Acta Oncologica, 2014; 53: 577–579

EDITORIAL

Advancing our quantitative understanding of radiotherapy normal tissue morbidity

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This and the preceding issue of Acta Oncologica contain several papers adding to our understanding, and ability to predict, normal tissue morbidity in individual patients treated with radiotherapy (RT) [1–7]. The overall goal of normal tissue complication probability (NTCP) modeling is to establish predictive models – or sets of models – of treatment-limiting toxicities, that have general validity and good performance for a wide range of patient, disease, and treatment characteristics. That is, the models should have 'generalizability' and 'validity'. Two of the papers presented in this issue use large institutional databases to test/validate/invalidate dose-volume predictive factors reported elsewhere [1,2]. Short of actual data-pooling, this is an appropriate, and important, methodology. However, due to the (understandable) limited variability of local treatment characteristics – and to some extent patient and disease characteristics as well – variations in NTCP modeling results are not only possible but indeed to be expected. Tucker et al. test for effects of heart dose on radiation pneumonitis and find little evidence for significance when taking the mean dose to the normal lungs as the 'baseline' model [1]. This is in contrast to results from the Washington University in St. Louis published previously in this journal [8] – as well as a confirmatory test in an independent cohort from the same institution [9] – showing that heart doses were not only important, but they were as important in multivariate modeling as lung doses. Also other pre-clinical and clinical data, especially from the Groningen group, indicate that radiation damage to the heart can lead to lung damage, and vice versa [10–13]. Obviously, we still do not fully understand the source of the difference in these results.

The picture is clearer when it comes to another important normal tissue in RT, the parotid glands, and the dose limits of this organ aiming at reducing salivary dysfunction. In this issue, Beetz and co-workers present a very nice analysis showing that the QUANTEC guidelines [14] appear to be useful in their local patient cohort [2]. Going beyond that, they demonstrate a striking impact of age that should be tested by other groups. Their study used patient-reported outcomes, whereas the QUANTEC guidelines were developed based on salivary flow measurements; the consistency of results is therefore all the more impressive. It is important to re-emphasize, however, that salivary function is likely even better preserved when the spared parotid gland mean dose can be kept well below the 25 or 20 Gy threshold (say, at 10 or 15 Gy) [14].

Incorporation of clinical factors is the key element of the innovative approach taken by Appelt and collaborators [3]. The paper establishes a new and powerful tool: using the results of meta-analyses as a guide to adding clinical factors, and their odds ratios, to dose-volume predictive models. Starting from a blank canvas for every predictive model now makes little sense. The previous encouragement to adopt a 'data pooling culture' [15] is therefore echoed here, as this appears to be essential for further progress in this field. While creation of web-based databases enabling data-mining should be our overall aim [16,17], data such as dose-volume histograms can already now easily and effectively be shared using the features of online

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(Received 18 March 2014; accepted 18 March 2014)

ISSN 0284-186X print/ISSN 1651-226X online © 2014 Informa Healthcare
DOI: 10.3109/0284186X.2014.907055

appendices/supplementary materials that most journals in our field offer, including Acta Oncologica [18, see appendix E2 therein].

