LARGE CELL NEUROENDOCRINE CARCINOMA OF THE URINARY BLADDER. BIBLIOGRAPHIC REVIEW

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Summary.- OBJECTIVES: Large cell neuroendocrine carcinoma (LCNEC) of the urinary bladder is very rare. We intend to update diagnostic criteria, pathologic and immunohistochemical characteristics, prognosis and treatment options. All published articles related with LCNEC of the urinary bladder have been reviewed and a descriptive study has been done.

RESULTS: A total of 17 LCNEC of the bladder has been found. The 50% of all LCNEC of the bladder are mixed histological variant. This variant implies a better prognosis than the pure variant. The 70% of LCNEC of the bladder were ≥T3 at the time of diagnosis and the survival rate was 25%, whereas T2 tumors showed a survival rate of 100%. Radical cystectomy with lymphadenectomy combined with chemotherapy can sometimes reduce local and distant recurrence and improve survival of LCNEC of the bladder.

CONCLUSIONS: LCNEC of the bladder is a tumor with high rate of local and distant recurrence, as well as low survival, requiring early diagnosis and aggressive combined treatment.

Keywords: Bladder carcinoma. Neuroendocrine cell. Large cell neuroendocrine carcinoma.

Resumen.- OBJETIVO: El Carcinoma Neuroendocrino de Células Grandes (CNCG), es un tumor poco frecuente en vejiga. Pretendemos actualizar los criterios diagnósticos, características anatomopatológicas e inmunohistoquímicas, pronóstico y tratamiento de esta patología.

MÉTODO: Realizamos una revisión bibliográfica y estudio descriptivo de los casos de CNCG de vejiga publicados en la literatura internacional.

RESULTADOS: Existen 17 casos publicados de CNCG de vejiga. Las variantes histológicas mixtas constituyen el 50% y muestran escasa mejor supervivencia que las puras. El 70% son ≥T3 al diagnóstico, y presentan una supervivencia libre de enfermedad (SLE) del 25%, mientras que la SLE para los T2 es del 100%. La cistectomía radical con linfadenectomía, combinada con quimioterapia preferiblemente neoadyuvante, consigue reducir la recurrencia local y a distancia, así como aumentar la supervivencia del CNCG de vejiga.
A patient on our service was recently diagnosed with LCNEC of the bladder, which prompted us to undertake a systematic review of the literature. We collected the published cases of LCNEC of the bladder and updated our knowledge of the diagnostic criteria, tumor behavior, and optimal treatment for this disease.

After analyzing all the published cases, we made a descriptive analysis of the patients' age and sex, clinical picture at the time of diagnosis, medical history, tumor appearance and size, presence of tumor necrosis, concomitance with other tumors, staging, immunohistochemical features, treatment received, tumor recurrence, length of the follow-up period, and survival rate.

Neuroendocrine tumors are common in lung tissue and the gastrointestinal tract and may appear in almost any organ that has epithelial tissue. They belong to the spectrum that includes the carcinoid tumors, the large cell neuroendocrine carcinomas, and the small cell undifferentiated carcinomas (1).

Neuroendocrine tumors of the bladder are rare, accounting for about 1% of bladder tumors (2). They may coexist with other tumors such as transitional cell carcinomas, adenocarcinomas, squamous cell carcinomas, lymphoepithelioma-like carcinomas, and carcinosarcomas (1). The most common neuroendocrine tumor of the bladder is the small cell neuroendocrine tumor (SCC), followed by the carcinoid tumors (typical and atypical) and the large cell neuroendocrine tumor (LCNEC) (1).

The large cell neuroendocrine tumor of the bladder was first described by Abenoza et. al in 1986 and, until now, only 17 cases have been published in the international literature (Table I). Some authors have mentioned the possibility that this bladder tumor has been underdiagnosed, for it was previously included in other variants of neuroendocrine tumors (2, 4).

The origin of neuroendocrine differentiation in bladder tumors is not clear. Various theories have been proposed to explain it.

