

Who can benefit from postoperative radiotherapy following biochemical recurrence after radical prostatectomy? – looking for the “Rosetta Stone” of prostate cancer

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Over the last 10 years, there has been a growing interest to find a personalized and customized treatment approach for prostate cancer patients, aiming to optimize cancer control and improve functional outcomes.

The biology of prostate cancer is considerably wide, ranging from relatively non-aggressive slow-growing tumours that can be suitable for active surveillance to more aggressive neoplasms that need to be actively treated, either by surgery or radiation therapy.

Nowadays, nearly 20% of patients undergoing a radical prostatectomy will experience biochemical recurrence and up to 77% of patients with recurrent disease will die of cancer-related causes (1). These results may be improved by adjuvant therapies, which should be however carefully considered for each single patient based on clinical/pathological features, and cost/effectiveness and morbidity of the treatments. Several prognostic models have been developed to support physicians in clinical decision making, aiming to identify prostate cancer patients suitable for adjuvant therapies due to a high risk of biochemical failure (2-5). In general, adjuvant radiotherapy and hormonal therapy are considered in case of high-risk pathological findings and in case of postoperative detectable prostate-specific antigen (PSA) values, with the objective to reduce biochemical recurrence rate as well as cancer-related death (6-8). However, this practice needs to be further supported by clinical studies.

Three randomized clinical trials investigated postoperative adjuvant radiation therapy following radical prostatectomy

by comparing immediate postoperative radiotherapy versus a wait and see approach (9-11). Although postoperative radiation therapy provided improvement of biochemical recurrence-free survival and overall survival in all these trials, the role of postoperative radiotherapy is still debated. In the South-West Oncology Group trial (SWOG) (9), patients with PSA recurrence in the wait and see arm were offered salvage radiotherapy. This patient sub-group was matched with the adjuvant radiotherapy group. Interestingly, the authors found that the 5-year PSA-failure rate was lower in the salvage radiotherapy group. However, these data should be taken with caution, since the RADICALS (NCT00541047) (12) and RAVES (NCT00860652) (13) randomized clinical trials, which hypothesize that salvage radiotherapy can guarantee a cancer control similar to adjuvant radiotherapy, are still ongoing. Overall, the results of these trials may help physicians to identify the best timing of postoperative radiotherapy.

The major concern about adjuvant radiation treatment is the related risk of toxicity. Radiotherapy is not free of side effects: toxicity analysis performed on patients enrolled in the Radiation Therapy Oncology Group (RTOG), SWOG, and European Organisation for Research and Treatment of Cancer (EORTC) trials showed an increase in acute and late gastrointestinal toxicity, urinary strictures and incontinence after adjuvant radiation therapy, while erectile function and quality of life were not substantially impaired (6). Of note, in these trials 3-dimensional conformal radiotherapy

with multiple fields techniques was used, whereas intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) combined with image-guided radiotherapy (IGRT) are nowadays frequently preferred given their improved ability to spare the organs at risk, thereby resulting in a lower morbidity profile with reduced risk of urinary and rectal side effects. To maximize the benefit of radiotherapy the use of a proper technique is important, but the adequate dose level and target coverage are also crucial (14). From a radiation biology standpoint, a dose-escalation regimen can increase biochemical control as shown after radical radiotherapy, where every Gy increases gain by 2% (8). However, the definition of the target field in the adjuvant setting is still largely debated. Regardless recommendations from several guidelines, interobserver variations in contouring the tumour bed are still an unresolved issue (6).

In a recent article, Gandaglia *et al.* (15) proposed a new nomogram to identify patients at higher risk of prostate cancer-specific mortality (CSM) following radical prostatectomy. Given that the persistence of a detectable PSA after radical surgery may not necessarily reflect a poor oncological outcome, the authors analyzed the impact of adjuvant radiotherapy on CSM based on the individualized patients risk calculated by the proposed nomogram, that includes postoperative PSA as a continuous variable. The persistence of detectable PSA could be indeed related either to benign prostatic tissue left behind during surgery or to well differentiated tumour cells growing slowly, which may not necessarily require further treatment. This scenario could be theoretically similar to the diagnosis of an organ confined low-risk prostate cancer that nowadays may be managed expectantly.