The QUANTEC effort represented a step forward for the NTCP modeling field [19–21], but many of the analyses were somewhere between qualitative and quantitative due to the lack of access to original, high-quality data, and the lack of reporting standards. New follow-up studies underline that we still have many things to learn about the specific tissues responsible for complications from RT [22–30]. The paper by Cella et al. in this issue is another example: the high-dose (30 Gy) volume in the left lung appears to be a better predictor of toxicity than the high-dose volume in both lungs together, for patients receiving radio-chemotherapy for Hodgkins lymphoma [4]. The authors raise the question of whether the left lung itself is the key factor, or does this reflect a connection to heart irradiation? The recent paper by Johansen and colleagues [5] examines the under-studied issue of the cause of arm and shoulder pain in breast cancer patients following surgery and RT. The authors contoured the shoulder joint for each patient, and showed that the corresponding V15 had the strongest association with post-therapy pain and arm stiffness. Again, this raises the question of whether there is a more specific anatomic structure responsible for the symptoms. New methodologies that map a cohort of patient dose distributions to a given 'reference patient', whether to an idealized geometry [31,32] or a particular (anonymized) patient [33], to look for dose versus outcome correlation hot spots, may prove very valuable to sort out these questions of anatomic specificity. Experience has taught us that NTCP modeling is Sisyphean, in the sense that every new answer creates new questions. Unlike Sisyphus, however, we are making considerable progress.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Tucker SL, Liao Z, Dinh J, Bian SX, Mohan R, Martel MK, et al. Is there an impact of heart exposure on the incidence of radiation pneumonitis? Analysis of data from a large clinical cohort. Acta Oncol 2014;53:590–6.
[2] Beetz I, Steenbakkers RJ, Chouvalova O, Leemans CR, Doornaert P, van der Laan BF, et al. The QUANTEC criteria for parotid gland dose and their efficacy to prevent moderate to severe patient-rated xerostomia. Acta Oncol 2014;53:597–604.
[3] Appelt AL, Vogelius IR, Farr KP, Khalil AA, Bentzen SM. Towards individualized dose constraints: Adjusting the QUANTEC radiation pneumonitis model for clinical risk factors. Acta Oncol 2014;53:605–12.
[4] Cella L, Liuzzi R, D'Avino V, Conson M, Di Biase A, Picardi M, et al. Pulmonary damage in Hodgkin's lymphoma patients treated with sequential chemo-radiotherapy: Predictors of radiation-induced lung injury. Acta Oncol 2014;53: 613–9.
[5] Johansen S, Fosså K, Nesvold IL, Malinen E, Fosså SD. Arm and shoulder morbidity following surgery and radiotherapy for breast cancer. Acta Oncol 2014;53:521–9.
[6] Lindblom U, Garskog O, Kjellen E, Laurell G, Jaghagen EL, Wahlberg P, et al. Radiation-induced trismus in the ARTS-CAN head and neck trial. Acta Oncol 2014;53:620–7.
[7] Chow TL, Louie AV, Palma DA, D'Souza DP, Perera F, Rodrigues GB, et al. Radiation-induced lung injury after concurrent neoadjuvant chemoradiotherapy for locally advanced breast cancer. Acta Oncol 2014;53:697–701.
[8] Huang EX, Hope AJ, Lindsay PE, Trovo M, El Naqa I, Deasy JO, et al. Heart irradiation as a risk factor for radiation pneumonitis. Acta Oncol 2011;50:51–60.
[9] Deasy J, Robinson C, Huang E, Molotievschi A, Bradley J. Independent test of a model to predict radiation pneumonitis after definitive radiation therapy for locally advanced non-small cell lung cancer: Heart irradiation is (again) a statistically significant risk factor (abstr). Int J Radiat Oncol Biol Phys 2012;84(Suppl 1):S32.
[10] Novakova-Jiresova A, van Luijk P, van Goor H, Kampinga HH, Coppes RP. Pulmonary radiation injury: Identification of risk factors associated with regional hypersensitivity. Cancer Res 2005;65:3568–76.
[11] van Luijk P, Novakova-Jiresova A, Faber H, Schippers JM, Kampinga HH, Meertens H, et al. Radiation damage to the heart enhances early radiation-induced lung function loss. Cancer Res 2005;65:6509–11.
[12] van Luijk P, Faber H, Meertens H, Schippers JM, Langendijk JA, Brandenburg S, et al. The impact of heart irradiation on dose-volume effects in the rat lung. Int J Radiat Oncol Biol Phys 2007;69:552–9.
[13] Ghobadi G, van der Veen S, Bartelds B, de Boer RA, Dickinson MG, de Jong JR, et al. Physiological interaction of heart and lung in thoracic irradiation. Int J Radiat Oncol Biol Phys 2012;84:e639–46.
[14] Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. Int J Radiat Oncol Biol Phys 2010;76(Suppl 3): S58–63.
[15] Deasy JO, Bentzen SM, Jackson A, Ten Haken RK, Yorke ED, Constine LS, et al. Improving normal tissue complication probability models: The need to adopt a "data-pooling" culture. Int J Radiat Oncol Biol Phys 2010;76(Suppl 3): S151–4.
[16] Roelofs E, Persoon L, Nijsten S, Wiessler W, Dekker A, Lambin P. Benefits of a clinical data warehouse with data mining tools to collect data for a radiotherapy trial. Radiother Oncol 2013;108:174–9.
[17] Roelofs E, Dekker A, Meldolesi E, van Stiphout RG, Valentini V, Lambin P. International data-sharing for radiotherapy research: An open-source based infrastructure for multicentric clinical data mining. Radiother Oncol 2014;110:370–4.
[18] Mutter RW, Liu F, Abreu A, Yorke E, Jackson A, Rosenzweig KE. Dose-volume parameters predict for the development of chest wall pain after stereotactic body radiation for lung cancer. Int J Radiat Oncol Biol Phys 2012; 82:1783–90.
[19] Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative Analyses of Normal Tissue

