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REVIEW

Zhang et al: NEBC: Molecular and immune insights

Molecular and immune characteristics of neuroendocrine bladder carcinoma — Implications for diagnosis, prognosis, and therapy: A review

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ABSTRACT

Neuroendocrine bladder carcinoma (NEBC) is a rare but highly aggressive histologic subtype of bladder cancer with poor prognosis, often driven by delayed diagnosis and limited therapeutic options; despite widespread use of next-generation sequencing, its cellular origin remains unclear and controversial. We aimed to synthesize up-to-date molecular and immune features of NEBC and translate them into practical guidance for diagnosis and treatment. We performed a narrative review of English-language studies indexed in PubMed and Web of Science (January 2000–August 2025) using predefined keywords, integrating genomic, transcriptomic, immunohistochemical, and clinical outcome data. Key findings indicate frequent co-occurrence and probable common clonal origin with urothelial bladder carcinoma, with hallmark *TP53* and *RB1* alterations, prevalent APOBEC-driven mutagenesis, and recurrent *TERT* promoter mutations; tumor mutation burden is heterogeneous but can be high. Despite this, NEBC commonly exhibits an immune-cold or immune-excluded microenvironment characterized by low PD-L1 expression and T-cell dysfunction, which may blunt responses to immune checkpoint inhibitor monotherapy. Diagnostic practice still relies on morphology supported by immunohistochemistry (synaptophysin, chromogranin A, CD56, GATA3), with emerging tools such as INSM1 and a decision-tree model using synaptophysin, CD117, and GATA3 that improve accuracy. Therapeutically, neoadjuvant chemotherapy—most commonly EP or IA—followed by radical cystectomy improves outcomes compared with initial cystectomy alone, while metastatic disease is typically managed with EP chemotherapy and radiotherapy with limited durability. Early data support immunotherapy, particularly immune checkpoint inhibitors, and suggest potential benefit from chemoimmunotherapy; a prospective trial of neoadjuvant anti-PD-L1 plus EP is underway, and antibody-drug conjugates and bladder-sparing multimodality strategies are emerging. In conclusion, comprehensive molecular and immune characterization is critical to refine diagnosis, optimize patient selection, and accelerate prospective trials that evaluate neoadjuvant chemotherapy, chemoimmunotherapy, and targeted approaches in NEBC.

Keywords: Neuroendocrine bladder carcinoma, driver genes, immune microenvironment, molecular features, immune checkpoint inhibitors.

INTRODUCTION

Bladder cancer (BC) is the most common malignant tumor of the urinary system, accounts for more than 570,000 new cases and over 210,000 deaths worldwide annually [1,2]. BC is a heterogeneous tumor encompassing multiple histological subtypes, including urothelial carcinoma, adenocarcinoma, squamous cell carcinoma, and neuroendocrine carcinoma [3]. Neuroendocrine tumors can arise in different anatomical sites, including the sympathetic nervous system, adrenal gland, lung, pancreas, bladder, and prostate [4]. Regardless of their organ of origin, neuroendocrine tumors comprise neuroendocrine cells that secrete bioactive substances and proteins, such as somatostatin, insulin, gastrin, serotonin, and synaptophysin [5]. Histologically, neuroendocrine bladder carcinoma (NEBC) presents as small cell carcinoma, large cell carcinoma, and mixed neuroendocrine carcinoma [6,7]. Although rare, accounting for less than 2% of BC diagnoses, NEBC is an extremely malignant disease [8]. Furthermore, NEBC is typically diagnosed at an advanced stage, with a high metastatic potential and a 5-year survival rate less than 10% [9,10]. Therefore, early diagnosis and multimodal treatment strategies are critical for NEBC management [11-13]. Currently, the diagnosis of NEBC lacks a gold standard and primarily relies on morphological findings with adjunct immunohistochemical stains [14]; tumor imaging serves only as a supportive tool and is not essential for definitive diagnosis [15].

