



Long term results of the NRG/RTOG 9413: a key study but one of the most confusing study in prostate cancer radiotherapy!

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The NRG/RTOG 9413 study has been designed in 1993 to address two major questions at that time: the benefit of whole pelvic nodes radiotherapy (WPRT) compared to “prostate only” radiotherapy (PORT) and the benefit of neoadjuvant and concomitant (NHT) versus adjuvant hormonal therapy (AHT) (1).

While the question of the need of lymph nodes radiotherapy (RT) is still debated, the use of hormonal therapy (HT) at least concomitantly to RT has become a standard, partly thanks to the first publication of this study showing a benefit (in terms of progression free survival) of pelvic radiotherapy compared to PORT (2).

If only the authors have not asked these two questions simultaneously, the NRG/RTOG 9413 would probably have been an indisputable proof of the effectiveness of pelvic RT, however, only on secondary outcomes (no benefit in terms of clinical endpoints). Unfortunately, when looking at the results, what would have been the worst of the four arms according to the hypotheses of the promoters (PORT + AHT) proved to be as effective as the expected best arm (WPRT + NHT). Even if a statistically significant interaction between the radiation field and hormone timing has been shown, there are still no clear explanation for this, other than chance, even if as stated by the authors “chance should be assumed only very cautiously”.

Is the debate of concomitant vs. adjuvant hormonal therapy definitively closed?

Based on scientific evidence the answer is no, and this randomized study that raised this question was not able

to answer it. The authors provided in their early results in 2003 a comparison when pooling the arms with NHT versus AHT, showing an equivalence of both sequences (2). This comparison has not been provided in this paper, but it is more than likely that the results would have been similar. To our best knowledge, there have been no other comparative studies assessing that question. In the NRG/RTOG 9413 trial, a benefit of neoadjuvant and concomitant HT *vs.* adjuvant HT has been observed for patients receiving nodes RT in addition to prostate RT. This should be explained by a sort of synergetic effects between HT and RT, especially when delivering quite low dose for the nodes. However a potential deleterious effect of NHT (*vs.* AHT) when associated with PORT put into questions this conclusion.

Indeed, may HT when concomitantly associated with RT be deleterious in terms of oncologic and toxicity outcomes compared to its use as adjuvant only therapy?

Regarding breast cancer which is another hormone sensitive cancer, the use of concomitant *vs.* sequential HT has also and is still been debated. Interestingly, also based on radiobiological data, the same question was raised in the late 90' regarding negative impact of local control of tamoxifen when used simultaneously to RT. However this was not clinically demonstrated (3,4). Concomitant HT compared to sequential tamoxifen has also been associated with a higher risk of late toxicities in retrospective studies, however not confirmed in recently published prospective

studies for Tamoxifen or aromatase inhibitors (5,6). However, as opposed to prostate cancer, most of the present recommendations and guidelines for breast cancer is to start HT after the completion of RT.

In prostate cancer patients, to our knowledge, the NRG/RTOG 9413 is the only prospective comparative study that addressed this question. A recent report from Weller *et al.* based on their “prospectively maintained” cancer registry identified 515 pts treated with a short term 6 months HT initiated either 2 to 3 months before the start of RT (311 pts) or immediately after the completion of RT (204 pts) (7). All patients received high dose RT (78 GyEQD2) to the prostate with no pelvic radiotherapy. No significant differences were observed for biological disease-free survival nor distant metastases or overall survival between the two sequences.

Regarding toxicities, several retrospective or prospective studies have reported that HT was associated with an increase of acute genito-urinary (GU) toxicity (8), despite a significant prostate volume shrinkage when used as neoadjuvant therapy. Some authors also reported a higher risk for late rectal toxicity (9,10). In these studies, RT did not encompass pelvic nodes. However, the pooled analysis of the RTOG studies (all with pelvic radiotherapy and concomitant HT) reported a statistically significant lower probability of severe gastro-intestinal (GI) and GU, toxicities and severe GU toxicity with respectively short-term HT and long term HT + RT compared with RT alone (11).

In the NRG/RTOG 9413 the authors also observed interactions between HT sequence and RT volume, resulting conversely to the pooled RTOG RT-HT randomized studies (11) in a higher rate of late gastro-intestinal toxicity in the WP + NHT arm compared to the three others associations. This has to be taken into consideration if one consider—based on this study—NHT should be preferred to AHT when pelvic irradiation is proposed. However, as stated by the authors, toxicity figures of this study are probably not relevant for present radiotherapy recommendations as conventional techniques have been used.