- One theory hypothesizes that these tumors originate in the multipotential, undifferentiated cells or “stem cells” present in urothelial tissue (1, 3). This theory is supported by the fact that this type of tumor is frequently associated with other histological subtypes (3).

Having observed this tumor association, Cheng (5) performed a molecular analysis and found an almost identical loss of alleles and the same chromosome X inactivation pattern between the SCC and the urothelial carcinoma, which suggests that both tumor components originate in the same cell in the urothelium.

- Another theory suggests that the neuroendocrine cells originate within normal urothelium from either a urothelial metaplasia or a neuroendocrine cell population that is present in the submucosa but not yet defined (1, 3).

- Abenoza et. al also proposed that LCNEC of the bladder may originate in the epithelium of urachal remnants within the bladder; in fact, he presented his case as an LCNEC of the bladder of probable urachal origin.

LCNEC of the bladder widens the spectrum of undifferentiated bladder carcinomas, which includes the undifferentiated small cell carcinoma, the giant cell carcinoma, and the lymphoepithelioma-like carcinoma, which has a more favorable prognosis because of its good response to cisplatin therapy (1, 3).

RESULTS

A full review of the international literature was conducted with 17 cases of LCNEC of the bladder found, which are summarized in Table I along with our patient’s case.

Clinics characteristics

LCNEC of the bladder usually occurs in men (4:1), 77.7% were men and 22.2% were women with a mean age of 59.3 years (20-82).

The clinical picture at the time of diagnosis, where documented, was hematuria in 80% of cases, dysuria/micturition syndrome in 30%, and mucosuria in 10%. Only in our patient’s case were there no symptoms whatsoever at the time of diagnosis.

In 3 cases, there was a history of chemotherapy or radiation therapy prior to the onset of LCNEC of the
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bladder: one case of RT for prostate cancer, one case of chemotherapy for urothelial tumor, and another case of RT for cervical cancer.

**Histological and immunohistochemical characteristics**

Tumor appearance was variable: of the 13 cases in which it is described, in all of them it was a single, non-papillary tumor; in 7 cases (54%) it had an ulcerated appearance; and in 2 cases it was defined as polypoid. In the 9 cases where tumor size was indicated, the mean size was 3.9 cm (2.5-6.0). Its location in the bladder was quite variable: 40% left lateral wall, 30% anterior wall, 20% posterior wall, and 10% right lateral wall.

The histological diagnosis was 50% pure LCNEC and 50% mixed (9 cases), of which 11% were mixed with carcinosarcoma, 22% with adenocarcinoma, and 66.6% (6 cases) with transitional cell carcinoma; of these last 6 cases, one had a coexisting squamous cell carcinoma and another lymphoepithelioma-like carcinoma. Microscopic or macroscopic necrosis was present in all cases. Whether the TUR was diagnostic for LCNEC was reported in 14 cases: in 28.6% of them, it was not.

The features that distinguish LCNEC from small cell carcinoma are those shown in Table II, which is based on the work of Aranda (6). The specific diagnostic criteria for LCNEC include (6, 7):

- **Microscopic features:**
  - Neuroendocrine morphology (organoid nests, palisades, rosettes, trabeculae) (Figure 1).
  - Numerous mitoses (>11 mitoses per 2 mm²), average 70 per 2 mm², occasionally with atypical forms.
  - Necrosis (often over large areas) accompanied by karyorrhexis and apoptotic cells.
  - Cytological aspects of LCNEC: large, polygonal cells with abundant cytoplasm; low nucleus-to-cytoplasm ratio; thick granular or vesicular nuclear chromatin; frequent, prominent nucleoli (Figure 2).
  - Immunohistochemistry positive for neuroendocrine markers such as chromogranin, synaptophysin, Leu-7, or bombesin (other than neuron-specific enolase) and/or neuroendocrine granules on the ultrastructural analysis. Up to 40% of cases of SCC of the bladder express TTF1, according to W.J. Lee et. al. (Figures 3 and 4).
  - At the molecular level, the majority show positivity for p53 and bcl-2 and negativity for Rb protein. Half of the cases show c-KIT overexpression.