Therapeutically, clinical guidelines for NEBC primarily extrapolate from management strategies for urothelial carcinoma and other neuroendocrine carcinomas (e.g., small cell lung cancer), which are supported by limited high-level evidence [16]. Furthermore, the scarcity of NEBC cases in clinical trials restricts the development of novel therapeutic approaches [10]. In recent years, immunotherapy has been a major advance in the field of urothelial cancer and other neuroendocrine carcinomas [17]. Among these, immune checkpoint inhibitors (ICIs), particularly those targeting the PD-L1/PD-1 pathway, enhance T-cell-mediated tumor cytotoxicity, thereby exerting anti-tumor effects [18]. Our recent study also demonstrated the superior efficacy of combined chemoimmunotherapy in NEBC [19]. However, a comprehensive understanding of the molecular and immune mechanisms underlying NEBC is still lacking.

In this review, we synthesize current knowledge of the molecular and immune landscape of NEBC and provide translational insights for implementing these findings in individualized clinical management.

LITERATURE SEARCH STRATEGY

This literature review was undertaken to examine recent advances in the molecular and immune characteristics of NEBC and their implications for diagnosis and treatment. We searched in the PubMed and Web of Science databases for published English-language articles from January 2000 to August 2025. The search strategy included a combination of keywords, including “neuroendocrine bladder carcinoma”, “bladder cancer”, “immune microenvironment”, “molecular features”, “immune checkpoint inhibitors”, and “neuroendocrine cancer”. Boolean operators (AND/OR) were employed to enhance the search outcomes.

THE ORIGIN OF NEBC

Common clonal origin hypothesis

Emerging evidence suggests that NEBC and urothelial bladder carcinoma (UBC) share a common cellular origin. In 2005, Cheng et al. first proposed the common clonal origin of small cell carcinoma of the bladder (SCBC) and UBC at the molecular genetic level [20]. They identified similar allelic imbalance and X-chromosome inactivation patterns between SCBC and coexisting UBC, suggesting that these tumors may originate from undifferentiated, multipotent progenitor cells within the urothelium [7,20]. The heterogeneity of NEBC poses significant challenges to the accurate immunohistochemical identification of large cell NEBC [21]. NEBC and UBC are often found together during the process of histopathological examination [7]. It has been reported that approximately 40% of SCBC cases exhibit mixed histological components of small cell and urothelial carcinomas [13]. Furthermore, NEBC and UBC usually display similar somatic mutations in the same lesion, suggesting the clonal correlation between the two types of BC [20,22]. Studies employing comparative genomic hybridization, next-generation sequencing, and immunohistochemistry have suggested that urothelial carcinoma may transform into NEBC through the accumulation of genetic mutations [23,24]. Subsequently, Shen et al. showed that the genomic portraits of NEBC are similar to those of conventional

UBC [25]. In particular, NEBC and UBC exhibit similar carcinogenesis pathways driven by age-related and *APOBEC*-mediated mutational processes. By comparing genomic data from tumor samples of 87 SCBC cases with those of 303 high-grade UBC and 149 small cell lung cancers, T. Chang et al. identified a similar histology-specific mutational pattern of somatic *RB1* and *TP53* driver mutations in SCBC and UBC, but absent in small cell lung cancers [23]. Based on a comparative analysis of 25 BC cases coexisting with SCBC and non-small-cell phenotypes in the urothelium, researchers identified an identical somatic mutation in the *TERT* promoter across both components [22]. At the experimental level, Wang et al. constructed a patient-derived xenograft model to demonstrate that genetically engineered urothelial cells give rise to mixed histological subtypes of NEBC and UBC [26]. Furthermore, another study suggested that *miR-145* could induce a stem cell-like phenotype in urothelial carcinoma cells and promote their differentiation into neuroendocrine cells by inhibiting syndecan-1 [27]. Additionally, a case report from Robert-Bosch Hospital demonstrated that the invasive tumor arose within a classical urothelial carcinoma in situ. In this case, they reported a mixed tumor composed of urothelial carcinoma in situ, NEBC, and an adenocarcinomatous component, which exhibited concurrent upregulation of *p53* and strong cytoplasmic and membranous β-catenin staining [28]. Collectively, this evidence supports the hypothesis of a common origin between NEBC and UBC. However, further preclinical experimental models, especially organoid models, need to be explored to validate this hypothesis. Such studies have been conducted in small cell lung carcinoma and neuroendocrine prostate cancer [29-33].

