



Primary tumor size as a prognosticator in anal cancer patients

Pierfrancesco Franco, Umberto Ricardi

Department of Oncology, Radiation Oncology, University of Turin, Turin, Italy

Correspondence to: Pierfrancesco Franco, MD, PhD. Department of Oncology, Radiation Oncology, University of Turin School of Medicine, Via Genova 3, 10126, Turin, Italy. Email: pierfrancesco.franco@unito.it.

Comment on: Goffredo P, Garancini M, Robinson TJ, *et al.* A National-Level Validation of the New American Joint Committee on Cancer 8th Edition Subclassification of Stage IIA and B Anal Squamous Cell Cancer. *Ann Surg Oncol* 2018;25:1654-60.

Submitted Mar 03, 2019. Accepted for publication Mar 06, 2019.

doi: 10.21037/atm.2019.03.16

View this article at: <http://dx.doi.org/10.21037/atm.2019.03.16>

Combination therapy with concurrent chemo-radiation is considered the standard therapeutic option for anal cancer patients, providing both tumor eradication and sphincter preservation (1). Survival rates depend on the global stage at presentation ranging from 60% to 80% at 3–5 years (2–4). As described by Glynne-Jones *et al.*, prognostic factors are specific measurable parameters extrapolated and quantified during the observation of a specific patient population to explore a potential correlation with clinical outcomes (5). In anal cancer, prognostic factors have been reported in retrospective case series or in prospective randomized phase III trials (3,5,6). The EORTC 22861 has shown that male sex, nodal involvement and skin ulceration are able to independently predict for loco-regional control and overall survival (6). Mature data coming from the ACT-I trial suggested that palpable lymph nodes and male sex can be considered as prognostic factors for loco-regional recurrence and overall survival. The same trial and a confirmatory retrospective analysis showed that a low baseline hemoglobin level is able to predict for cancer-related death and death from any cause (5,7). The positivity to Human Papilloma Virus infection has also been shown to predict for overall and disease-specific survival (8). Finally, the RTOG 98-11 trial outlined a significant correlation between male sex and nodal involvement and loco-regional recurrence and established tumor size (>5 cm) as an independent predictor for disease-free and overall survival in this setting (9). This finding prompted the American Joint Committee on Cancer (AJCC), in the 8th edition of the TNM staging system, to subdivide stage II squamous cell carcinoma of the anal canal into stage IIA (cT2N0M0) and stage IIB (cT3N0M0), based on primary tumor maximum dimension (≤ 5 vs. >5 cm) (10).

In the study by Goffredo *et al.*, the authors performed a national-level validation of the new AJCC sub-classification (stage IIA vs. IIB), using 2 representative databases, namely the National Cancer Database (NCDB) and the Surveillance, Epidemiology and End Results program (SEER) (11). After analyzing more than 9,000 stage IIA (2–5 cm) and more than 2,400 stage IIB (>5 cm) patients, the authors observed a 5-year overall survival rate of 72% and 69% for stage IIA cases (NCDB and SEER databases, respectively) vs. 57% and 50% for stage IIB patients, with a final hazard ratio for stage IIB of 1.58 and 2.01 for the 2 datasets (both $P < 0.001$), after adjusting for the available demographic and clinical confounding factors (11). The importance of primary tumor dimension is a well-known clinical variable that may affect treatment outcome. As for examples, tumor size (with a threshold at 5 cm) was found to be the most important prognostic factor for loco-regional recurrence, distant metastasis and overall survival in the retrospective series by Kapacee *et al.* on 148 anal cancer patients (12). In the retrospective series reported by the group at MD Anderson Cancer Center, tumor stage was found to predict for loco-regional failure and overall survival, while tumor size (>4 vs. ≤ 4 cm) was shown to predict for the likelihood to develop distant metastasis (13). It is a crucial point that the size parameter has been incorporated into the detailed definition of stage II disease. This helps in stratifying patients into appropriate risk categories to appropriately tailor treatment strategies (14). Stage IIB anal cancer patients represent a subset at higher risk for local and distant relapse and thus do deserve a more aggressive treatment, including new combination approaches or dose-escalated treatments to improve tumor control and survival. As an example, the new UK PLATO Trials (personalising

