In this issue of ONCOLOGY, Kamat and Mathew provide an excellent overview of the current status and future imperatives of bladder cancer treatment and research. As the authors highlight, and as other experts have recently written,[1] a paradigm shift is long overdue. The basic management of bladder tumors has remained essentially unchanged for over 50 years, and despite its importance—on account of the incidence, prognosis and cost of the disease—bladder cancer research remains significantly underfunded.[2] Every aspect of our perception and management of this disease requires change; abandoning the use of the term "superficial" bladder cancer is just the first step[3]—the term is both inaccurate and implies a lack of importance that is completely wrong. In particular, given the very high costs to healthcare systems from long-term surveillance and treatment of the disease,[4] it is particularly surprising that there has not been more emphasis on the disease from health policy makers and pharmaceutical companies.

Demographically, the industrializing nations will contribute to a significant rise in the global incidence of bladder urothelial carcinoma,[5] with particularly large numbers likely in China given the rapid improvement in the standard of living and the high prevalence of smoking. However, despite the falling incidence in developed nations, specific challenges remain, chiefly stemming from the aging population and increased life expectancy. Within two large cohorts separated by 15 years (1991-92 and 2005-10), we have recently demonstrated an increase in age at presentation of 4 years, with an increase from 13% to 24% in the proportion of patients over 80 years.[6] Technically, treatment in this aging cohort may become more feasible with the advances in minimally invasive and robot-assisted surgery. There is also significant scope for improving the primary surgery that we offer to all patients: transurethral resection. New instruments may allow us to move away from the "incise and scatter" nature of existing procedures,[7] and we already know that new optical and image-enhancement technologies allow us to carry out more thorough tumor resections.[8] In addition, a rethink of the view that cystectomy is the gold standard for invasive bladder cancer is long overdue. Comparisons of large surgical[9] and radiotherapy[10] series suggest very similar long-term survival rates, and population-based studies do not appear to show any survival differences linked to mode of treatment.[11] Moreover, most large surgical series have median ages in the mid-60s[9,12], well below the (rising) disease population median, suggesting that the results may not be applicable to many or even most patients with invasive bladder cancer. Use of bladder preservation varies worldwide from around 10% in the US[13] to 25% in Scandinavia[14] to around 50% in the UK.[15] Furthermore, there is good evidence that older or less fit patients in low-volume centers are less likely to be referred for surgery, although they are likely to be fit for radiotherapy.[13,14] In contrast, recent large randomized radiotherapy series from the UK suggest that radical radiotherapy with sensitization, either with low-dose chemotherapy[16] or with hypoxia-targeting agents,[17] is effective and well tolerated by elderly patients (median age in both studies, 72 to 73 years). Long-term functional outcomes with radiotherapy are excellent,[16-18] making it particularly suitable for less fit patients who may struggle with a urinary diversion. The role of systemic chemotherapy has probably reached a plateau, and for advanced disease there has been depressingly little progress since the advent of gemcitabine (Gemzar) more than 10 years ago. Further progress is likely to come from the targeted molecular approaches summarized in the article. The role of neoadjuvant chemotherapy appears to have been somewhat downplayed in the review. Although the absolute survival advantage is around 5%,[19] this does not mean that only 1 in 20 benefit: it means that all patients receiving neo-adjuvant chemotherapy on average live longer than those receiving only surgery or radiotherapy. In the case of the Intergroup MVAC trial,[12] this median survival improvement was highly clinically significant (46 vs 77 months). Three to four cycles of platinum-based combination chemotherapy is generally well tolerated, particularly now with the use of gemcitabine-based combinations. Neoadjuvant therapy also allows time for detailed planning...
of the definitive procedure—eg, continent diversion, bladder preservation, etc. Given these data, and the poor tolerability of postoperative (compared to pre-operative) chemotherapy, it is hard to see how the poor uptake of this modality in most countries is justified; similar survival gains from adjuvant chemotherapy in breast cancer, for example, are enthusiastically implemented. New technologies may allow us to reduce the frequency of cystoscopic follow-up, and hence reduce the significant costs associated with bladder cancer surveillance[20] while we continue to develop accurate urine analyses or biomarkers. To date, as Kamat and Mathew point out, use of biomarkers has been unhelpful. Future tests are likely to utilize advanced platforms, such as proteomics, metabolomics, and next-generation sequencing, or combinations thereof.[21] It may also be possible to use markers to help guide treatment pathways—eg, by expediting treatment for high-risk disease—rather than for primary diagnosis and screening.[22] The development of accurate prognostic tools may allow us to better tailor management approaches to specific patients. As Kamat and Mathew discuss, the EORTC bladder cancer "calculator" is a step in the right direction,[23] but better prognostic tools based on molecular markers of disease biology should improve on this. Next-generation sequencing platforms may be required to ultimately deliver "personalized medicine"[24] as well as the new high-quality targets that the authors emphasize are needed. To deliver successful and durable therapies, we also need to develop our understanding of the tumor microenvironment, tumor immunology, and the cancer stem cell phenotype.[25] The authors succinctly describe the research priorities, priorities that we wholeheartedly support. We have established a biorepository of relevant specimens and patient information to contribute to this work,[26] but the challenging research funding environment hampers the full exploitation of such resources. Closer working relationships with the pharmaceutical industry will be required to translate research into patient benefit.

Financial Disclosure: Dr. Bryan serves as an unpaid consultant to Olympus Medical Systems. Dr. James has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:

REFERENCES


