Clinical and therapeutic aspects of extrapulmonary small cell carcinoma

Annemiek M.E. Walenkamp a,*, Gabe S. Sonke b,1, Dirk T. Sleijfer a,2

Department of Medical Oncology, University Medical Centre Groningen and University of Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands

1 Department of Medical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Postbus 90203, 1006 BE Amsterdam, The Netherlands

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SUMMARY

Extrapulmonary small cell carcinoma (EPSCC) is usually treated similarly to small cell lung cancer. Differences in aetiology, clinical course, frequency of brain metastases, and survival, however, warrant a differential therapeutic approach. In this review, we focus on the treatment of the most predominant sites of origin of EPSCC; the gastrointestinal tract, the genitourinary tract, the head and neck region, and small cell carcinoma of unknown primary. Furthermore we review the available data concerning the controversial issue of prophylactic cranial irradiation (PCI) after optimal treatment of EPSCC. We found in the literature a significant lower incidence of brain metastases in EPSCC as compared to pulmonary small cell carcinoma when PCI is omitted and therefore we do not recommend PCI. An exception is EPSCC originating from the head and neck region which is associated with a higher incidence of brain metastasis, justifying addition of PCI.

Introduction

Small cell carcinoma (SCC) is most commonly of pulmonary origin. Due to its unique histology and biology, small cell lung cancer (SCLC) is a distinct clinicopathologic entity well recognised for its aggressive clinical behaviour, usually associated with spread at the time of diagnosis. SCC may also originate in non-pulmonary organs as initially reported by Duguid and Kennedy. Since the original publication, cases of small cell carcinoma have been documented in multiple sites of origin, most commonly the gastrointestinal tract, particularly the oesophagus and large bowel, the genitourinary tract, particularly the bladder and uterine cervix, and the head and neck region, particularly the larynx (Table 1). In a few cases, the primary site remains undetected; tumours known as small cell carcinoma of unknown origin.

Epidemiology and pathology

Overall, approximately 1000 new cases of extrapulmonary SCC (EPSCC) are diagnosed yearly in the United States, which represents 2.5–5% of all SCC. The age distribution of EPSCC is wide with a peak in incidence in the seventh decade. While the data are inconsistent, there seems to be a mild male predominance. Specific risk factors for the development of EPSCC have not been identified, although these appear similar to those predisposing to the development of other types of cancer in the same organ. Cigarette smoking is strongly associated with SCLC, whereas EPSCC has a weaker association with tobacco use. Irrespective of their site of origin, small cell cancers share distinctive histochromic and electronmicroscopic features. EPSCC shows ultrastructural evidence of both primitive epithelial and neuroendocrine differentiation. Histologically, these tumours are composed of small cells with scant eosinophilic cytoplasm, oval to spindle-shaped nuclei with stippled nuclear chromatin, and inconspicuous nucleoli. Mitotic figures and areas of prominent necrosis are frequently seen. Tumours may contain mixed elements of small cell carcinoma, adenocarcinoma, and squamous cell carcinoma. It is postulated that these tumours originate from multipotent stem cells that are native to all tissues. These stem cells can differentiate into various cell types which may explain the frequent coexistence of mixed tumours that is noted in pathological specimens. In cases in which EPSCC is mixed with another histologic tumour type, the natural history of the disease is determined by the presence of the small cell component.

Clinical presentation

Small cell histology cannot be suspected from the presenting symptoms, as these are similar to those of other histological types of tumours arising in the same site. Constitutive symptoms such as general malaise, weight loss, fatigue, sweating, nausea and vomiting may be the initial manifestation. Similar to SCLC, paraneoplastic syndromes such as Cushing’s Syndrome and Syndrome of Inappropriate ADH secretion may occur.
Table 1  
Frequency of EPSCC per site of origin.  

<table>
<thead>
<tr>
<th>Site of origin</th>
<th>Percentage of SCC/total per site of origin</th>
<th>Estimated number of patients in US per year'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>15–20%</td>
<td>32,250–43,000</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>0.8–2.4%</td>
<td>130–395</td>
</tr>
<tr>
<td>Larynx</td>
<td>0.5–1%</td>
<td>60–120</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.3–1.0%</td>
<td>200–680</td>
</tr>
<tr>
<td>Cervix</td>
<td>≤1%</td>
<td>≤110</td>
</tr>
<tr>
<td>Prostate</td>
<td>≥2%</td>
<td>≥250</td>
</tr>
<tr>
<td>Unknown</td>
<td>7–30% of all EPSCC</td>
<td>70–300</td>
</tr>
</tbody>
</table>

SCC denotes small cell carcinoma; EPSCC denotes extrapulmonary small cell carcinoma.  