The immunohistochemical analysis is reported in 13 of the cases, though they did not all analyze the same markers. There was positivity for enolase in 91.7%, synaptophysin in 91.7%, cytokeratin (CK)
in 80%, chromogranin in 75%, TTF1 in 75%, and epithelial membrane antigen in 66.7%. Negativity was found for S100, PSA, and LCA in 100% and for vimentin in 75%.

In 1999, the WHO published a new lung tumor classification8 that established 4 groups within the neoplasias of neuroendocrine morphology: typical carcinoid (low grade), atypical carcinoid (medium grade), LCNEC (high grade), and small cell lung carcinoma (high grade).

There are 4 types of LCNEC that are based on the neuroendocrine morphology, as determined by the microscopic features, and on the neuroendocrine differentiation, as determined by immunohistochemistry and/or electron microscopy (7, 8):

- LCNEC with neuroendocrine morphology and neuroendocrine differentiation as detected by immunohistochemistry and/or electron microscopy.
- Large cell carcinoma (LCC) without neuroendocrine morphology but with neuroendocrine differentiation detectable by immunohistochemistry and/or electron microscopy.
- LCC with neuroendocrine morphology but without neuroendocrine differentiation by immunohistochemistry or electron microscopy.
- Classic LCC without neuroendocrine morphology and without neuroendocrine differentiation.

Differential diagnosis

The differential diagnosis of LCNEC includes metastasis of a pulmonary or gastrointestinal LCNEC1 and local invasion of the bladder by a poorly differentiated prostatic carcinoma (1).

As the primary site, the differential diagnosis must include large cell malignant lymphoma (1, 3) and, in small specimens, it must be distinguished from chronic cystitis - in which inflammatory cells with scant cytoplasm may resemble tumor cells (2)- and from poorly differentiated transitional cell carcinoma - which is often concomitant with urothelial carcinoma in situ (1, 3). Immunohistochemical analysis together with electron microscopy helps to make the differential diagnosis.

Analysis of tumor extent

For analysis of tumor extent, in addition to CT scan and/or MRI, some authors suggest using 111In-DTPA-octreotide scintigraphy (Octreoscan) and PET for detection of the neuroendocrine tumor location because these tumors are associated with neuropeptide and ectopic hormone secretion.

The Octreoscan is useful for identifying primary tumors and distant metastases in patients with neuroendocrine tumors. The main advantage of octreotide scintigraphy in comparison with CT scan and MRI is that it can explore all regions of the body (4).
Prognosis

The behavior of LCNEC of the bladder is believed to be similar to that of SCC (1, 2). It is a very aggressive tumor with a strong tendency to present at an advanced stage and a high incidence of recurrence and progression despite surgical intervention and even chemotherapy.

Of the 17 articles in which initial staging was reported, 35.3% were T4, 35.3% were T3, and 29.4% were T2. In 41.2% of the cases, adenopathies or distant metastasis was present at the time of diagnosis.

Treatment and recurrence of LCNEC of the bladder

Treatment was varied, being reported in 13 cases in the series of articles reviewed:

- In one case, no treatment was applied following TUR; the bladder tumor recurred 2 months later and was treated with partial cystectomy and chemotherapy, but the patient died.

- In another case, the patient underwent partial cystectomy following TUR; there was a local recurrence that was treated with TUR and RT, and the patient had no evidence of disease after 24 months.

- In another case, the patient underwent partial cystectomy with chemotherapy; metastases appeared 12 months later, which were treated with chemotherapy and RT, but the patient ultimately expired.

- Five patients underwent radical cystectomy and lymphadenectomy with no other treatment; three of them died due to tumor dissemination, and in the other two cases, there was no evidence of disease at the end of the follow-up period.

- Radical cystectomy with radiation therapy and/or chemotherapy was performed in five cases; of these, three patients were disease-free at the end of the follow-up period, one showed persistence of the disease after 16 months, and one died after 12 months due to disease progression.

