, and cost efficient treatments. Investments in radiotherapy research through public funds and national governments would have a crucial impact, and could facilitate the transfer of innovation to standard care.

To demonstrate the superiority of a new treatment over the current standard, properly conducted trials in radiation oncology are required. Prospective quality control becomes a standard in EBRT and brachytherapy, as in surgery. Thus, accreditations, dummy run, data monitoring, quality assurance and continuous education of physicians, physicists and research technicians are increasing. Such items are the subject of publications, since they determine the reliability of the results of study [100–105]. High-tech radiotherapy studies require particularly high quality control. Protocol deviations, with a potential impact on tumor control or toxicities, have for example been reported in 31% of patients in a prospective clinical trial assessing urethra-sparing SBRT [100]. In the LAP 07 trial, assessing chemoradiation *versus* chemotherapy in locally advanced pancreatic cancer patients, minor deviations were reported in 60% of cases, and major deviations in 14%, with a trend for worst survival (17.0 months vs 13.4 months respectively, $p=0.055$) [101].

In the context of international public health emergency related to the COVID-19 outbreak, radiotherapy adapted quickly in order to ensure treatment continuity for patients and safety of caregivers. In this context, hypofractionated radiotherapy RCT have brought particularly interesting data, providing in many cases comparable outcomes to the standard treatment, with several advantages including shorter treatments limiting the risk of COVID-

19 transmission, higher convenience for patients, and decreased costs and healthcare resources consumption.

Many other aspects are in developments within the scope of radiation oncology and will hopefully soon be tested within well-designed RCT (**Figure 3**). Newer DNA interfering agents (PARP, ATR, ATM inhibitors) will be assessed in combination with ionizing radiation. Various newer predictive signatures (gut microbiota, circulating biomarkers) are tested and could promote individualized radiotherapy. Liquid biopsy (including DNA repair genomic signature, residual disease..) or and imaging-based artificial intelligence (radiomics, connected tools...) clinical implementation is fastly moving forward and needs to be prospectively authenticated. Newer technologies (nano-technologies, protons, plasma laser, photobiomodulation...) will hopefully decrease side effects in longer term cancer survivors. Finally, newer concepts such as lymph-node sparing radiotherapy or radiation therapy used as an *in situ* vaccine are being developed. The individual prediction of the best therapeutic index combined with the integration of new technologies will ideally allow RCT validation of highly personalized radiation therapy.

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Table 1. Main practice changing and emerging concepts in radiation therapy randomized clinical trials.

	Tumor type	Stage	Context	Comparison	Main endpoint	Study names	References
RADIOSENSITIZATION							
Chemotherapy or targeted therapy	Head and neck	LA	CTRT vs TTRT	CDDP > cetuximab	OS	De-ESCALaTE HPV, NRG Oncology RTOG 1016, TROG 12.01	[2–4]
	Head and neck	LA	CTRT	Nedaplatin = CDDP	PFS	-	[10]
	Oesophageal	L+LA	CTRT	CTCR (S-1) > EBRT	OS	ZJCH-E-E	[9]
	Uterine	LA	CTRT	CTRT + adjuvant CT > EBRT	OS, PFS	PORTEC 3	[6,7]
New radiosensitizers	Head and neck	LA	CTRT	Debio > placebo	LRC	Debio 1143-201	[11]
	Sarcomas	LA	Preop EBRT	NBTXR3 > no NBTXR3	pCR	Act.In.Sarc	[12]
	Head and neck	LA	CTRT	Placebo = avelumab	PFS	JAVELIN head and neck 100	[14]
	Lung	L	Preop	Durvalumab + SBRT > durvalumab	pCR	-	[13]
	Lung	M	ICI naive	SBRT + pembrolizumab > pembrolizumab	OS	PEMBRO-RT	[17]
TREATMENT INTENSIFICATION							
External beam radiotherapy indications	Head and neck	M	After induction CT	CTRT > CT	OS	SYSUCC5010	[26]
	Oesophageal	LA	Preop	CTRT > no CTRT	OS	CROSS, NEOCRTEC5010	[22,23]
	Prostate	LA	High-risk cN0	Whole pelvis EBRT > prostate EBRT	BDFS	POP-RT	[25]
	Prostate	M	Synchronous low volume met(s)	Prostate EBRT > no	OS	STAMPEDE	[27]
Dose escalation	Lung	LA	CTRT	60 Gy > 74 Gy	OS	RTOG 0617	[28]
	Oesophageal	LA	CTRT	50.4 Gy > 61.6 Gy	Local	ARTDECO	[29]