Staging  

The initial evaluation of a patient with SCC should include computed tomography (CT) of the chest to detect possible primary SCLC. The primary tumour and regional lymph nodes should be evaluated to assess the extent of locoregional disease and it should be determined whether or not distant metastases are present. Imaging procedures that can be useful include CT and bone scans. Even though the cumulative evidence suggests that positron emission tomography (PET) added to conventional staging improves the sensitivity in detecting extra cranial disease in SCLC the frequency of changes in stage attributable to PET is still unknown and is plagued by wide confidence intervals in the estimates of diagnostic and staging accuracy.14,15 Data on the role of other imaging studies, such as or radiolabelled somatostatin analogue scans are currently absent or insufficient to advocate their use. Magnetic resonance imaging (MRI) of the brain is recommended if neurological symptoms are present. Bone marrow biopsy is indicated only if there are abnormal blood cell counts or findings of the peripheral smear, without other evidence of disseminated disease.  

Prognosis  

In general, patients with EPSCC do poorly with less then 15% five-year survival, although some patients enjoy a prolonged survival and even cure.7,11,12 As expected, patients with locoregional tumour extension have significantly better survival compared to patients with distant metastases and worse compared with patients with disease confined to the organ of origin. In addition, differences in clinical course and prognosis of SCC from various origins have been described.  

Treatment  

Given the rarity of the disease and the difference in organs of origin, no large randomised trial has been performed to guide the treatment of patients with EPSCC. Information on the role of various therapies in EPSCC is therefore derived from case reports and small retrospective series. This lack of data and its pathological similarity to the much more common primary SCLC led most investigators to adopt similar principles to the treatment of EPSCC (Table 2).  

Treatment of small cell lung cancer  

Chemotherapy improves the survival of patients with limited-stage and extensive-stage SCLC, but is curative in only a minority of patients.16,17 Mature results of prospective randomised trials in limited disease suggest that combined modality therapy consisting of radiation plus chemotherapy shows an improvement in three-year survival rates of about 5% compared with chemotherapy alone.18,19 Various chemotherapeutic combination regimens have been explored in the first-line treatment of SCLC including cisplatinum and etoposide (CE); cyclophosphamide, adriamycin and vincristine (CAV); adriamycin, cyclophosphamide and etoposide (ACE) and ifosfamide, carboplatin and etoposide (ICE).10 Two randomised trials that substituted carboplatin for cisplatin in combination with etoposide, or with tenoposide and vincristine, did not find a significant difference in response rate or median survival.20,21 In a randomised phase 3 study in extensive SCLC the Japanese clinical oncology group found irinotecan plus cisplatin more effective than etoposide plus cisplatin,22 but this benefit could not be reproduced in a North American study.23 Recently a third randomised phase 3 study concluded that irinotecan plus carboplatin prolongs survival in SCLC.24 This study, however, used different eligibility criteria, a different dosing scheme of carboplatin, an oral formulation of etoposide, and age mandated dose reductions.25 Definite conclusions about the efficacy of this regimen over etoposide plus cisplatin can therefore not be drawn. Interestingly, several studies report high rates of complete remission of dose intensified regimens with stem-cell transplant support.26 Unfortunately benefits to long-term survival cannot be reliably assessed due to small sample sizes and absence of control groups, and this strategy should not be used outside a clinical trial. The combination of etoposide and cisplatin chemotherapy with concurrent chest radiation therapy has now been used in multiple single institutional studies as well as in cooperative group studies with an overall response rate of 65–90%, complete response rate of 45–75%, a median survival of 18–24 months and two-year survival of 40–50%.27,28  

Table 2  
Treatment data of small series of small cell carcinomas of different origins.  

<table>
<thead>
<tr>
<th>Site of origin</th>
<th>Treatment arm</th>
<th>Study treatment arm</th>
<th>Outcome</th>
<th>N</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus</td>
<td>Surgery or RT</td>
<td>RT/surgery + chemotherapy</td>
<td>MS 5 versus 20 mth</td>
<td>199</td>
<td>Casas75</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>–</td>
<td>MS 20 mth</td>
<td>25</td>
<td>Kuo87</td>
</tr>
<tr>
<td>Larynx</td>
<td>RT</td>
<td>–</td>
<td>MS 11 versus 19 mth</td>
<td>56</td>
<td>Baugh51</td>
</tr>
<tr>
<td></td>
<td>Surgery and/or RT</td>
<td>–</td>
<td>5-yr OS 60%</td>
<td>12</td>
<td>Choong77</td>
</tr>
<tr>
<td>Bladder</td>
<td>RT + chemotherapy</td>
<td>–</td>
<td>HR for OS 0.15</td>
<td>106</td>
<td>Mackey74</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>Surgery + chemotherapy</td>
<td>1-yr OS 45% versus 66%</td>
<td>64</td>
<td>Cheng75</td>
</tr>
<tr>
<td>Cervix</td>
<td>Surgery</td>
<td>Surgery + chemotherapy</td>
<td>3-yr OS 60%</td>
<td>31</td>
<td>Hoskins96</td>
</tr>
<tr>
<td></td>
<td>Surgery + chemotherapy</td>
<td>–</td>
<td>14 mth</td>
<td>14</td>
<td>Sheets83</td>
</tr>
<tr>
<td>Prostate</td>
<td>Surgery</td>
<td>MS 14 mth</td>
<td>47 mth</td>
<td>47</td>
<td>Chang94</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>Surgery</td>
<td>HR for OS 0.46</td>
<td>60</td>
<td>Mackey74</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>Surgery + chemotherapy</td>
<td>MS 11 mth</td>
<td>26</td>
<td>Papandreou96</td>
</tr>
<tr>
<td></td>
<td>Watchful waiting</td>
<td>Surgery</td>
<td>11 mth</td>
<td>3</td>
<td>Kageyama97</td>
</tr>
</tbody>
</table>