Other hypotheses

Although considerably less common, other researchers propose alternative theories regarding the origin of NEBC. A study using lineage tracing in a murine model of BC suggested that fundamental differences in the cell of origin may lead to variations in clinical course, prognosis, and histological morphology, which could explain the distinctions between NEBC and UBC [34]. Furthermore, in a case study by Olivieri et al., UBC was found to express cytokeratin but lacked synaptophysin expression, whereas NEBC tended to co-express both markers. Rather than arising from urothelial cells, they proposed that NEBC originates from the neuroendocrine system [35].

MOLECULAR CHARACTERISTICS OF NEBC

Accumulating evidence indicates that BC is one of the most frequently mutated among human tumors, following lung and skin cancer in terms of mutation frequency [36,37]. Here, we explore the key molecular alterations and their potential implications for NEBC.

TP53 and RB1

The inactivation of *TP53* and *RB1* is a key biomarker of NEBC [38]. Alterations in *TP53* and *RB1* are detected in nearly 80% of poorly differentiated neuroendocrine carcinomas [39]. *TP53* and *RB1* dysfunction is associated with histological progression to neuroendocrine carcinoma in lung and prostate cancers [40-43]. In the field of BC, recent studies have reported high mutation frequencies of *TP53* and *RB1* in NEBC. For example, one study of 61 SCBC patients reported mutation frequencies of up to 90% for both *TP53* and *RB1* [23]. Moreover, 80% of SCBC patients exhibited *TP53* and *RB1* double mutations. Similar findings were reported in a study by the Johns Hopkins Greenberg Bladder Cancer Institute, which documented mutation frequencies of 92% for *TP53*, 75% for *RB1*, and 72% for concurrent *TP53*/*RB1* mutations in 132 SCBC patients [44]. Another study also detected genetic alterations of *TP53* and *RB1*, which were associated with reduced responsiveness to targeted therapies [25]. Interestingly, based on integrative analyses of muscle-invasive BC across multiple molecular platforms, Robertson et al. identified a neuronal subtype, in which 10 of 20 (50%) tissues exhibited either both RB1 and *TP53* alterations or *E2F3* amplification [38]. Furthermore, they found that 17 of the 20 (85%) tumor samples harbored somatic mutations in the p53/cell-cycle signaling pathway. Notably, cases of UBC have been reported to harbor inactivating mutations in *TP53* and *RB1* in 12% of cases, suggesting that these mutations may be sufficient but not necessary for driving the transformation into NEBC [45].

APOBEC

Apolipoprotein B mRNA editing enzyme, catalytic polypeptide (*APOBEC*) family is a group of cytosine deaminases [46]. Analyses of TCGA data have revealed that APOBEC-mediated mutagenesis is a significant contributor to BC carcinogenesis [45]. However, another study integrating whole-exome sequencing, next-generation sequencing, and transcriptome analysis suggested that high *APOBEC* activity is

associated with favorable prognosis, immune activation, and response to immune-checkpoint blockade in BC [47]. In the specific context of NEBC, *APOBEC*-driven mutational events, occurring in 95% of SCBC patients, potentially induce a high mutation burden in SCBC [23]. Our previous study also identified a prevalent *APOBEC*-mediated subtype characterized by distinct mutational signatures in NEBC patients [19,25,48]. Furthermore, Robertson et al. identified a neuronal subtype in muscle-invasive bladder cancer based on genes mutated in association with *APOBEC* activity [38,48].

TERT promoter

Mutations in the TERT promoter are a frequent molecular feature of NEBC. In one study, *TERT* promoter mutations were detected in 55% (29 of 53) cases of SCBC [22]. Another study reported that 100% (10 of 10) of NEBC exhibited the *TERT* promoter *C228T* mutation [24]. However, none of the SCCs from other cancer types, including prostate, lung, cervix, esophagus, and skin, harbored TERT promoter mutations, suggesting its potential as a diagnostic biomarker [24,49]. Furthermore, the rs2853669 common allele within the TERT promoter mutation was associated with reduced overall survival and an increased risk of tumor recurrence in BC [50,51].

IMMUNE FEATURES OF NEBC

The bladder urothelium is continuously exposed to urinary carcinogens, such as tobacco-derived compounds, microbiota, and aromatic hydrocarbons. This constant exposure renders bladder cancer (BC) a highly immunogenic disease, often characterized by a high somatic mutation rate and an abundance of tumor neoantigens [52,53]. Consequently, BC is particularly amenable to immunotherapy, which has led to the approval of multiple ICIs for clinical use [54]. However, immunotherapy demonstrates limited efficacy in a subset of BC patients. Urgent investigation is needed to comprehensively characterize the immune microenvironment of NEBC, identify responsive patient subgroups, and develop optimized therapeutic strategies.