The variables used by the authors to build up the nomogram include pathologic grade pattern (≥ 4 *vs.* < 4), lymph-node status (positive *vs.* negative), extra-prostatic disease (pT3b, pT4 *vs.* \leq pT3a), and surgical margin status (positive *vs.* negative). In addition, they included immediate androgen deprivation therapy (ADT). The authors observed that PSA persistence after radical prostatectomy was associated with decreasing cancer-specific survival among patients with worse pathologic features, i.e., those with predicted CSM risk $> 10\%$. Interestingly, in patients presenting a CSM risk $> 30\%$, a clear survival benefit was observed when adjuvant radiotherapy was performed.

Nomograms are very useful clinical tools to calculate the risk of tumour progression by incorporating clinical variables potentially predictive of tumour recurrence. In

the scenario of a raising PSA after surgery that may reflect a progressive cancer, a nomogram may help physicians to identify those patients who will benefit from adjuvant treatment.

Nomograms may therefore act as the “Rosetta Stone” of prostate cancer. The ancient “Rosetta Stone” was a stele reporting a decree inscribed in three languages with different symbols, including hieroglyphic, demotic and ancient Greek. The finding of Rosetta stone was an amazing discovery because allowed to understand the ancient Egyptian literature misunderstood until that time by deciphering the Hieroglyphic text using the Greek text.

Although the study of Gandaglia *et al.* is interesting and clinically relevant, the analysis presents some biases, addressed by the authors in the discussion. The major bias is related to the retrospective design of the study, including prostate cancer patients treated by surgery in a wide time period. The criteria for clinical risk assessment as well the treatment strategies including surgery and radiotherapy as well as the indications to adjuvant hormonal therapy have rapidly evolved over time, therefore potentially leading physicians and patients to choose different treatment options. Moreover, the authors considered only a single PSA value as a variable in the nomogram, instead of choosing a dynamic assessment of PSA kinetics (e.g., using the PSA doubling time). The kinetics of biomarkers is more likely to reflect the biology of a tumour rather than a single assessment, especially in the scenario of a potentially recurrent disease following surgery. Despite these limitations, Gandaglia *et al.* concluded that detectable post-operative PSA values between 0.1 and 2.0 ng/mL are not always indicative of persistence of cancer and should be correlated with pathological findings before addressing patients to an immediate adjuvant treatment. Moreover, when patients had a higher CSM risk ($> 10\%$), lower PSA levels correlated with a higher cancer-specific survival. These results support other findings of the literature suggesting that biochemical disease-free survival is better among patients who undergo radiotherapy with relatively low postoperative PSA levels (16,17).

Another relevant issue concerning adjuvant treatment is the indication to hormonal therapy. Gandaglia *et al.* included immediate ADT as a variable to build the nomogram. Of note, only a minority of patients (22% of the overall population and 40% of patients who did not receive postoperative radiotherapy), received immediate hormonal therapy. This group of patients should have been excluded from the analysis as ADT may act as a confounder

by potentially improving survival. Carrie *et al.* in the GETUG-AFU 16 trial (18) and Shipley *et al.* (19) in an RTOG NRG trial observed that patients receiving adjuvant ADT had improved overall and progression-free survival when combined with salvage radiotherapy. The ongoing RADICALS trial aims at answering the uncertainties on the role of both postoperative radiotherapy and ADT by randomizing nearly 4,000 men to adjuvant or salvage radiotherapy with or without ADT (12).

In conclusion, clinical decision making in prostate cancer patients with persistently elevated PSA levels following radical surgery remains a daunting task, requiring a holistic approach that incorporates the assessment of clinical and pathological prognosticators of cancer progression (including PSA kinetics), and the analysis of cost/effectiveness and treatment-related morbidity of adjuvant/salvage therapies.

Future research on prostate cancer needs to test new imaging modalities, including PSMA PET-scan (20), and new treatment modalities, such as robotic surgery and innovations in radiation oncology including highly hypofractionated regimens by stereotactic body radiotherapy (SBRT), particles (protons and ions) and intraoperative radiotherapy (21,22). The advent of these new tools and treatment options represents an additional reason to decipher the “Rosetta Stone” of prostate cancer, in order to accurately predict the prognosis and therefore the best treatment option for each individual patient.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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