(RT) denotes radiotherapy; (N) denotes number of patients; (MS) denotes median overall survival; (OS) denotes overall survival; (HR) denotes hazard ratio.
Since overt disseminated disease is present in patients with extensive disease, combination chemotherapy is the cornerstone of treatment of this stage of SCLC. Surgery and radiation therapy may be applied to palliate local symptoms. The relative effectiveness of most two- to four-drug combination programs appears similar, and many potential combinations are available. Doses and schedules used in current programs yield overall response rates of 70–85% and complete response rates of 20–30%. The optimal duration of chemotherapy is not clearly defined, but no obvious improvement in survival occurs when the duration of drug administration exceeds six months. Combination chemotherapy plus radiation therapy does not improve survival compared with chemotherap y alone and most patients with extensive disease are therefore treated with five to six cycles of cisplatinum plus etoposide.

Second line chemotherapy in refractory or relapsed SCLC shows moderate response rates of 10–20%, usually for short duration. Only a single study compared chemotherapy to best-supportive care alone with a small increase in median survival associated of oral topotecan (26 versus 14 weeks). Quality of life also appeared to improve with chemotherapy. Other single agent drugs, all with comparable reported activity in second line SCLC include paclitaxel, docetaxel, oral etoposide (after previous intravenous etoposide), vinorelbine, and gemcitabine. Reinduction with the same (platinum-based) regimen as used in first line has been attempted in older studies with median response duration of three months (range 2–4 months) in relapsed SLCL. Responses were mostly seen in case of excellent initial response and prolonged time to treatment failure. Combination regimens showed increased activity over single agent treatment, but at the expense of increased toxicity. The latter generally restrains the applicability of combination treatment. Whenever possible, however, patients should be enrolled in a clinical study.

Clinical and therapeutic aspects of extrapulmonary small cell cancer

Gastrointestinal tract (GIT)

SCC of the gastrointestinal tract is rare; approximately 650 cases have been reported in the literature. About 50% of all gastro-intestinal tract-SCC are located in the oesophagus, 25% in the large bowel, and another 25% in less common locations such as the liver, bile ducts, and small intestine. Patients with SCC of the gastrointestinal tract do poorly. The median survival is described in the range of 6–20 months or of only several weeks, for treated or untreated patients, respectively. In a series of 64 gastrointestinal tract-SCC patients, Brenner and colleagues found no difference in pathological features, response to chemotherapy, incidence of progression, and survival between the different anatomical localisations. Around half the patients present with limited disease (LD). Local treatment approaches include surgery, radiotherapy and chemoradiation. Even when disease is localised, however, virtually all patients recur with distant metastases. In a multivariate analysis performed by Casas et al. on 1997 previously reported oesophageal SCC patients, the median survival of patients who were treated with local therapy only was five months. In patients who received local treatment plus chemotherapy, the median survival was 20 months. They conclude that the addition of chemotherapy to local treatment should be considered as standard treatment for limited disease of SCC of the oesophagus. There is still some debate about whether surgery or radiotherapy optimises local treatment. Recent data from Memorial Sloan Kettering Cancer Centre supports the use of induction chemotherapy followed by consolidative chemoradiation for patients with limited disease oesophageal SCC. Median survival found in this single institute retrospective study of 25 oesophageal SCC patients was 20 months with two limited disease patients alive and free of disease after five years of follow-up. These authors conclude that surgery may not be necessary as part of initial therapy if a clinical CR is achieved after chemoradiation and that surgery may be reserved for salvage after documented local failure. Patients presenting with distant metastasis are treated with four to six courses of platinum based combination chemotherapy resulting in a median survival of approximately eight months.

Patients with SCC in other sites in the gastrointestinal tract (stomach, colon, gallbladder) typically present with a tumour mass that is indistinguishable from other tumours arising in the same site. Microscopic findings are similar to those of SCLC. Gastric SCC appears more common in Japan and typically arises in the upper one-third of the stomach. SCC develops throughout the colon. In a review of 75 cases, the most common site of origin was the rectum followed by the caecum, sigmoid colon, transverse colon, and ascending colon (38%, 27%, 17%, 12%, and 6%, respectively). Synchronous or multiple EPSSC lesions have also been reported.