Tumor mutation burden (TMB)

TMB, defined as the number of mutations in the tumor, reflects the level of neoantigens and the likelihood of T-cell recognition in humans [55,56]. The significant association between TMB and response to immunotherapy has been reported in various types of tumors, including non-small cell lung cancer, melanoma,

and urothelial carcinoma [57-59]. NEBC tends to exhibit heterogeneous TMB levels. A study of 132 cases of small cell carcinoma of the bladder and upper urinary tract reported that 26% of SCBC samples exhibited TMB ≥ 10 mutations/Mb, 3% had TMB ≥ 20 mutations/Mb, and the median TMB value was 6.2 mutations/Mb [44]. Another study conducted on 17 SCBC patients reported a high mutational burden, with a median TMB of 10.7 (range from 1.2 to 41.1) mutations/Mb, significantly higher than that observed in other genitourinary tumors [23]. Furthermore, in a study of 12 genitourinary neuroendocrine neoplasms resected from the bladder, Shen et al. reported an average mutation rate of 12.91 (range from 0.6 to 41.4) mutations/Mb in NEBC [25]. Using a linear regression model, a meta-analysis of 27 tumor types demonstrated that the average response rate was positively correlated with the logarithm of TMB [60]. It has been reported that BC with a neuroendocrine-like molecular subtype is among the most sensitive tumors to ICIs, suggesting promising therapeutic efficacy of immunotherapy for NEBC [61,62].

Immune infiltration

Based on the tumor immune microenvironment—particularly CD8+ T cell infiltration associated with anti-tumor effects, NEBC can be classified into two (immune-cold and immune-hot) or three primary immunophenotypes (immune-inflamed, immune-excluded, and immune-desert) [63-65]. Despite high TMB, NEBC tends to exhibit an immune-cold phenotype. Based on transcriptome sequencing of 24 SCBC cases and 51 UBC cases, Jean Hoffman-Censits et al. demonstrated that the expression of T-cell-related markers and inflammatory signaling pathways was suppressed in SCBC [44]. Another study comparing potential predictors between 12 SCBC and 69 UBC by immunohistochemistry concluded that SCBC primarily exhibited an immune-excluded subtype, which is characterized by the absence of PD-L1 expression and few tumor-infiltrating lymphocytes in the center of the cancer [66]. Similar results were also reported in a small cell lung cancer study [67]. Joseph M. Chan et al. observed an immunosuppressive tumor microenvironment in small cell lung cancer by single-cell sequencing, which is characterized by CD8+ T cell exhaustion [68]. The distinct immune-excluded phenotype of NEBC may compromise the therapeutic efficacy of monotherapy with ICIs.

CLINICAL MANAGEMENT OF NEBC

Diagnosis

NEBC is characterized by an aggressive clinical course, with advanced stage at presentation and a propensity for metastasis, and is associated with a low overall 5-year survival rate (8%-25%). Key negative predictors of outcome include age>65 years, advanced TNM stage, and metastatic disease at diagnosis, with tumor stage being the strongest [3]. The diagnosis of NEBC presents a significant challenge for both pathologists and clinical doctors [69]. Current clinical diagnosis of NEBC relies primarily on pathological morphology and immunohistochemistry [70]. Small cell neuroendocrine carcinoma is classified by its histologic characteristics, such as sheets and nests of small cells, scant cytoplasm, speckled nuclei, and indistinct nucleoli [71,72]. In the urinary bladder, NEBC tends to present as a mixed component of SCBC and non-SCBC [12,73]. The diagnosis of large cell NEBC is considered more challenging than that of SCBC based on morphologic features. Compared to SCBC, cases of large cell NEBC and mixed NEBC often exhibit enlarged nuclei, leading to potential misdiagnosis as high-grade urothelial carcinoma and subsequent delays in appropriate clinical intervention [6]. Furthermore, the key distinguishing features between SCBC and large cell NEBC include larger tumor cells, a lower nuclear-to-cytoplasmic ratio, and the presence of prominent nucleoli in large cell NEBC [74]. Traditional neuroendocrine markers for NEBC, including synaptophysin, chromogranin A (CGA), and CD56, exhibit limitations respectively. For instance, CGA exhibits a lack of sensitivity [7,75]. CD56 shows high sensitivity but low specificity [76]. A combination of morphologic features and traditional immunohistochemistry markers, including GATA3, CGA, and synaptophysin, is widely used for NEBC diagnosis in clinical practice (Figure 1) [71,75]. However, immunohistochemical marker staining may exhibit focal or weak intensity, and usually only a few markers yield positive results. Therefore, histomorphology alone may suffice for diagnosis, since all neuroendocrine markers may be negative in 10% of cases [77]. Novel diagnostic methods that enhance diagnostic accuracy for NEBC are urgently needed. Kim et al. developed a decision tree model based on synaptophysin, CD117, and GATA3, which exhibits 98.4% accuracy in identifying neuroendocrine differentiation in NEBC [71]. Furthermore, insulinoma-associated protein 1 (INSM1) has been reported as a diagnostic biomarker for neuroendocrine

