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Reply: We thank Tulchinski et al and Flux et al for clearly pointing out that several open points still persist in the management of thyroid cancer.

We agree that several confounding variables may be present in retrospective studies, but available data on thyroid cancer patients are mostly retrospective. Therefore, treatment strategies are based on low level evidence and always open to challenge. Efficacy of RAI treatment may be related to patient age, histology, lesion size and number, FDG uptake, treatment preparation (THW vs rhTSH), administered activity, number of treatments, cumulative activity, radiation dose to tumor foci and assessment of response. Most of these factors have been taken into account and discussed in our study.

Tulchinski et al point out differences in mortality rates of French comparing to American women but this does not apply in our statistical analysis. We agree that metastatic patients aged < 20 y have frequently excellent response to RAI treatment with 100% survival rate at 10 years in both MSKCC and GR previous reports (1,2). In our study they represent 9.9% of GR (23/231) and 7.4 % of MSKCC cohort (9/121). Excluding these patients from the analysis, GR patients still present a median younger age at the discovery of distant metastases comparing to MSKCC patients (45 vs 54 y respectively, P= 0.01) but in the multivariate analysis OS still remains not statistically different (P = 0.16). Furthermore, there is still no difference in OS between the two centers in predefined matched group including patients of age < 40 y: five year OS is 94 % for both centers for group 1 (vs 96% reported in our paper) and 92% and 87% (with no changes in that reported in our paper) for group 2 for GR and MSKCC patients, respectively.

We underline in the Discussion that a limit of the study is that GR and MSKCC patients were not perfectly matched because MSKCC patients were older and with more aggressive disease. This is the most critical population for whom it is crucial to define the best approach to improve OS, as commented by Flux et al. That is why we performed separate analysis in predefined matched subgroups based on age and metastases extension (2).

We agree with Tulchinski et al about the confounding bias of comparing rhTSH preparation for dosimetry and treatment applied at MSKCC to THW preparation for empiric administered activities applied at GR. RhTSH preparation is not the standard approach in metastatic disease and may induce a lower RAI uptake than THW preparation. However, limited data from retrospective studies comparing RAI efficacy treatment in metastatic patients after THW or rhTSH did not demonstrate a clinically meaningful advantage of THW over rhTSH preparation in terms of OS or response to therapy (3-4). In our study MSKCC patients prepared by rhTSH received at least 2-3 fold higher activities per treatment course following rhTSH based WB/BC dosimetry compared to empiric activities administrated after THW at GR, and older patients with extensive disease received two fold higher median cumulative activities. We did not find any beneficial effect on OS even considering the higher administered activities. The only other retrospective available study comparing in a smaller number of metastatic patients empiric vs WB/BC dosimetry approach partially based on rhTSH aided treatment preparation for both groups did not find an effect on PFS (5). Only prospective studies including homogeneous groups of patients may clearly determine whether different preparations and whether empiric vs dosimetry-based approach can impact on RAI efficacy.

In conclusion, routine use of a WB/BC dosimetry management approach relying on high administered activities given under rhTSH stimulation does not show significant advantage in routine practice when compared to an empiric dosing approach using lower administrated activities under THW preparation in metastatic thyroid cancers. However, as underlined by Flux et al, WB/BC dosimetry could be used in selected patients to minimize the risk of acute dose related toxicities or in association to lesional dosimetry to optimize therapeutic efficacy. We strongly support the concept that lesion absorbed dose should be a major predictive factor of the tumoricidal effect of RAI, and in this context the combined use of WB/BC dosimetry with lesional dosimetry is expected to provide the optimal individualized safe and effective RAI activity to be administered, as suggested with I124PET studies (6). Finally, as underlined by Flux et al optimal outcomes in patients with metastatic thyroid cancer can only be achieved through an integrated multidisciplinary management approach considering all of the various available treatment modalities (e.g., radioactive iodine, surgery, localized therapies, new drugs either as specific therapies or as redifferentiation agents to improve the efficacy of RAI therapy).

The authors declare that there is no conflict of interest regarding the publication of this paper.

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