As with oesophageal SCC, most patients with gastric SCC have (micro-)metastases at the time of diagnosis. The liver is the most frequent site of metastatic disease, but metastases have been described at virtually all sites. Despite rare reports of long-term survivors, surgery alone is inadequate therapy, even for apparently localised disease. Adjuvant RT for incompletely resected disease and systemic chemotherapy are widely recommended, although the effectiveness of a combined modality approach has not been firmly established. Despite aggressive multimodality therapy including surgery and systemic chemotherapy, the median survival in colorectal SCC was six months, with only 15% of patients alive at one-year. Data from Memorial Sloan Kettering Cancer Centre show a median survival of ten months for patients with colorectal SCC. One-year, two-year, and three-year survival was 46%, 26%, and 13%, respectively. There was no significant difference in survival based on pathologic subtypes. In a series of 53 cases of gallbladder SCC, those with disseminated disease had a median survival of eight months after treatment with combination chemotherapy. One and two year survival rates were 28% and 0%, respectively.

We conclude that patients presenting with limited disease SCC of the gastrointestinal tract should be treated with local treatment consisting of radiotherapy, surgery or both, combined with platinum based chemotherapy. Patients presenting with distant metastasis should be treated with platinum based combination chemotherapy.

Head and neck

EPSSC arises at various sites in the head and neck region, but the larynx is the most commonly affected site. The epidemiology, risk factors like tobacco and alcohol use, and clinical features for laryngeal SCC are generally similar to that for other laryngeal tumours. Laryngeal SCC is often associated with (micro-)metastases at the time of diagnosis. Perlito et al. reported two- and five-year survival rates of 16% and 5%, respectively. Treatment with total laryngectomy may control the primary tumour, but does not offer any chance for cure, with very few patients surviving beyond 12 months. In the same report, radiation therapy was reported to be equally successful in achieving local control compared to surgery. Most investigators thus feel that debilitating total laryngectomy should be avoided except for the rare patient with extremely early and limited disease.

The greatest impact on survival is achieved by systemic chemotherapy. Aguilar reported a difference in two-year survival of 42% between patients treated with local therapy alone consisting mainly of radiotherapy or in combination with chemotherapy.
(10% versus 52%). In the data by Baugh et al., patients who received chemotherapy survived longer than those who did not, with comparative median survivals of 19 and 11 months. Three of 14 patients with laryngeal SCC reported by Ferlito et al. were free of disease five years after treatment with a multidrug chemotherapy regimen and radiotherapy. A wide range of chemotherapeutic agents is used, but platinum-based chemotherapy regimens have become the mainstream of treatment, usually in combination with etoposide.

We advise treatment with systemic chemotherapy in all patients with SCC of the larynx. To achieve maximum local control, combined radiotherapy and chemotherapy can be considered for most patients, while debilitating surgical resection should be limited to those few patients who are thought to have truly early local disease and to those who otherwise fail to achieve locoregional control.

SCC can also develop in the parotid, submandibular, and minor salivary glands. The parotid gland is the most common site for salivary gland SCC. Between one to three percent of all salivary gland tumours are SCC, with a male preponderance. SCC of the oral cavity or pharynx usually has its origin in the minor salivary or secretory glands, although this is not certain in all cases. Salivary gland SCC has a strong potential for aggressive early invasion and metastasis. Roughly half of the patients have nodal or distant metastasis at the time of diagnosis. Nevertheless, the prognosis for patients with SCC of the salivary glands appears somewhat better than SCC of the lung or non-salivary gland sites in the head and neck region, with an estimated two- and five-year survival of 70% and 46%, respectively. Other investigators reported similar median survival of 14 months for SCC of various head and neck sites.

Decisions regarding therapy are largely based upon individual experience with other salivary gland tumours and historical case series. Local excision of the involved gland with associated ipsilateral lymphadenectomy is commonly recommended. Adjuvant radiotherapy can be considered although its efficacy has never been documented. Chemotherapy is often administered in the treatment of larger primary tumours, those with more extensive local infiltration, and certainly for patients with regional recurrences or distant metastases. As with SCC of other sites, platinum-based regimens are presently favoured by most.

Baugh et al. concluded that patients with SCC originating from the paranasal sinuses have a propensity for local recurrence rather than early metastasis and that surgery is likely to be curative. They found a one-year survival of 81% and five-year survival of 71% after local resection. In the evaluation by Galanis et al., however, 80% of patients treated at the Mayo Clinic with surgery alone (five patients) and radiotherapy alone (one patient) had distant failure with a median relapse-free period of ten months. Similarly, Rosenthal et al. reported local failure rate, after treatment with induction chemotherapy followed by radiotherapy, at five years was 33%, the regional failure rate was 44%, and the distant failure rate was 75%, with six of seven patients dying of their disease within five years of diagnosis. At present, it appears that chemotherapy, using a platinum-based regimen, should at least be a part of the treatment program, with insufficient data in this setting to favour whether it is given as induction, concomitant, or later adjuvant therapy.