carcinomas arising from various anatomical locations, including the uterine cervix, pancreas, prostate, thoracic cavity, and head and neck, with both high sensitivity and specificity [78-81]. After evaluating INSM1 staining in NEBC, a study demonstrated that INSM1 was positive in 87% (28 of 32) of cases, highlighting its potential as a diagnostic tool for NEBC [82]. Interestingly, neuronal markers identified by either RNA-sequencing or immunohistochemistry can also be used to define the neuroendocrine subtype in urothelial carcinoma, as these tumors may not exhibit the classic morphologic features of neuroendocrine neoplasms [38,83].

Treatment

The sensitivity of neoadjuvant chemotherapy (NAC) in NEBC has been verified in reports from various institutions [13,84]. Recent studies have demonstrated significantly improved outcomes in SCBC patients receiving NAC, with 5-year cancer-specific survival rates increasing from 38% to 78% [85]. We summarized prior studies of large NEBC patient cohorts (Table 1), we found that IA (ifosfamide and doxorubicin) or EP (etoposide and cisplatin)-based NAC combined with radical resection resulted in significantly better survival outcomes than those observed in patients who did not receive NAC [85-90]. However, for patients with metastatic NEBC that is not amenable to surgery, the current standard treatment methods are limited to EP chemotherapy and radiotherapy for metastatic lesions [38,91]. Although this therapy achieves a relatively favorable response rate, limited progression-free survival and drug resistance remain prevalent [88,92]. Given the high immunogenic potential of BC, immunotherapy, particularly ICIs, represents a promising therapeutic strategy for various BC subtypes, including NEBC [93]. A study reported that a NEBC patient with recurrent metastases achieved a favorable response to pembrolizumab therapy in the sixth-line setting, with minimal drug toxicity [94]. However, another retrospective study suggested that BC patients with neuroendocrine features exhibited shorter overall survival following ICI therapy compared to those with pure urothelial carcinoma [95]. Furthermore, our real-world experience with off-label ICI use suggested that chemoimmunotherapy—a combination of chemotherapy and immunotherapy—could potentially offer a promising therapeutic advantage for certain NEBC patients compared to chemotherapy alone [19]. Building on these promising preliminary findings, we have initiated a prospective clinical trial (ClinicalTrials.gov identifier: NCT06091124; Registration date: November 16, 2023;

Registry: Ren Ji Hospital) to formally assess the efficacy and safety of neoadjuvant adebrelimab (anti-PD-L1) plus EP in patients with NEBC. Additionally, novel targeted therapies, particularly antibody-drug conjugates such as rovalpituzumab tesirine and sacituzumab govitecan, have recently shown preliminary efficacy for small cell lung cancer and NEBC [95-97]. In addition, novel bladder-preserving approach have been widely used in the treatment of muscle invasive bladder cancer. For instance, our preliminary findings suggest the safety and efficacy of combining disitamab vedotin with toripalimab and radiotherapy as a multimodal organ-sparing strategy for muscle-invasive bladder cancer [98]. With the maturation of these approaches, their future application in bladder-preserving therapy for non-metastatic NEBC holds promise. Taken together, compared to other neuroendocrine carcinomas, therapeutic options for NEBC remain limited. Additional novel therapies should be evaluated in prospective clinical trials involving NEBC patients.