In 11 cases, local and distant recurrence was reported at 45.5% and 36.4%, respectively. Local and distant recurrence was seen in 40% of cases treated with radical cystectomy alone. Of the patients who underwent radical cystectomy with radiation therapy and/or chemotherapy, local and distant recurrence was 33% and 0%, respectively.

Treatment of SCC of the bladder vs. LCNEC

With regard to treatment of SCC, in an M. D. Anderson Cancer Center study (9) of 46 patients with SCC of the bladder who were treated with cystectomy and adjuvant or neoadjuvant chemotherapy, the cancer-specific 5-year survival rate for those treated with neoadjuvant chemotherapy was 78% compared to 36% for those who received adjuvant chemotherapy. This suggests that neoadjuvant chemotherapy with cystectomy may improve survival rates in these high-risk patients. As Table I shows, however, in almost 30% of the patients, the LCNEC was not diagnosed in the TUR, which means that chemotherapy prior to cystectomy was limited.

The chemotherapy regimens that appear to offer superior management in SCC of the bladder are etoposide with cisplatin or ifosfamide with doxorubicin (9).

In the published cases of LCNEC of the bladder, Akamatsu et al. and Bertaccini (4) administered etoposide and carboplatin to their patients following the same regimen as for LCNEC of the lung. These were the only T3-stage cases in which the patient’s disease-free survival was achieved—even with positive margins in Akamatsu’s case and positive adenopathies in Bertaccini’s case.

In the Quek (2) study, although no difference was found between adjuvant and neoadjuvant chemotherapy, there were statistically significant differences in survival rates when comparing patients treated with cystectomy alone and those treated with cystectomy and chemotherapy.

Sved et al., in their study of 123 patients with SCC of the bladder, highlighted the role of chemotherapy in addition to cystectomy or radiation therapy for local disease management.

In a multi-center study conducted by Cheng et al. of 64 patients with SCC of the bladder, the cancer-specific 5-year survival rate was 16%. This study reported 68% mixed histological patterns and found no statistically significant difference in survival rates between the pure and mixed histological forms. There was also no difference found between patients treated with cystectomy alone and those who received a combination of treatments.

