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Title: SBRT for localized prostate cancer: is it ready for take-off?

Running head: SBRT for localized prostate cancer

The IJROBP Genitourinary editorial group

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Healthcare systems are often compared to the aviation industry. Progress in both is highly desired but must always be achieved with safety in mind. Everyone wants to get from point A to point B faster and more comfortably. But how much risk of uncertainty is one ready to accept to achieve that extra speed? Both industries also share the aspect of competition for customers. In the field of localized prostate cancer, patients have an ever-increasing choice of options – radical surgery (open vs laparoscopic vs robot-assisted), external beam radiation therapy (with photons or protons), brachytherapy (LDR or HDR), focal ablative therapies (irreversible electroporation therapy vs laser ablation vs ultrasound ablation vs vascular targeted photodynamic therapy vs cryotherapy). And – perhaps the most important option, especially for patients with low-risk prostate cancer – active surveillance(1, 2).

External beam radiation therapy is one of the first line options for patients with localized prostate cancer(1), but the length of treatment has always been one of the factors that deterred some patients from choosing this option. It took 4 large randomized clinical trials – RTOG 0415, CHHiP, HYPRO and PROFIT - to convince many radiation oncologists to shorten the duration of the external beam treatment length from historical 8-9 weeks down to 4-6 weeks(3-6). All four studies followed patients for 5 years, and all studies revealed no evidence that moderately hypofractionated external beam RT jeopardizes patient's oncological outcomes. A large meta-analysis of these trials revealed a small increase in acute GI toxicity with shorter treatments, but no evidence of increased late GI or GU toxicities(7). Based on the results of these prospective studies, the ASTRO/ASCO/AUA panel of experts in 2018 gave the moderate hypofractionation an official clearance for take-off(8).

Can we go faster? There have been multiple prospective non-randomized studies assessing ultra-hypofractionated courses of EBRT (between 4-7 fractions each delivering > 5 Gy per fraction), suggesting both similar toxicity and disease control profiles to conventionally fractionated courses of EBRT. A very recent large meta-analysis of over 6,000 patients treated on 38 prospective studies revealed very favorable oncological outcomes, toxicity profiles, and patient reported outcomes(9). Another recent individual patient level meta-analysis reported the long-term 10-year results from multiple prospective studies for patients with low- and intermediate-risk disease(10), similarly demonstrating excellent tumor control outcomes and remarkably low toxicity. These two meta-analyses reveal an impressively low ≤1-2% late grade ≥3 toxicity, even with long-term follow-up. These results were further supported by the recent presentation of the analysis of acute toxicity in PACE-B trial - a randomized Phase III trial comparing SBRT (36.25 Gy in 5 fractions) to more conventionally fractionated forms of prostate EBRT (78 Gy in 39 fractions or 62 Gy in 20 fractions). There was no difference in acute toxicities between the groups and less than 1% of patients in either group developed acute grade ≥3 toxicity(11).

But the missing piece, holding the plane of ultra-hypofractionated EBRT for localized prostate cancer on the ground was the lack of published results of a randomized trial. The results of the HYPO-RT-PC randomized, non-inferiority, phase III trial with 5-years outcomes have been published in The Lancet on June 18, 2019(12). In this trial, 1200 patients across 12 centers in Sweden and Denmark with intermediate risk (90%) and high risk (10%) prostate cancer were randomized to either 78 Gy in 39 fractions delivered daily, or 42.7 Gy in 7 fractions, delivered every other day. Only the prostate gland with a 7 mm planning margin was irradiated, with 80% of patients receiving 3D-CRT and 20% receiving IMRT. Failure-free survival at 5 years was 84% in both groups, supporting the non-inferiority of ultra-hypofractionated form of prostate gland irradiation. Acute side-effects (both GU and GI) were higher in

the 7-fractions arm at the end of treatment. Late toxicity was similar between the two arms, except for the higher urinary toxicity at 1 year in the 7-fractions arm (RTOG grade 2 or above 6% vs 2%, p=0.037). Patient reported toxicity outcomes were in line with physician reported results. These results are strikingly similar to the results from the 4 moderate hypofractionated trials that have shown often a transiently higher acute toxicity with hypofractionation, but no difference in late toxicity, patient-reported QOL, or tumor control.