**Bladder**

Although EPSCC of the urinary bladder is one of the most common sites of EPSCC in the genitourinary tract, it accounts for less than one percent of all bladder tumours. Literature on the biologic behaviour and prognosis is limited. Nevertheless, disease related death is observed between weeks and several months without treatment. About one third (14–44%) of the patients present with limited disease. Local treatment approaches for limited disease include surgery, radiotherapy, and combined chemoradiation.

Surgical excision via transurethral resection or cystectomy is usually the initial local treatment modality for early T-stage tumours. In muscle invasive (T2–3) node negative tumours, radical cystectomy is frequently applied to remove the small cell tumour. Choo et al. observed a five-year survival rate of 64% in 12 patients with stage II (T2aN0) disease after radical cystectomy. Because six of eight (75%) patients with stage II disease in their study achieved a cure, they do not recommend any adjuvant chemotherapy for this patients group. Only one of eight patients who underwent radical cystectomy alone for stage III (T3aN0-T4a) disease was cured and one out of two patients who received adjuvant chemotherapy for stage III disease was alive and disease-free at 14.4 years. In all three patients with stage II disease who underwent partial cystectomy local pelvic recurrence and distant metastasis occurred, but two of these three patients had no evidence of disease after chemotherapy for tumour recurrence. Therefore, the authors recommend platinum based adjuvant chemotherapy for stage III and partially resected stage II patients. For patients presenting with stage IV (T4bN1–3) disease without distant metastasis, adjuvant chemotherapy is recommended because the only two survivors of the 14 patients in this group had received adjuvant chemotherapy. The five-year survival rates for stage III and IV disease were 15.4% and 10.5%, respectively. MacKey et al. retrospectively reviewed the records of 180 patients with genitourinary SCC, including 106 bladder SCC. On univariate analysis only cisplatin containing chemotherapy predicted prolonged survival (hazard ratio = 0.15). Cheng et al. analysed 64 bladder SCC patients retrospectively and found no significant difference in overall survival between patients who did or those who did not undergo cystectomy for local treatment. Still, a one-year disease specific survival difference of 66% versus 45% was observed among patients who received combination therapy, compared to those who underwent cystectomy only. A study from the Anderson Cancer Centre reviewed the records of 88 patients with small cell bladder carcinoma. Forty-six of these patients underwent cystectomy, including 25 who were treated with initial cystectomy and 21 who received preoperative chemotherapy. For patients treated with initial cystectomy, median cancer specific survival (CSS) was 23 months, with 36% disease-free at five years. For patients receiving preoperative chemotherapy, median CSS was not reached. CSS at five years was 78% with no cancer related death observed beyond two years. Of 17 patients reported by Holmang et al. with stages T2–4M0 SCC bladder cancer treated locally with surgery and radiotherapy, four had no evidence of disease after a median observation of ten years (range six to 18) and 13 died of disease after a median of 7.3 months (range 0.5–19). Because relapses outside the radiation field are common, radiotherapy seems to have no role in the adjuvant treatment of bladder SCC. Like in SCLC, radical surgery such as cystectomy may be avoided when chemotherapy and radiation are given concurrently, with a reported two and five-year survival of 70% and 44% in ten patients.

Patients with stage IV disease have a poor prognosis. Nineteen patients with stage IV disease were analysed in the study of Choong et al., 14 without obvious distant metastasis. Only two of 13 patients who underwent radical cystectomy were alive and disease-free after 6.7 years and 7.6 years; both underwent radical cystectomy followed by adjuvant cisplatin and etoposide. There was no significant difference in the survival curves for patients with stage IV disease with or without distant metastasis, although the sample size was small. Distant metastatic disease, either at diagnosis or at recurrence, is treated with primary chemotherapy with poor outcome (median survival of 2–8 months in small series). The most commonly used regimens include cisplatin and etoposide, carboplatin and etoposide, cyclophosphamide, doxorubicin, and vincristine.
In conclusion, for localised disease most institutions recommend combined local treatment with (neo)adjuvant platinum-based chemotherapy for example four cycles of etoposide plus cisplatinum. Distinct metastatic disease is treated with primary combination chemotherapy.