According to these studies, the response of SCC of the bladder to chemotherapy and/or radiation therapy is variable and appears to be similar to that seen in LCNEC (1, 2).
<table>
<thead>
<tr>
<th>Review</th>
<th>Sex/Age</th>
<th>Symptoms</th>
<th>Smoker/Med Hx</th>
<th>Appearance/Size (cm)</th>
<th>Site</th>
<th>Histo/Necrosis</th>
<th>Dxg TUR</th>
<th>Stage</th>
<th>Immuno</th>
<th>Treatment</th>
<th>Recurrence</th>
<th>Site of Metastasis</th>
<th>F/U Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abenoza et al.</td>
<td>H55</td>
<td>Hematuria Mucosuria</td>
<td>NA/NA</td>
<td>Single, ulcerated, exophytic / 5</td>
<td>CAnt</td>
<td>Mixed with ADC / Yes</td>
<td>NA</td>
<td>T3N+M-</td>
<td>NSE+, CK-, Cg+, CEAs-, EMA- So±, Se±</td>
<td>RTU+ CPR +LND+ ombligec- tonia</td>
<td>6m: Gl: UN+C Mass +10xQt(ACis)</td>
<td>24m: Gl: QT (Cy F) 30m: mtx</td>
<td>Lung, brain, bone, liver, heart</td>
</tr>
<tr>
<td>Hailemariam (3)</td>
<td>H73</td>
<td>Hematuria Pain</td>
<td>NA/Prostate cancer to RT + Renal Trans. (ID)</td>
<td>Single, ulcerated, solid, gray, &amp; friable / 4</td>
<td>CI</td>
<td>Pure / Yes</td>
<td>Yes</td>
<td>T3N-M-Margin+</td>
<td>NSE-, CK+, Cg+, Syp+, LCA, PSA, VIP, PP, In, Glu, So, SP, Sa-</td>
<td>RTU+ CPR+LND 2m: mtx</td>
<td>Lung, bone, liver, pancreas, kidney, thyroid, peritoneum</td>
<td>2/DOD</td>
<td></td>
</tr>
<tr>
<td>Evans (1)</td>
<td>H82</td>
<td>Hematuria</td>
<td>Yes/DM II</td>
<td>Single, polypoid, friable / 4.7x4.3</td>
<td>Cl*</td>
<td>Mixed with infiltrating ADC / Yes</td>
<td>Yes</td>
<td>T2N-M-Margin+</td>
<td>CK+, Syp+, Cg, LCA, PSA, VIM, PAP.</td>
<td>RTUx2+ CP+LND izqda 8m: Intravesical: RTU+ RT</td>
<td>No</td>
<td>24/NED</td>
<td></td>
</tr>
<tr>
<td>Dundr et al.</td>
<td>M54</td>
<td>Hematuria</td>
<td>Yes/Ca Cervix + HT+SOOB+RT</td>
<td>exophytic / 4</td>
<td>Base + Ureter</td>
<td>Mixed with CCT + CCL / NA</td>
<td>No</td>
<td>T3N-M-Margin+</td>
<td>NSE+, CK+, Cg+, Syp+, VIM, St100</td>
<td>CR+ Ureterectomy + Qtx6 (CPGH)</td>
<td>11m: Gl: QT 16m: Gl: QT</td>
<td>No</td>
<td>16/AWD</td>
</tr>
<tr>
<td>Li Y et al.</td>
<td>H61</td>
<td>Hematuria Micturition syndrome</td>
<td>Yes/COPD</td>
<td>NA/NA</td>
<td>CD</td>
<td>Mixed with CS / Yes</td>
<td>No</td>
<td>T2N-M-</td>
<td>NSE+, CK+, Cg+, Syp+, VIM, S100, SMA-</td>
<td>RTU+ CPR+LND</td>
<td>No</td>
<td>No</td>
<td>8/NED</td>
</tr>
<tr>
<td>Quek (2) 5 pacientes</td>
<td>4H1M /72a (61-79)</td>
<td>NA/NA</td>
<td>4 ulcerated &amp; 1 polypoid / NA</td>
<td>NA</td>
<td>2 pure &amp; 3 mixed with CCT (Cis) / 5 Yes</td>
<td>64%</td>
<td>1pT0-pT2 y 4pT1N+M+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>11.8 yr (18d-15yr)/ 13 months (1 lived &gt;11yr)</td>
</tr>
<tr>
<td>Lee KH et al.</td>
<td>H32</td>
<td>Hematuria</td>
<td>NA/None</td>
<td>Single, exophytic, ulcerated / 3</td>
<td>CAnt</td>
<td>Pure / Yes</td>
<td>Yes</td>
<td>pT3N-M-</td>
<td>NSE+, CK-, Cg+, Syp+, EMA+ CD56+, St100 LCA, PSA, VIM</td>
<td>RTU</td>
<td>2m: Intravesical: CP + 2xMVA-Cis + 1xGcis 12m: mtx</td>
<td>Lung, liver</td>
<td>12/DOD</td>
</tr>
<tr>
<td>Trimeche et al.</td>
<td>H78</td>
<td>Micturition syndrome</td>
<td>NA/None</td>
<td>Solid/6x4</td>
<td>CI</td>
<td>Mixed with CCT/Yes</td>
<td>Yes</td>
<td>T4NxM-</td>
<td>NSE+, CK+, Cg+, Syp+, EMA+, PSA, TFF1-</td>
<td>RTU+ CPR</td>
<td>7m: Locoregional: RT</td>
<td>7/DOD</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE I.**
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<table>
<thead>
<tr>
<th>Review</th>
<th>Sex/Age</th>
<th>Symptoms</th>
<th>Smoker/ Med Hx</th>
<th>Appearance/ Size (cm)</th>
<th>Site</th>
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<th>Dxg TUR</th>
<th>Stage</th>
<th>Immuno</th>
<th>Treatment</th>
<th>Recurrence</th>
<th>Site of Metastasis</th>
<th>F/U Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alijo et al. 2 pacientes</td>
<td>H40</td>
<td>NA</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>NA</td>
<td>Pure/Yes</td>
<td>NA</td>
<td>TNM II</td>
<td>NSE+, TTF1+, Leu7+, PSA- **Cg+ 1 de 2, **Syp+ 1 de 2</td>
<td>RTU+CPR + QT</td>
<td>NA</td>
<td>NA</td>
<td>13/NED</td>
</tr>
<tr>
<td></td>
<td>M43</td>
<td>NA</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>NA</td>
<td>Pure/Yes</td>
<td>NA</td>
<td>TNM IV</td>
<td>NSE+, TTF1+, Leu7+, PSA- RTU + RT</td>
<td>NA</td>
<td>NA</td>
<td>12/DOD</td>
<td></td>
</tr>
<tr>
<td>Akamatsu et al.</td>
<td>H63</td>
<td>Hematuria</td>
<td>NA/NA</td>
<td>Nodular /3,5</td>
<td>CI</td>
<td>Mixed with CCE y CU /NA</td>
<td>Yes</td>
<td>T3NxM- Margin+</td>
<td>NSE-, Cg-, Syp+ RTU+ CPR+ 2xQT (E Ca)</td>
<td>None</td>
<td>No</td>
<td>16/NED</td>
<td></td>
</tr>
<tr>
<td>Bertaccini (4)</td>
<td>H37</td>
<td>Hematuria</td>
<td>Yes/NA</td>
<td>NA/2x2,5</td>
<td>CPost</td>
<td>Pure/NA</td>
<td>Yes</td>
<td>T3N+M-</td>
<td>NSE+, CK+, Cg+ Syp+ RTU+ CPR+ LND + 6xQT (E Ca)</td>
<td>None</td>
<td>No</td>
<td>20/NED</td>
<td></td>
</tr>
<tr>
<td>Lee WJ et al.</td>
<td>H20</td>
<td>NA</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>NA</td>
<td>Pure/Yes</td>
<td>NA</td>
<td>NA</td>
<td>NSE-, Ck+, Sy+, TTF1+, CD56+ RTU+ CP+ QT</td>
<td>12m: mtx: QT+RT 14m: mtx</td>
<td>Cutaneous. Lung, adenopathies</td>
<td>14/DOD</td>
<td></td>
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<tr>
<td>Nuestro Caso</td>
<td>M69</td>
<td>None</td>
<td>No / Uterine adhesions + DL + tonsillectomy</td>
<td>Protrusion of mucosa / 3</td>
<td>CAnt</td>
<td>Pure/Yes</td>
<td>Yes</td>
<td>T2NM-</td>
<td>NSE+, CK-, Cg+, Sy+, ST00-, HMB45- RTU+ CR+LND</td>
<td>None</td>
<td>No</td>
<td>12/NED</td>
<td></td>
</tr>
</tbody>
</table>