anal cancer radiotherapy dose) employs different prescription doses according to the risk categories of the patient (15). To de-escalate treatment for intermediate risk patients (including T2 disease ≤ 4 cm), the ACT 4 trial randomize patients between 2 dose levels (41.4 Gy in 23 fractions *vs.* 50.4 Gy in 28 fractions) concurrent to mitomycin C and capecitabine. To intensify treatment for high-risk patients (including T3 disease, which is sized > 5 cm), the ACT 5 trial randomize patients into 3 dose levels, specifically 53.2 *vs.* 58.8 *vs.* 61.6 Gy in 28 fractions delivered with simultaneous integrated boost and intensity modulated radiotherapy, concomitantly to mitomycin C and either 5-fluorouracil or capecitabine (15). This approach represents a targeted strategy to implement personalized medicine based on appropriate risk stratification, which consistently relies on the correct and precise identification of risk factors, prognostic and predictive clinical parameters such as tumor size in the setting of anal cancer.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Franco P, Mistrangelo M, Arcadipane F, et al. Intensity-modulated radiation therapy with simultaneous integrated boost combined with concurrent chemotherapy for the treatment of anal cancer patients: 4-year results of a consecutive case series. *Cancer Invest* 2015;33:259-66.
2. Franco P, Arcadipane F, Ragona R, et al. Volumetric modulated arc therapy (VMAT) in the combined modality treatment of anal cancer patients. *Br J Radiol* 2016;89:20150832.
3. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA* 2008;299:1914-21.
4. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 \times 2 factorial trial. *Lancet Oncol* 2013;14:516-24.
5. Glynne-Jones R, Sebag-Montefiore D, Adams R, et al. Prognostic factors for recurrence and survival in anal cancer: generating hypotheses from the mature outcomes of the first United Kingdom Coordinating Committee on Cancer Research Anal Cancer Trial (ACT I). *Cancer* 2013;119:748-55.
6. Bartelink H, Roelofs F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 1997;15:2040-9.
7. Franco P, Montagnani F, Arcadipane F, et al. The prognostic role of hemoglobin levels in patients undergoing concurrent chemo-radiation for anal cancer. *Radiat Oncol* 2018;13:83.
8. Serup-Hansen E, Linnemann D, Skovrider-Ruminski W, et al. Human papillomavirus genotyping and p16 expression as prognostic factors for patients with American Joint Committee on Cancer stages I to III carcinoma of the anal canal. *J Clin Oncol* 2014;32:1812-7.
9. Ajani JA, Winter KA, Gunderson LL, et al. Prognostic factors derived from a prospective database dictate clinical biology of anal cancer: the intergroup trial (RTOG 98-11). *Cancer* 2010;116:4007-13.
10. Amin MB, Edge S, Greene F, et al. *AJCC Cancer Staging Manual*. 8th edition. New York: Springer, 2017.
11. Goffredo P, Garancini M, Robinson TJ, et al. A National-Level Validation of the New American Joint Committee on Cancer 8th Edition Subclassification of Stage IIA and B Anal Squamous Cell Cancer. *Ann Surg Oncol* 2018;25:1654-60.
12. Kapacee ZA, Susnerwala S, Wise M, et al. Chemoradiotherapy for squamous cell anal carcinoma: a review of prognostic factors. *Colorectal Dis* 2016;18:1080-6.
13. Das P, Bhatia S, Eng C, et al. Predictors and patterns of recurrence after definitive chemoradiation for anal cancer. *Int J Radiat Oncol Biol Phys* 2007;68:794-800.
14. Arcadipane F, Franco P, Ceccarelli M, et al. Image-guided IMRT with simultaneous integrated boost as per RTOG 0529 for the treatment of anal cancer. *Asia Pac J Clin Oncol* 2018;14:217-23.
15. Cancer Research UK. Personalising anal cancer radiotherapy dose (PLATO trials). Available online: www.cancerresearchuk.org

Cite this article as: Franco P, Ricardi U. Primary tumor size as a prognosticator in anal cancer patients. *Ann Transl Med* 2019;7(7):157. doi: 10.21037/atm.2019.03.16