Uterine cervix

SCC of the female genital tract constitutes less than 2% of all gynaecologic malignancies. It may originate in the endometrium, ovary, fallopian tube, vagina, and vulva, but most frequently in the cervix. Patients with SCC of the uterine cervix have a worse prognosis compared to patients with squamous cell cervical carcinoma (five-year disease-free survival 36% versus 71%). Local treatment approaches include surgery, radiotherapy and chemoradiation. Sheets et al. reported a median survival of 13.5 months, with 12 of 14 patients dying from their disease after hysterectomy as single therapy. Chang analysed 40 cases of small cell cervical carcinoma treated with primary hysterectomy followed by adjuvant chemotherapy. Median survival was 47 months, signifying the importance of adjuvant chemotherapy. Viswanathan reported 15 patients with stage I disease and six with stage II or III disease. Survival was strongly correlated with tumour size and stage; none of the women with >1B1 disease survived more than 30 months. Local treatment was radical hysterectomy in six and radiation therapy in 15 patients. Several chemotherapy combinations were given to 13 (62%) of the 21 patients before or after local treatment, but did not result in a significant increase in relapse-free survival.

In the series of Hoskins et al., 31 patients were treated with a combined modality regimen consisting of upfront platinum-based combination chemotherapy, external-beam radiation, brachytherapy, and adjuvant combination chemotherapy resulting in a three-year overall survival of 60%. Thirty-four patients were reported by Chan et al. In that study the initial treatment consisted of surgery or radiotherapy, with or without cisplatinum-based chemotherapy. The role of several treatment modalities remains unclear from their study but yields uniformly poor results, particularly with advanced lesions. A recent study from Korea retrospectively reviewed 68 patients. Seven were treated with radical surgery alone; 11 with neoadjuvant chemotherapy followed by radical surgery; 24 with radical surgery followed by adjuvant chemotherapy; and 26 with radical surgery followed by adjuvant radiation or chemoradiation. After a median follow-up of 44 months, the two-year and five-year survival for all patients was 65% and 47%, respectively. Patients who received neoadjuvant chemotherapy had a poorer prognosis than those who did not receive neoadjuvant chemotherapy. Adjuvant chemoradiation did not improve survival compared with adjuvant chemotherapy alone. Virtually no data are available for patients treated for distant metastasis. For some, palliative chemoradiotherapy could be considered.

In conclusion, the treatment of cervical SCC for early stages (FIGO stage 1B1 ≤4 cm) should include radical hysterectomy followed by platinum-based adjuvant chemotherapy. For selected patients with higher stages, upfront platinum-based combination chemotherapy followed by chemoradiotherapy and adjuvant combination chemotherapy is a treatment option.

Prostate

Pure SCC is rare at initial presentation, accounting for less than two percent of all prostate malignancies. In about half of the cases, pure adenocarcinoma of the prostate preceded recognition of the small cell component. Median survival for treated patients diagnosed with SCC of the prostate is approximately one-year and long-term survival is rare. Local treatment, such as radical prostatectomy or radiotherapy, can be directed towards palliation in the setting of advanced disease but is potentially curative in selected cases of localised disease. In a recent large single centre study performed at M.D. Anderson Cancer Centre, 21 of 83 patients had no evidence of metastatic disease at the time of diagnosis. There was a difference in median disease-free survival between patients with non-metastatic versus those with metastatic SCC, 17.7 months versus 12.5 months, respectively. The most common form of initial therapy for SCC of the prostate was systemic chemotherapy containing etoposide and/or a platinum compound, given either alone (38 patients), combined with androgen deprivation therapy (ADT) (29 patients), with radiotherapy and ADT (six patients), or with surgery and ADT (three patients). Only four of the 21 patients (19%) without evidence of metastatic disease at the time of diagnosis received local therapy in addition to systemic therapy. The mean DSS duration for the three patients who underwent cystoprostatectomy was 4.0 years (range, 1.8–6.1 years). The patient who was treated with definitive external beam radiotherapy was alive with no evidence of disease at the time of last follow-up, 1.3 years after radiotherapy. The use of systemic chemotherapy was not found to be a predictor of PFS and DSS in this study, because the majority of patients (92%) received it as initial therapy. Although based on a small number, these authors and others believe that surgical resection with or without radiotherapy should be evaluated further as treatment strategies for selected patients with non-metastatic SCC of the prostate because they may provide better local control and a potential survival benefit when combined with systemic therapy compared with systemic therapy alone. In fact, primary surgery was the only independent prognostic factor for prolonged survival in one retrospective study of 60 patients. This finding suggests that hormonal manipulation and systemic chemotherapy have little effect on the natural history of this disease. However, the use of primary surgical therapy is not expected to affect survival in the setting of micrometastatic or macrometastatic disease. Metastatic disease has poor prognosis with median disease specific survival of 10–15 months after treatment with platinum based chemotherapy. A phase II trial adding doxorubicin to the frequently used etoposide/cisplatinum regimen caused more toxicity and failed to improve outcome.

The role of hormonal therapy in small cell carcinoma remains controversial. Moore et al. compared the effectiveness of hormonal versus chemotherapy in 1992. In the setting of mixed histologies, hormonal therapy can be included in the treatment schedule, but should not be the sole therapy in SCC of the prostate. In conclusion, non-metastatic SCC of the prostate must be treated with platinum-based chemotherapy in combination with local treatment. Metastatic disease is treated with systemic combination platinum based chemotherapy.

