Editorial Commentary

Primary tumor size as a prognosticator in anal cancer patients

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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 intensificate 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.

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Footnote

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

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