	Prostate	L	Interm and high-risk	95 Gy > 77 Gy	PFS BDFS	FLAME	[30]
Systemic treatment induction/consolidation	Head and neck	LA	Pre-CTRT	CDDP-gemcitabine > observation	RFS	-	[33]
	Head and neck	LA	Post-CTRT	Capecitabine > observation	DFS	CAN	[36]
	Lung	LA	Post-CTRT	Durvalumab > placebo	OS	PACIFIC	[40,41]
	Oesophageal	LA	Post-CTRT	Nivolumab > placebo	DFS	CheckMate 577	[42]
	Rectal	LA	Preop	CT-->CTRT > CTRT	DFS	PRODIGE 23	[34]
	Rectal	LA	Preop	RT-->CT > CTRT + adjuvant CT	DFS	RAPIDO	[35]
	Prostate	LA	High risk (EBRT)	Docetaxel + ADT > ADT	OS	RG Oncology RTOG 0521	[37]
Prostate	LA	High risk (EBRT)	Abiraterone + ADT > ADT	MFS	STAMPEDE	[38]	
Local ablative treatments for oligometastases	Mixed	M	Metach met(s)	SBRT + SoC > SoC	OS	SABR-COMET	[43]
	Prostate	M	Metach met(s)	SBRT > observation	DFS	ORIOLE	[44]
PERSONALIZED EBRT							
MRI	Prostate	LA	Multiparametric MRI	95 Gy > 77 Gy	BDFS	FLAME	[30]
Nuclear medicine	Lung	LA	¹⁸ FDG PET-based CTRT	IF > ENI	LRPFS	PET-Plan	[46]
	Hodgkin lymphoma	LA	Post-CT ¹⁸ FDG PET	EBRT = observation	PFS	GITIL/FIL HD0607	[48]
	Hodgkin lymphoma	L	Post-CT ¹⁸ FDG PET	EBRT = observation	PFS	GHSB HD17	[49]
Biomarkers	Breast	L	Adjuvant EBRT	TGFB1 > no TGFB1	Fibrosis	-	[56]
	Prostate	PSA+	Salvage EBRT	ADT > observation	PFS	GETUG-AFU 16	[51]
REDUCING TREATMENT BURDEN, ENHANCING PATIENTS QUALITY OF LIFE AND SATISFACTION							
(Ultra)hypofractionation	Breast	LA	Postop WBRT	43.5Gy/15f = 50Gy/25f	LR	-	[60]
	Breast	L	Postop WBRT	26Gy/5f = 40Gy/15f	IBTR	FAST-Forward	[61]
	Breast	L	Postop WBRT	28.5Gy/5 once weekly f = 50Gy/25f	NTE	FAST	[62]

	Breast	L	Postop APBI	30Gy/5f = 50Gy/25f	IBTR	APBI-IMRT-Florence	[63]
	Prostate	L	Intermediate and high-risk	42.7Gy/7f = 78Gy/39f	PFS	HYPO-RT-PC	[67]
Refining EBRT indication	Lung	LA	Postop EBRT	Observation = postop EBRT	DFS	Lung ART, PORT-C	[79,80]
	Breast	L	Postop EBRT	Observation = postop EBRT	IBTR	NRG Oncology/RTOG 9804	[86]
	Retroperitoneal Sarcomas	LA	Preop EBRT	Observation = preop EBRT	ARFS	EORTC-62092, STRASS	[78]
	Prostate	L	Postop EBRT	Salvage > Adjuvant	EFS	GETUG-AFU 17, RTOG 08.03/ANZUP RAVES, RADICALS-RT	[73–76]
Shared decision making	Breast	LA	Postop WBRT	IM-MS EBRT = no IM-MS EBRT	OS	EORTC 22922/10925	[94]
	Breast	L	Postop EBRT boost	APBI BT = EBRT	QoL	GEC-ESTRO APBI	[85]
Reducing toxicity with high-tech EBRT	Uterine	LA	Postop EBRT	IMRT > 3DRT	Toxicity	NRG Oncology-RTOG 1203, PARCER	[88,89]
	Brain mets	M	Postop EBRT	SRS > WBrRT	Toxicity	JCOG0504	[93]
	Oesophageal	LA	CTRT	PBT > IMRT	Toxicity	NRG-GI006	[95]
	Mixed	M	Bone mets	SBRT (1f) > 3DRT (10f)	Pain relief	NCI-2014-01482	[97]
Pain relief	Mixed	M	Spinal mets	SBRT (2f) > 3DRT (5f)	Pain relief	CCTG SC.24/TROG 17.06	[98]