Despite the lack of strong evidence, and contrary to breast cancer, a non-formal consensus has been established favoring concomitant HT in prostate cancer. Accordingly, all historical and also recent major studies that addressed the benefit of hormonal treatment in addition to RT, used HT concomitantly with RT based on this consensus. Their success to demonstrate the clinical benefit of HT has certainly reinforced this consensus, and led the authors to also abandon this question in their ongoing phase

3 NRG/RTOG 0924 trial. As a matter of fact, in their “interpretation” the authors omitted the PO + AHT arm as a potential alternative to WP + NHT!

Based on these conclusions, and if acting as if this study did not address the question of HT timing, would additional large randomized studies be necessary to assess the added value of pelvic irradiation?

Indeed, at least 2 randomized trials combining radiation and HT (NRG/RTOG 0924 for intermediate-risk and favorable high-risk patients and GETUG-AFU-23 for unfavorable high-risk patients) are ongoing, using advanced radiation therapy techniques and more accurate nodal CTV definition and doses.

The answer is definitively “yes” for several reasons. First of all because two other randomized studies, including the contemporary GETUG-01 study (12) failed to demonstrate any statistical benefit (nor a trend) for pelvic radiotherapy, and secondly because the NRG/TRTOG9413 did not demonstrate any significant clinical benefit (overall survival; metastasis free survival) despite a long follow-up.

Another particular reason is that a demonstrated need of pelvic RT would put into questions the use of moderately hypofractionated RT scheme (20 sessions) that have been shown to be at least equivalent in terms of progression free survival (PFS) with no or few increase of late toxicity compared to conventionally fractionate scheme (13,14). Indeed, most of these RT scheme used in daily practice are based on 20 fractions, whereas schemes with pelvic RT are based on conventional fractionation with at least 23 to 25 sessions for lymph nodes irradiation and 35 to 40 sessions to the prostate. Medico-economic considerations should also be interesting. Conversely this would not impact the association of external beam RT (EBRT) and brachytherapy that also demonstrated its superiority in terms of PFS compared to EBRT in association with HT (15).

The others reasons are the outcomes of major progress in patients’ selection and radiotherapy techniques, both factors that may bring some major contribution to demonstrate the benefit of lymph nodes irradiation or at least to better define in which patients this may be useful. Thus, the major part of the discussion section of this paper is dedicated to these aspects.

The very first objective with RT is to obtain a local control and the doses delivered to the prostate either within the NRG/RTOG 9413 or the GETUG-01 were obviously inadequate. Regarding HT, the duration is also questionable

(probably insufficient in most of the NRG/RTOG 9413 patients) and should be adapted to prognostic factors group. The extent of the lymph nodes area including in the RT volume may also be a major factor. In a previously report of that study, Roach *et al.* have demonstrated (in the NHT arms) a better outcome with whole pelvis RT (superior limit L5/S1) compared to “true” PO-RT and larger PO-RT volume called “mini-pelvis” (16). The S1/S2 upper limit in the GETUG for pelvic RT was an intermediate level between the Roach’ “mini-pelvis” and whole pelvis.

But, the most important are selection criteria. As stated by the authors, to demonstrate the benefit of pelvic radiotherapy, one should select patients with a significant (>15%?) risk of pelvic nodes involvement, but with a low risk of more distant nodes nor bone metastases. To date, this has been based on nomograms such as the so-called Roach Formula or Partin Tables that in fact do not select the same patients. In addition, the addition of HT in patients classified as favorable intermediate risk has not been demonstrated, and there may be a role for pelvic irradiation without HT in these patients, as suggested by the GETUG-01 trial (12).

Fortunately we should have within the next few years new and more powerful imaging tools such as PSMA-PET (17) and/or biological markers that may either show presently undetectable nodes, or improve the predictability of occult lymph nodes. The good news is that we will have the means for a better individualization of pelvic nodes irradiation (i.e., treated volume and dose) and the need for HT. The bad news is that the results of the ongoing studies may be considered as non-relevant and we will have to launch new randomized studies for N0 but also TEP-CT based N+ (even M+) patients!

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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