CONCLUSION

Given its aggressive nature and unfavorable prognosis, NEBC demands prompt clinical intervention (Figure 2). The origin of NEBC remains unclear and controversial, necessitating further research to elucidate this phenomenon. Notably, the coexistence of high TMB and immune exclusion in the NEBC microenvironment provides novel insights for guiding immunotherapy. Enhanced understanding of the molecular characteristics and an increased number of well-designed clinical trials are essential for addressing this aggressive BC subtype.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Representative studies exhibit the survival outcomes of NAC in NEBC patients

Study (first author）	Treatment	Number of patients	Regimen	Downstaging rate*	Median survival months	5-year survival rate
Siefker-Radtke [85]	RC only	25	NA	-	23 (CSS)	36%
	NAC+RC	21	IA or EP	57%	Not Reached	78%
Siefker-Radtke [86]	NAC+RC	18	IA or EP	78%	58 (OS)	-
Lynch [87]	RC only	47	NA	-	18.3 (OS)	20%
	NAC+RC	48	IA or EP etc.	62%	159.5 (OS)	79%
Vetterlein [88]	RC only	144	NA	-	17.3 (OS)	-
	NAC+RC	125	cisplatin-based	15.2% (pCR)	34.7 (OS)	-
Alhalabi [89]	RC only	38	NA	21.1%	20.6 (OS)	22%
	NAC+RC	141	EP or IA etc.	49.5%	86.1 (OS)	57%
Bakaloudi [90]	NAC+RC	29	EP or CE or GC	-	46 (OS)	41%

*Downstaging rate refers to pathologic stage ≤ pT1N0 proportion at cystectomy; "–" represents unclear data. The study from Vetterlein is a study of a broader variant-histology cohort, while the other five studies are about NEBC-only cohorts. Abbreviations: RC: Radical cystectomy; NAC: Neoadjuvant chemotherapy; IA: Ifosfamide plus doxorubicin; EP: Etoposide and cisplatin; CE: Carboplatin and

etoposide; GC: Gemcitabine and cisplatin; CSS: Cancer specific survival; OS: Overall survival; pCR: Pathologic complete response.

