In most cases, localized small-cell bladder cancer requires cystectomy for optimal cure rates.

The small-cell undifferentiated or anaplastic variant of bladder cancer presents a challenging clinical problem, both because of its rarity and the consequent paucity of level I data to guide treatment paradigms. Representing only 1% to 2% of incident bladder cancers, depending on the site of reporting, this entity is most likely the product of a stem cell tumor, with differentiation along an unusual pathway.[1] We have previously modeled the existence of a bladder cancer stem cell, demonstrating preclinically and clinically its potential to differentiate along varied pathways, most commonly glandular or squamous.[2,3] There is extensive evidence to support the common clonal origin of small-cell bladder cancer (SCBC) and urothelial cancer.[4] The fundamental biology of SCBC has not yet been elucidated, although the general consensus is that it is a smoking-related disorder, with common aberrant patterns of chromosomes and gene expression, as well as presence of neuroendocrine biochemical markers.[5,6] If this tumor does not have a stem cell origin, it most likely represents de-differentiation from the scattered neuroendocrine cells in the bladder wall.

Analogous to small-cell tumors arising in other sites, such as bronchus and prostate tumors, SCBC is a highly aggressive variant with a propensity for early local invasion and distant metastasis.[1,5] What is somewhat unusual is the frequent coexistence of urothelial carcinoma in situ,[7] a single-layer thick, but a pattern that is notoriously resistant to radiotherapy or chemotherapy, and which usually only responds to surgical resection or intravesical immunotherapy or chemotherapy.

Metastatic SCBC

There really is little controversy about the management of metastatic SCBC. Analogous to small-cell tumors arising from other primary sites, the definitive management is chemotherapy. These tumors are initially very responsive to chemotherapy, although responses in metastatic disease usually only last less than a year.[1,5] Active agents include etoposide, carboplatin, cisplatin, paclitaxel, doxorubicin, cyclophosphamide, ifosfamide, and gemcitabine, each with a single-agent objective response rate of 15% to 25%; higher response rates are associated with lymph node and pulmonary disease, and lower response rates are seen in hepatic and osseous metastases.[1,5,8,9] These single agents can be combined into doublet or triplet regimens, yielding somewhat higher response rates and slightly more durable survival figures, but the majority of patients continue to die within the first 1 to 3 years, depending on their responsiveness to chemotherapy and the pattern and extent of disease.[1,5,8,9] Second-line responses are quite common, but usually of much shorter duration. The dramatic progress in lung cancer treatment from the measurement of programmed death ligand 1 (PD-L1) in tumor tissue with its associated predictive value for response to T-cell functional enhancers, such as pembrolizumab, has not yet been applied to SCBC. Occasional immunotherapy responses have been seen in small-cell lung cancer, and it is possible that a similar situation will apply to SCBC. In the domain of novel cytotoxic agents, scant progress has been made since the introduction of gemcitabine into clinical management of small-cell undifferentiated cancers more than a decade ago.

Clinically Localized SCBC: Conventional Approaches

The management of clinically nonmetastatic SCBC is a much more controversial issue.[1,5,10-14] There is general consensus that these tumors respond well to combination cytotoxic chemotherapy, radiotherapy, or combinations of both. Response rates in the range of 40% to 60% have been recorded in response to two-, three-, or four-drug regimens,[1,5,8,9] often in combination with locoregional radiotherapy, although response does not equate with cure. As previously noted, SCBC...
has a propensity for early metastasis, and up to 40% of clinically nonmetastatic tumors have proven to be resistant to chemotherapy. Approximately 15% to 20% of nonmetastatic cases of SCBC can be cured by chemotherapy alone or by the combination of chemotherapy and radiotherapy. Similarly, objective response to radiotherapy alone may be as high as 50% to 70%, sometimes leading to cure. In each instance of SCBC, one of the greatest challenges is posed by the propensity for early visceral metastasis, as well as the proclivity of these tumors to lodge micrometastases within the brain, often manifesting themselves well after completion of initial staging and treatment. As a result, cure rates can be disappointingly low. Given the high initial response rates and potential for a significant proportion of long-term survivors who received chemoradiation, it has been suggested that prophylactic cranial irradiation is a reasonable option that may prolong survival, analogous to the situation in small-cell undifferentiated lung cancer. This has not become standard practice, but is being increasingly explored; however, the lower frequency of brain metastases from SCBC compared with the lung cancer equivalent has precluded this from being viewed as any standard of care.[15]