Abbreviations:

EBRT: external beam radiotherapy; LA: locally advanced; L: localized; M: metastatic; PSA+: prostate-specific antigen concentration increased from 0.1 ng/mL to between 0.2 ng/mL and 2.0 ng/mL after radical prostatectomy; CTRT: concomitant chemoradiation; TTRT: concomitant target therapy and external beam radiotherapy; preop: pre-operative; ICI: immune checkpoint inhibitor; postop: post-operative; LR: locoregional; cN0: clinically node negative; CT: chemotherapy; metach: metachronous; met(s): metastasis(es); WBRT: whole breast radiotherapy; APBI: accelerated partial breast irradiation; CDDP: cisplatin; NBTXR3: high Z hafnium oxide (HfO₂) nanoparticle; SBRT: stereotactic body radiotherapy; Gy: gray; SoC: standard of care; IF: involved-field; ENI: elective node irradiation; ADT: androgen deprivation; TGFB1: transforming growth factor beta 1; f: fractions; IM-MS: internal mammary and medial supraclavicular; IMRT: intensity-modulated radiotherapy; 3DRT: three-dimensional conformal radiation therapy; SRS: radiosurgery; WBrRT, whole brain radiotherapy; PBT: proton beam therapy; OS: overall survival; PFS: progression-free survival; LCR: locoregional control; pCR: pathological complete response; BDFS: biochemical disease-free survival; RFS: recurrence-free survival; MFS: metastasis-free survival; LRPFS: locoregional progression-free survival; LR: locoregional recurrence; IBTR: ipsilateral breast tumor recurrence; NTE: normal tissue effects; ARFS: abdominal recurrence-free survival; EFS: event-free survival; QoL: quality of life.