Effects in the Clinic (QUANTEC): An introduction to the scientific issues. Int J Radiat Oncol Biol Phys 2010;76(Suppl 3):S3–9.

[20] Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76(Suppl 3):S10–9.

[21] Jackson A, Marks LB, Bentzen SM, Eisbruch A, Yorke ED, Ten Haken RK, et al. The lessons of QUANTEC: Recommendations for reporting and gathering data on dose-volume dependencies of treatment outcome. Int J Radiat Oncol Biol Phys 2010;76(Suppl 3):S155–60.

[22] Liu M, Moiseenko V, Agranovich A, Karvat A, Kwan W, Saleh ZH, et al. Normal Tissue Complication Probability (NTCP) modeling of late rectal bleeding following external beam radiotherapy for prostate cancer: A test of the QUANTEC-recommended NTCP model. Acta Oncol 2010;49:1040–4.

[23] Trott KR, Doerr W, Facoetti A, Hopewell J, Langendijk J, van Luijk P, et al. Biological mechanisms of normal tissue damage: Importance for the design of NTCP models. Radiother Oncol 2012;105:79–85.

[24] Mukesh M, Harris E, Jena R, Evans P, Coles C. Relationship between irradiated breast volume and late normal tissue complications: A systematic review. Radiother Oncol 2012;104:1–10.

[25] Vogelius IR, Bentzen SM. A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis. Acta Oncol 2012;51:975–83.

[26] Lee TF, Fang FM. Quantitative analysis of normal tissue effects in the clinic (QUANTEC) guideline validation using quality of life questionnaire datasets for parotid gland constraints to avoid causing xerostomia during head-and-neck radiotherapy. Radiother Oncol 2013;106:352–8.

[27] Ravn S, Holmberg M, Sørensen P, Frøkjær JB, Carl J. Differences in supratentorial white matter diffusion after radiotherapy – new biomarker of normal brain tissue damage? Acta Oncol 2013;52:1314–9.

[28] De Ruysscher D, Sharifi H, Defraene G, Kerns SL, Christiaens M, De Ruyck K, et al. Quantification of radiation-induced lung damage with CT scans: The possible benefit for radiogenomics. Acta Oncol 2013;52:1405–10.

[29] Thor M, Apte A, Deasy JO, Karlsdóttir À, Moiseenko V, Liu M, et al. Dose/volume-response relations for rectal morbidity using planned and simulated motion-inclusive dose distributions. Radiother Oncol 2013;109:388–93.

[30] Stenmark MH, Conlon AS, Johnson S, Daignault S, Litzenberg D, Marsh R, et al. Dose to the inferior rectum is strongly associated with patient reported bowel quality of life after radiation therapy for prostate cancer. Radiother Oncol 2014;110:291–7.

[31] Peeters ST, Lebesque JV, Heemsbergen WD, van Putten WL, Slot A, Dielwart MF, et al. Localized volume effects for late rectal and anal toxicity after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2006;64:1151–61.

[32] Heemsbergen WD, Al-Mamgani A, Witte MG, van Herk M, Pos FJ, Lebesque JV. Urinary obstruction in prostate cancer patients from the Dutch trial (68 Gy vs. 78 Gy): Relationships with local dose, acute effects, and baseline characteristics. Int J Radiat Oncol Biol Phys 2010;78:19–25.

[33] Liang Y, Messer K, Rose BS, Lewis JH, Jiang SB, Yashar CM, et al. Impact of bone marrow radiation dose on acute hematologic toxicity in cervical cancer: Principal component analysis on high dimensional data. Int J Radiat Oncol Biol Phys 2010;78:912–9.