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Title:

Comparison of Empirical Versus Dosimetry-Guided Radioiodine Therapy: The Devil is in the Details

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Short Running Title: Details in Comparing I-131 Therapies

Dear Editor:

Deandreis *et al*. aimed to compare two therapeutic interventions using radioactive iodine therapy (RAIT) in metastatic differentiated thyroid cancer (MDTC): the empirical standard (3.7 GBq) activity approach at Gustave Roussy (GR) and the dosimetric approach at the Memorial Sloan Kettering Cancer Center (MSKCC). (*1*) The overall survival (OS) was selected for the study outcome measure. This was a retrospective investigation that requires equal distribution of confounding factors in the cohorts, enabling unbiased comparison of the two tested approaches. I would like to highlight several inconspicuous confounders that require the authors' consideration and comment.

The GR cohort was mostly comprised of French woman who, in general, had approximately 22% lower overall probability of dying per 100,000 as compared to the American woman who made up most of MSKCC cohort – 84.92 in 1980 that declined gradually to 53.63 in 2010 as compared to 102.51 declining gradually to 77.16, respectively. (*2*) Hence, GR cohort had inherent advantage over the MSKCC cohort in OS that needs to be recognized and addressed.

The GR cohort was younger than MSKCC, which multivariate analysis attempted to correct for. But Table 1 revealed the presence of another important confounder – inclusion of pediatric patients into both cohorts. Published experience from MSKCC showed 100% survival in pediatric patients with MDTC. (*3*) This finding agrees with widely recognized notion that "biologic behavior of thyroid cancer can differ significantly between adults and children". (*4*) Pediatric MDTC is considered by most a different disease from adult MDTC. In survival studies the two should be investigated separately, which makes inclusion of pediatric patients into this study is a design error. Disappointingly, the exact numbers of pediatric patients per cohort were not disclosed. The younger median age suggests that GR cohort probably had a greater proportion of pediatric patients, which would have guaranteed OS advantage to GR approach. Multivariate analysis cannot correct for this basic design flaw.

Another confounding variable that cannot be corrected for is the difference in patient preparation. GR used thyroid hormone withdrawal (THW) while MSKCC used recombinant human thyroid stimulating hormone (rhTSH). The authors conceded that "rhTSH vs THW preparation on I131 efficacy still remains unknown". However, the available observational evidence showed better RAI uptake and retention in metastatic lesions after THW as compared to rhTSH. (*5-7*) This difference could also have given OS advantage to GR, if it depends presumably on effectiveness of RAIT.

Use of rhTSH in MDTC is off-label. MSKCC is a very rare practice, if not unique, that incorporated rhTSH into routine dosimetry protocol. But Deandreis *et al.* extrapolated conclusions to "WB/BC dosimetric approach" in general, which is not appropriate. Furthermore, some of the authors have previously

disclosed relationships with the company that manufactures rhTSH. (*8*) Off-label rhTSH use in the current report certainly requires at least a similar disclosure.

The above-addressed are not a complete list of deficiencies, but they are more than sufficient to show that this work failed to adequately balance confounders in the cohorts in favor of GR. Results from atypical dosimetry protocol (rhTSH preparation) at MSKCC should not be generalized. Practitioners of standard dosimetry-tailored, maximum tolerated activity approach can rest assured that there is still no evidence in the literature to equate their effectiveness to the one-size-fits-all empirical approach.

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