A (Adriamycin); ADC (Adenocarcinoma); AWD (Alive With Disease); C (Surgery); Ca (Carboplatin); CAnt (Anterior Wall); CCE (Squamous Cell Carcinoma); CCT (Transitional Cell Carcinoma); CD (Right Lateral Wall); Cg (Chromogranin); CI (Left lateral Wall); Cis (Cisplatin); CK (cytokeratin); CL (lymphoepithelioma-like Carcinoma); CP (Partial Cystectomy); CPost (Posterior Wall); CPR (Radical Cystoprostatectomy); CR (Radical Cystectomy); CS (Carcinosarcoma); CU (Urothelial Carcinoma); Cy (Cyt (Fluorouracil); F/U (Follicl Salpingo-oophorectomy); ID (Immunosuppressed); In (Insulin); LND (Lymphadenectomy); LCA (Leukocyte Common Antigen); M (Methotrexate); mtx (Metastasis); NA (Not Available); NED (No Evidence of Disease); NSE (Neuron-Specific Enolase); NU (Nephroureterectomy); P (paclitaxel); PAP (Prostatic Acid Phosphatase); PP (Pancreatic Polypeptide); QT (Chemotherapy); RT (Radiation Therapy); Se (Serotonin); So (Somatostatin); SP (Substance P); Sy (Synaptophysin); S-100 (S-100 protein); Tio (Treatment); V (Vincristin); Vim (Vimentin); VIP (Vasoactive Intestinal Polypeptide).