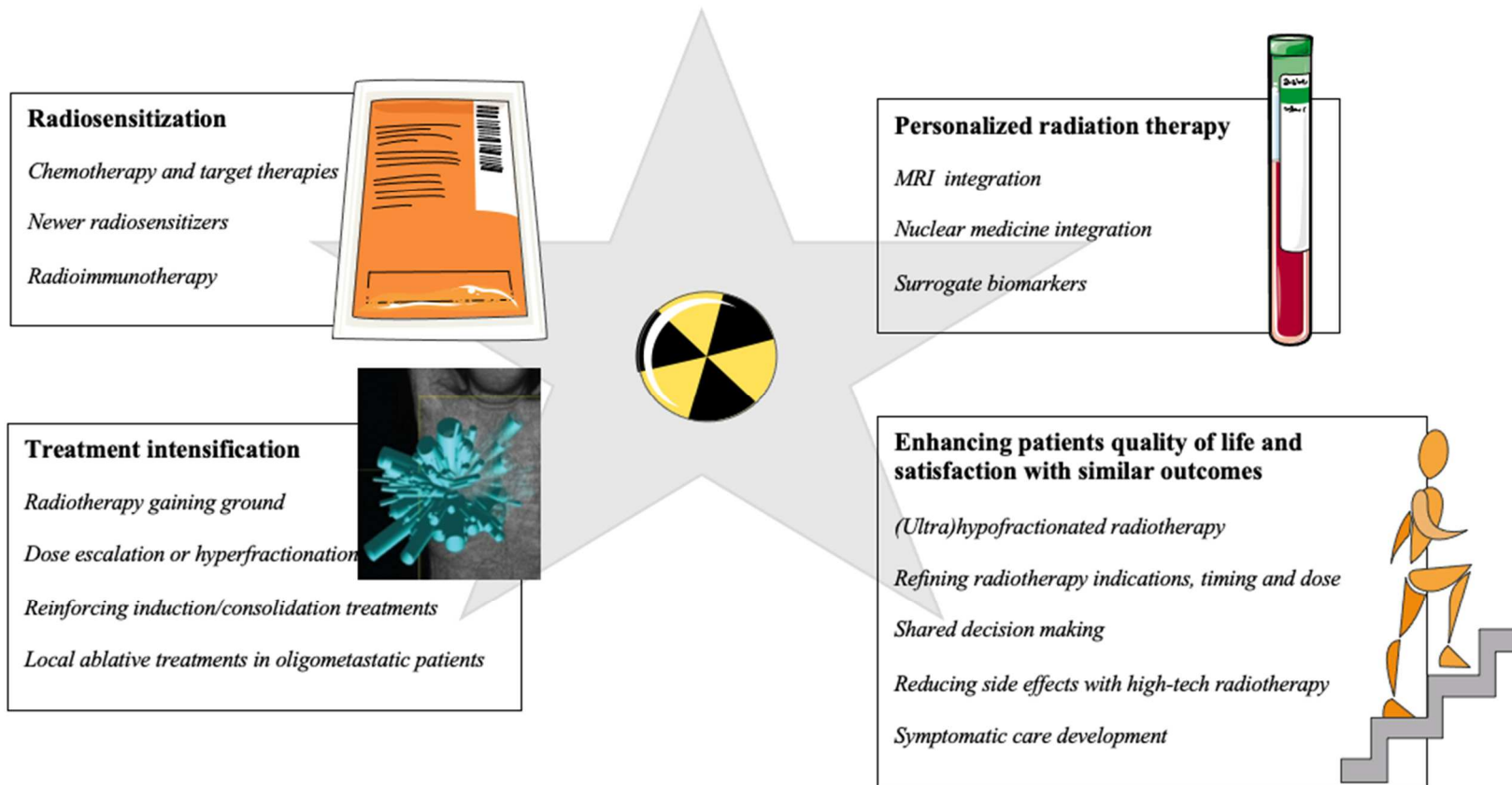


Figure 1. Main axes of radiation therapy practice changing trials.

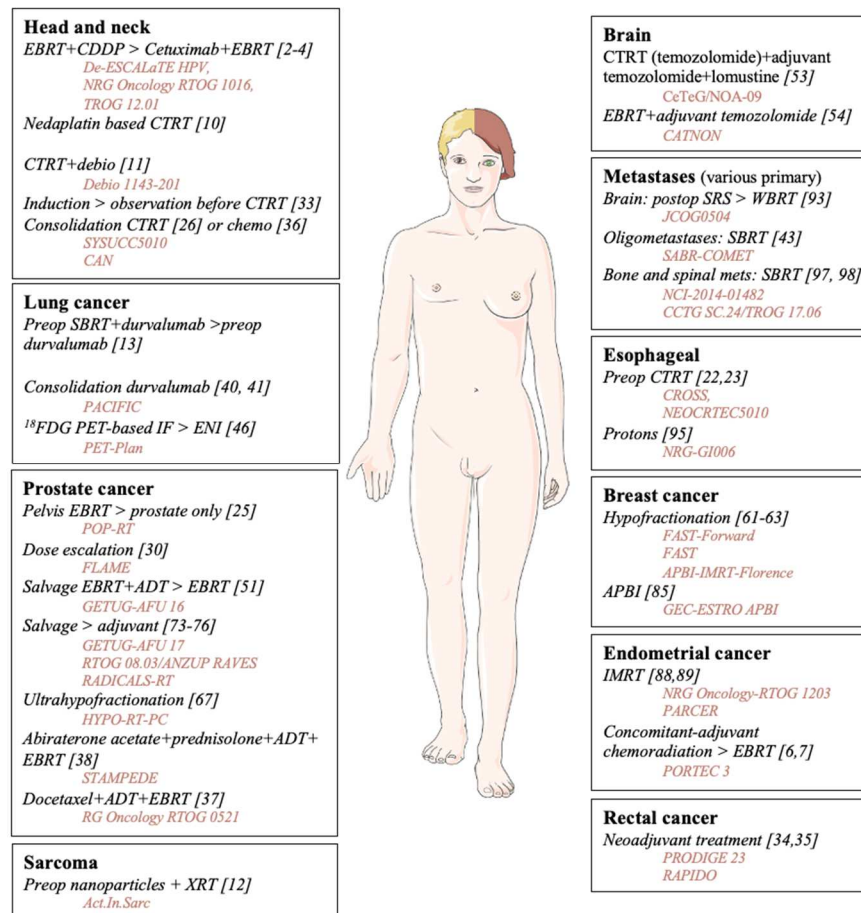


Figure 2. Main radiotherapy randomized clinical trials depending on the primary location.

Abbreviations:

EBRT: external beam radiotherapy; CDDP: cisplatin; CTRT: concomitant chemoradiation; Preop: pre-operative; SBRT: stereotactic body radiotherapy; ¹⁸FDG PET: ¹⁸FDG Positron Emission Tomography - Computed Tomography; IF: involved-fields; ENI: elective node irradiation; ADT: androgen-deprivation therapy; SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy; APBI: accelerated partial breast irradiation; IMRT: intensity-modulated radiotherapy.



Figure 3. Landscape of radiotherapy development.

Abbreviation:

MRI: magnetic resonance imaging.