It has conventionally seemed very attractive to avoid the mutilation and morbidity of cystectomy in the context of a relatively poor potential for cure,[12-14] and thus an emphasis has been placed on radiotherapy alone, chemotherapy alone, or combinations of the two.

**Clinically Localized SCBC: The Role of Surgery**

“Primum non nocere”—above all, do no harm—is a valid and valued principle of ancient and modern medicine. Given the significant morbidity and potential occasional mortality from the operative removal of the bladder, it is particularly important to establish whether metastases are already present when this option is being considered. There are well-established limitations to the clinical staging of small-cell malignancy, adding to the importance of ensuring that very clear goals of therapy are implemented. The results of cystectomy alone for SCBC have been quite disappointing,[5,10-12] with modest long-term survival figures.

For the elderly patient for whom quality of life and safety are paramount, the role of cystectomy assumes a lesser importance. However, for the patient (especially those who are younger and more robust) for whom length of survival is the key determinant, the majority of available data suggest that initial chemotherapy, followed by cystectomy, offers the greatest potential for cure.[1,5,7,16] It should be emphasized that this literature is heavily influenced by data recycled from MD Anderson Cancer Center, although it is important to note that they have the largest database of such cases. Of particular interest is a review of the National Cancer Data Base, covering all documented cases between 1998 and 2010, which showed a 3-year survival of 53% among patients who received neoadjuvant chemotherapy followed by cystectomy—the best outcome seen[12]; that said, the potential for case selection bias was substantial.

A very important factor is that 30% to 40% of SCBC cases are associated with coexistent carcinoma in situ,[7] which tends to be resistant to chemotherapy and radiotherapy. This connection has been missing from the isolated case reports and case series with only small numbers. This increases the importance of surgical resection, although it is not completely clear whether deep transurethral resection could be a sufficient replacement for radical cystectomy. Given the potential for multisite involvement of carcinoma in situ, it seems that cystectomy is the most prudent option.

It has also been reported that cystectomy followed by adjuvant chemotherapy is another effective option, with a 40% 5-year survival rate compared with 23% for surgery alone.[16,17] Once again, the potential for case selection bias and differences in supportive and salvage therapies is substantial; a randomized clinical trial would be needed to resolve this issue.

Regrettably, there are no level I data, and relatively weak level II data, with significant risk of case selection bias, to support the view that surgery is an essential part of treatment of nonmetastatic SCBC. Data from large databases, such as the Surveillance, Epidemiology, and End Results program, are limited in their accuracy and utility, and the absence of a differential in outcomes from surgery, radiotherapy, or combined-modality regimens in such reports[18] is probably more an artifact of imperfect data recording and capture than the reality of clinical practice. That said, the cure rate from the small reported series of chemoradiation alone is simply lower than the published cure rate associated with combined chemotherapy (with or without radiation) followed by surgery.

Until one of the cooperative cancer trial groups tackles this difficult problem in a multicenter collaboration, it seems to me that the safest approach for a young and robust patient is to offer initial multi-agent chemotherapy followed by restaging, and then cystectomy for patients without evidence of metastatic disease. In that setting, data from several centers suggest potential long-term survival of greater than 50% to 60%. Analogous to urothelial cancer, the data to support adjuvant chemotherapy are still modest, and I prefer to recommend a neoadjuvant strategy until
more information is available about the classical adjuvant approach.

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