**Intradiverticular tumor infiltrating the muscularis mucosae

** One of
Dresler et al., however, in their study of 40 patients with LCNEC of the lung, observed that, in contrast to SCC of the lung, LCNEC of the lung tends to present with earlier staging and has postsurgical disease-free intervals and survival rates that do not improve with adjuvant chemotherapy and/or radiation therapy.

**Survival**

In our review, the disease-free survival rate over an average follow-up period of 14 months and with a maximum follow-up of 20 month, was 46.2% for the 13 cases reporting it. (The Quek study, in which follow-up is not reported for 4 of the 5 LCNEC cases, was excluded.) For the mixed histological variants it was 50%, and for the pure variants it was 42.9%. For tumor stages ≤T2, it was 100%; for those ≥T3, it was 25%.

Tumors diagnosed as organ-confined had better long-term survival rates. The 5 patients with ≤T2 staging (including one in the Quek study) survived beyond the follow-up period whereas, of the 8 patients with ≥T3 staging (excluding 4 from the Quek study whose survival was not reported), 2 patients survived disease-free—the ones who were treated with etoposide plus carboplatin.

In the Quek study (2) of 20 patients with SCC of the bladder and 5 patients with LCNEC of the bladder, there was a 5-year global survival rate of 10% and a 5-year recurrence-free survival rate of 13%. No statistically significant difference in survival rate was found between SCC and LCNEC.

Mixed histological patterns (36% in their study) were noted to behave less aggressively than the pure patterns but, as in our review, with no statistically significant difference. There were statistically significant differences in global and recurrence-free survival rates between patients who underwent multimodal therapy (no difference between adjuvant and neoadjuvant chemotherapy) and those treated with cystectomy alone.

In the Dresler et al. study, the 5-year survival rate was 13%. In the Travis study 10 of 37 patients with LCNEC of the lung and 50 with SCC, the 5-year and 10-year survival rates for LCNEC was 27% and 9%, respectively, and for patients with SCC it was 9% and 5%; there were no statistically significant differences.

Alijo et al., in their study of 44 patients with SCC and 2 patients with LCNEC, looked at variables such as age, sex, smoking, tumor histology, use of chemotherapy and radiation therapy, staging,

**TABLE II. MICROSCOPIC CRITERIA FOR DIFFERENTIATING SMALL CELL CARCINOMA FROM LCNEC.**

<table>
<thead>
<tr>
<th>MICROSCOPIC FEATURES</th>
<th>SCC</th>
<th>LCNEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Size</td>
<td>Small</td>
<td>Larger</td>
</tr>
<tr>
<td>Nucleus-to-Cytoplasm Ratio</td>
<td>High</td>
<td>Lower</td>
</tr>
<tr>
<td>Nuclear Chromatin</td>
<td>Finely granular, uniform</td>
<td>Thick granular, vesicular</td>
</tr>
<tr>
<td>Nucleolus</td>
<td>Absent and not very prominent</td>
<td>Typical and prominent</td>
</tr>
<tr>
<td>Nuclear Molding</td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td>Fusiform Shape</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Polygonal shape/abundant cytoplasm</td>
<td>No</td>
<td>Typical</td>
</tr>
<tr>
<td>Nuclear Rupture</td>
<td>Typical</td>
<td>Rare</td>
</tr>
<tr>
<td>Basophilic staining of vessels and stroma</td>
<td>Occasional</td>
<td>Rare</td>
</tr>
</tbody>
</table>
REFERENCES AND RECOMMENDED READINGS
(*of special interest, **of outstanding interest)


