BJU Int 2025; **136:** 768–769 doi:10.1111/bju.70029

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Research Highlights

The growth and treatment of urologic cancers

This month's column focuses on the growth and treatment of urologic cancers. Yang et al. reported that histologic variant bladder cancer subtypes are found in up to 25% of all urothelial cancers and are associated with worse clinical outcomes. Researchers have made great strides in defining the molecular characteristics of pure urothelial cancers, but less is known about histologic variants such as micropapillary, plasmacytoid and adenocarcinoma. The authors generated a single-cell RNA sequencing atlas of histologic variant bladder cancers to identify potential targetable features. They detected a cancer cell state (Cluster 13) with clinical and mechanistic significance that contained a targetable protein (TM4SFI). This cell state contains several genes including CA125 that can be leveraged as biomarkers. They also found that most histologic variant cancers exhibit enriched expression of TM4SF1, a gene that encodes a surface protein and that has been implicated in the pathogenesis of aggressive bladder cancers and other cancer cell types.

Yang H, Song H, Yip E et al. Bladder cancer variants share aggressive features including a CA125+ cell state and targetable TM4SF1 expression. *Nature Communications* 2025; https://doi.org/10.1038/s41467-025-59888-8.

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Kamatani et al. reported results from a unique patient autopsy that revealed different treatment responses to anti-PD-1 therapy at each tumour site. They found that subsets of subclones can acquire driver mutations under treatment selection pressure. They noted that subclones resistant to immunotherapy form distinct immunosuppressive environments. Several factors such as hypoxia, nutrient deprivation, cancer-associated fibroblasts generated by antitumor agents differentially affect the host-tumour immune state. The different immune microenvironments that form under selective pressures from immunotherapy result in polyclonal competition resulting in different responses to immunotherapy.

McLeay et al. studied the growth rates of venous tumour thrombi in 141 patients over a period of 20 days. They found that venous tumour thrombi grew at a median rate of 0.3 mm/day. They also found a strong correlation between venous tumour thrombus growth rates and the level of disease. Sarcomatoid/rhabdoid features and the presence of metastatic disease were also associated with increased tumour thrombus growth rates. These findings should help with pre-operative triage and surgical planning.

Kamatani T, Umeda K, Iwasawa T et al. Clonal diversity shapes the tumour microenvironment leading to distinct immunotherapy responses in metastatic urothelial carcinoma. *Nature Communications* 2025; https://doi.org/10.1038/s41467-025-63309-1.

McLeay MT, Roberson DS, Dorr M, et al. Growth kinetics of venous tumor thrombus from renal cell carcinoma. *J Urol* 2025; https://doi.org/10.1097/JU.0000000000004750.

"Only men diagnosed with prostate cancer by PSA testing in their 50s and possibly early 60s are likely to gain significant benefit from a radical prostatectomy"

Finally, Holmberg et al. explored the long-term survival of men enrolled in the SPCG-4 prostate cancer trial. The trial enrolled 695 patients between 1989 and 1999 and randomized men to either a radical prostatectomy or usual care which consisted of androgen deprivation therapy once clinical symptoms occurred. The cumulative probability of prostate cancer death increased from 2.9% to 25.9% in the radical prostatectomy arm and 4.6% to 42.9% in the watchful waiting arm during 30 years of follow up. By year 30 the number of men needed to treat to prevent one prostate cancer death had fallen from 58 to 6. It is important to remember, however, that over 90% of these patients had clinically detected disease at the time of enrolment. The lead time associated with PSA testing is probably at least ten years. Therefore, based on these findings, only men diagnosed with prostate cancer by PSA testing in their 50s and possibly early 60s are likely to gain significant benefit from a radical prostatectomy.

Holmberg L, Garmo H, Andersson S-O et al. *Eur Urol* 2025; https://doi.org/10.1016/eururo/2025.07.001.

Research Highlights is written by Peter Albertsen.