Small cell carcinoma of unknown primary

Small cell carcinoma of unknown primary (SCUP) is an uncommon cancer that is usually diagnosed in the lymph nodes, liver, brain, or bone. The incidence of SCUP has been reported to comprise between 7% and 30% of EPSCCs. Two possible mechanisms have been proposed to explain the inability to detect the primary lesion. Involvement of the primary tumour via spontaneous or immunological regeneration has been described. An alternative hypothesis suggests that early metastases develop a proliferative advantage over the primary lesion, resulting in the manifestation of the metastases without identification of a primary lesion. Clinical presentation of patients with SCUP typically correlates with the site of organ involvement. SCUP is usually a systemic disease, but can be limited with regional lymph node involvement as the single manifestation.
Particularly isolated cervical lymph node involvement is associated with better prognosis. Excision biopsy used to obtain a diagnosis in SCUP may indeed render the patient with no measurable disease with some patients experiencing prolonged survival. Galanis et al. reported on surgical resection of six patients with SCUP. The median survival was 40 months, despite no adjuvant treatment. Hainsworth et al. reported on surgical resection of SCUP in three patients; all were alive at publication with survivals of 12, 20, and 93 months. Radiation therapy has also been used successfully to control localised disease. Four patients with single sites of disease receiving local therapy only remained disease-free one to ten years after completion of therapy. Nevertheless, distant failures are common in SCUP. One study reported a median survival among 31 patients with SCUP of only 2.5 months. Thus, the addition of chemotherapy should be considered in patients with apparently localised SCUP.

Management of extensive disease of SCUP, regardless of the site of disease, should include combination chemotherapy, with response rates similar to SCLC. There is no randomised study to help define the best chemotherapy regimen, although most investigators favour platinum-based treatment. Other modalities, such as radiotherapy or surgery, may be used to achieve local control and palliation of symptoms.

Cranial irradiation

SCLC patients treated with chemotherapy with or without chest radiation therapy who have achieved a complete remission can be considered for administration of prophylactic cranial irradiation (PCI). Patients whose cancer can be controlled outside the brain have a 60% risk of developing central nervous system metastases within two to three years after primary treatment. The majority of these patients relapse only in the brain, and nearly all of those who relapse in their central nervous system die of their cranial metastases. The risk of developing central nervous system metastases can be reduced by more than 50% by the administration of PCI in doses of 24 Gy. A meta-analysis of seven randomised trials evaluating the value of PCI in patients in complete remission reported improvement in brain recurrence, disease-free survival, and overall survival (OS). The three-year overall survival improved from 15% to 21% with PCI. Prospective studies showed that patients treated with PCI do not have significantly worse neuropsychological function than patients not treated. In addition, the majority of patients with small cell lung cancer have neuropsychological abnormalities before the start of cranial irradiation and have no detectable decline in their neurological status for as long as two years after cranial irradiation. A recent randomised trial of prophylactic cranial irradiation in patients with extensive disease SCLC who responded to chemotherapy, also showed a reduced risk of brain metastases within one-year (risk ratio = 0.36). Furthermore, irradiation was associated with an increase in median disease-free survival from 12.0 weeks to 14.7 weeks and in median overall survival from 5.4 months to 6.7 months. The authors conclude that PCI should be part of standard care for all patients with small-cell lung cancer who have a response to initial chemotherapy.

Differences in the frequency of brain metastases, and early death between EPSCC and SCLC exist. A retrospective single-centre study evaluated 65 SCC cases, including 11 (17%) cases of EPSCC and 54 (83%) cases of SCLC. None of the EPSCC patients had brain metastasis at diagnoses compared to 11 (20%) in SCLC. A smaller study presented by Soto et al. reviewed 18 patients with limited stage EPSCC. Fourteen patients had distant failure but only one had a brain failure. So brain failures in EPSCC were uncommon in this series.

Gastrointestinal tract

In the analysis of Brenner of 64 SCC of the gastrointestinal tract, one patient presented with brain metastasis at diagnosis. Hussein reported two patients with SCC of the large intestine presenting with CNS metastasis. Because the difference in incidence of brain metastasis at presentation and during follow up between gastrointestinal tract SCC and SCLC and because data on efficacy of PCI for gastrointestinal tract SCC are lacking, we do not recommend use of PCI.

Bladder

The incidence of brain metastases in SCC of the bladder is not mentioned in many publications, but seems to be lower than in SCLC. In the M.D. Anderson series, nine out of 55 (16%) patients had brain metastases. In a small series from Manchester, two out of 14 (14%) patients developed brain metastases. In the 25 patients reported by Bex et al., none of the patients died of brain metastases, although the incidence was not reported. After the development of brain metastases in one patient in a study by Lester et al., the authors decided to offer PCI to all patients achieving a complete response with chemotherapy and three patients received PCI, of whom one developed liver metastasis and two were free of disease after 30 months. However, the role of PCI in bladder SCC is controversial, and is not recommended for routine use.