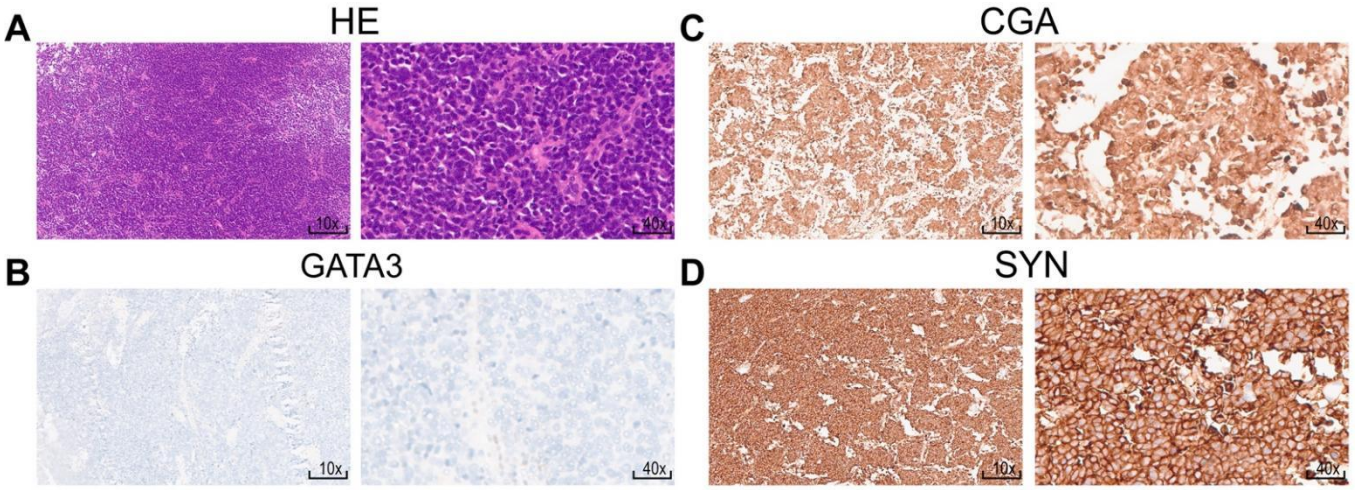

Figure 1. Hematoxylin-eosin and immunohistochemistry staining of representative markers for the diagnosis of NEBC. (A) Hematoxylin-eosin staining of NEBC tissues. Immunohistochemistry staining of GATA3 (B), CGA (C) and SYN (D) in NEBC samples. 10x corresponds to 200um, and 40x corresponds to 50um. The images and stains were done following the approval from the Ethics Committee of Ren Ji Hospital (approval code: KY2022-038-B). The following primary antibodies were used: anti-CGA (Proteintech, catalog no. 10529-1-AP, 1:500), anti-GATA3 (Proteintech, catalog no. 66400-1-Ig, 1:100), and anti-SYN (Proteintech, catalog no. 17785-1-AP, 1:1000). Abbreviations: NEBC: Neuroendocrine bladder cancer; GATA3: GATA-binding protein 3; CGA: Chromogranin A; SYN: Synaptophysin.

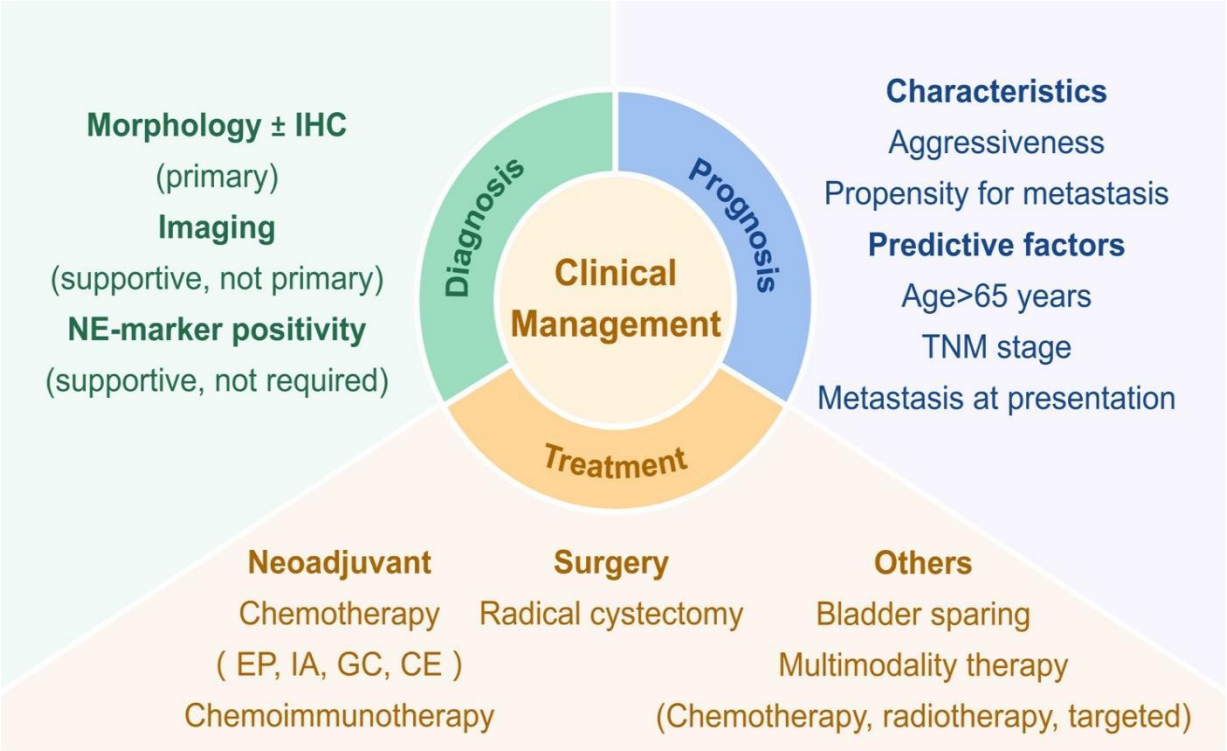

Figure 2. Overview of NEBC management: diagnosis, prognosis, and treatment. Abbreviations: IHC: Immunohistochemistry; NE: Neuroendocrine; EP: Etoposide and cisplatin; IA: Ifosfamide plus doxorubicin; GC: Gemcitabine and cisplatin; CE: Carboplatin and etoposide; TNM: Tumor-node-metastasis.