What have we learned from this trial, and will it change the standard of practice? Equivalent biochemical control at 5 years with no ADT allowed on the protocol is expected to give equivalent survival outcomes at 10 years, making the two fractionation schemes equivalent in terms of prostate cancer efficacy. 7-fractions EBRT is just as safe as 39-fractions EBRT when only the prostate gland requires irradiation. With significantly shorter duration of time, it offers patient convenience and reduced departmental workloads. But a faster treatment entails slightly increased acute toxicity. A shorter trip, but with a greater turbulence in the air. Perhaps this turbulence could be mitigated with contemporary advanced technology and more modern planning margin expansions.

First, it will be important to compare the toxicity between patients treated with 3D-CRT and IMRT on the HYPO-RT-PC protocol, as preliminary toxicity analysis of 3D-CRT vs IMRT on the high dose arm of the RTOG 0126 trial revealed association of IMRT technique with significant reduction in acute Grade 2+ GI and GU toxicities(13). A more recent meta-analysis of 23 studies demonstrated a significant association of IMRT use with decreased grade 2-4 acute and late GI toxicities(14). Second, the addition of SpaceOAR is also expected to further reduce the rectal toxicity, based on level 1 evidence established in the realm of conventionally fractionated prostate EBRT(15). Finally, the advent of better image guidance, including magnetic resonance, will continue to improve the ability to monitor and mitigate inter- and intra-fractional prostate motion, allowing physicians to reduce the planning margins as well as to manipulate intra-prostatic dose delivery so that urethral and bladder dose are minimized, potentially resulting in lower urinary toxicity.

Some have argued that there is more than enough data to adopt ultra-hypofractionated EBRT as “a” standard of care(9). These proponents cite examples in other disease sites, such as lung SBRT, which was largely adopted after several small single arm phase 2 trials showing improved results compared to historical conventional RT controls(16, 17). Similarly, SBRT for brain, liver, pancreas, and spine all have been adopted as parts of standard of care without associated randomized trials. Even modalities for prostate cancer, like brachytherapy, have minimal to no evidence to support the optimal dose and fractionation, yet numerous standard dosing schedules are routinely employed and endorsed by guidelines. The use of prostate SBRT continues to increase across the US and Canada as a standard treatment option(18) and is supported by national guidelines, such as NCCN, given the results of now over 40 prospective studies.

The adoption of ultra-hypofractionated EBRT, at least in the USA, would have been further expedited if the HYPO-RT-PC protocol studied a 5-fractions course, instead of a 7-fractions course. Seven-fractions are just 2-fractions over the definition of SBRT in the United States, the definition that is arbitrary in nature, but impacts reimbursement. This factor may keep the plane of prostate SBRT on the ground for select physicians in the United States whose practice is influenced by financial incentives.

So is prostate ultra-hypofractionation “a” standard of care? Yes. However, we encourage enrollment on ongoing randomized trials to determine if it should become “the” standard of care. The PACE-B

(NCT01584258) trial already mentioned is fully accrued and we are awaiting longer-term results. If 5-fractions SBRT is proven to be non-inferior, it will become the preferred standard of care given the cost-effectiveness and patient convenience. NRG GU005 (NCT03367702) in contrast is a superiority trial comparing moderately fractionated EBRT (70 Gy in 28 fractions) to SBRT (36.25 Gy in 5 fractions), and could make SBRT the unequivocal standard of care if it improves disease control or QOL.

We are confident, however, that by bringing the ultra-hypofractionated EBRT for prostate cancer into the spotlight, the HYPO-RT-PC will make moderately hypofractionated EBRT "the" standard by default for those physicians who may still be subjecting their patients to over 2 months of daily treatments. Ultra-hypofractionation appears to have already impacted the use of brachytherapy for localized prostate cancer, and may even impact the use of surgery given its convenience and favorable toxicity profile. So whether immediate or delayed, the HYPO-RT-PC is a game-changer in the field of localized prostate cancer management.

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