Cervix

None of the 21 patients in the study by Viswanathan received PCI and two had recurrences in the brain associated with simultaneous lung metastases. Other authors found higher incidences of brain metastasis. Two of the eight patients with initial stage I/II developed brain metastasis. Another patient with brain metastasis was stage IV with spread of disease to the cerebellum. In the study of Hoskins et al, only one of 24 patients did relapse in the central nervous system. Therefore, we do not recommend routine use of PCI in cervical SCC.

Prostate

Authors from the MD Anderson Centre analysed 16,280 patients with prostate cancer, the risk of brain metastasis in SCC (16%) was significantly greater compared with adenocarcinoma (0.8%). In the series reported by Spiess et al, eight of 83 patients (10%) presented with brain metastases. In contrast, none of the ten patients reviewed by Asmis and co-workers had documented symptomatic brain metastasis. As data on efficacy of PCI for prostate SCC are lacking, we do not recommend routine use, although the incidence seems to be about ten percent.

Head and neck

Ferlito et al. suggested that intracranial metastases from laryngeal SCC usually signals a terminal situation. Baugh and co-workers found that four of their 52 patients (7.7%) with laryngeal SCC developed intracranial metastasis, but not in patients who had received PCI. More recently, Barker and others treated 23 adults with non-metastatic primary neuroendocrine nonsinonasal (including laryngeal) carcinomas including 21 SCC from 1984 to 2001. The two-year and five-year rates of intracranial metastases were 25% and 44%, respectively. The brain was the only site of distant metastasis in 21% and 41%, respectively. By analogy to SCLC the authors consider PCI for patients who have had a complete clinical response to induction therapy. Rosenthal et al. treated 72 adults with non-metastatic, primary sinonasal neuroendocrine tumours from 1982 to 2002 including seven SCC. Three of four patients with SCC who had distant failures also developed brain metastases. The only long-term SCC survivor (no evidence of disease at 14 years) was treated with prophylactic cranial irradiation integrated.
with his primary local radiation. The issue of PCI remains a controversial matter. However, because of the high incidence of brain metastasis we recommend PCI to be considered for patients with head and neck SCC. Because of the proximity of the nose and paranasal sinuses to the cranial cavity, it seems best if PCI of the brain can be coordinated with any therapeutic radiotherapy treatment to the sinonasal region.

**Small cell carcinoma of unknown primary**

PCI is of proven benefit in SCUP. Nonetheless, one may speculate that patients with solitary cervical lymph node involvement resembling primary head and neck localisations who are surgically treated with no evidence of disease may benefit. For patients who have residual disease after primary therapy, observation until the development of CNS symptoms before implementation of CNS therapy is a reasonable alternative.

**Conclusions**

EPSCC is a clinical entity distinct from SCLC. Because of the rarity of EPSCC, the initial management of patients with locoregional disease is patterned after that for other tumour types arising in the same extrapulmonary site. Despite aggressive loco-regional treatment with surgery and/or radiation therapy, relapse is common and adjuvant systemic chemotherapy is generally recommended. Various chemotherapeutic combination regimens have been used in the first-line treatment of EPSCC including cisplatinum and etoposide (CE); irinotecan plus cisplatin (IC); carboplatin and etoposide; cyclophosphamide, Adriamycin and vincristine (CAV); Adriamycin, Cyclophosphamide and etoposide (ACE) and Ifosfomide, Carboplatin and etoposide (ICE). It must be noted, however, that all data on treatment effectiveness are derived from case reports and small retrospective series and no randomised clinical trial has been conducted. Despite adjuvant therapy, most patients develop metastatic disease and the prognosis is poor. Those patients with tumours arising from the head and neck region, especially the salivary gland and paranasal sinuses have a better prognosis with mostly local recurrences rather than distant metastases. Small cell cancer of unknown primary generally has a poor prognosis, although patients presenting with solitary cervical lymph node involvement may do better. These patients should be considered for multimodality treatment with curative intent.

The management of systemic disease with chemotherapy is patterned after the approach used in SCLC. Although objective responses are commonly observed, most are partial and of short duration. The prognosis for patients with disseminated disease is poor despite chemotherapy and is similar to that for patients with extensive SCLC. We recommend combination chemotherapy with a platinum-based regimen. The use of three- or four-drug combinations and that of maintenance therapy has not been shown to be beneficial. Patients with relapsed disease in good performance status may be offered second line treatment, preferably in a clinical study. A choice of single agent drugs has shown response in second line including topotecan, taxanes, and gemcitabine.

The incidence of symptomatic brain metastases is lower in EPSCC compared to SCLC and PCI is not generally recommended. An exception may be patients with a primary location in the head and neck region, for whom PCI should be considered.

**Conflict of interest statement**

There are no conflict of interest.


