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Neoadjuvant Chemotherapy in Extra-Pulmonary Neuroendocrine Carcinoma

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1. Introduction

Extrapulmonary neuroendocrine carcinoma (EP-NEC) have been found in most organs, but the most common sites are the gastrointestinal tract, cervix uteri and urogenital tract (Strosberg et al., 2010, Walenkamp et al., 2009). Recently it has been defined as a pathological entity in breast cancer (Tavassoli et al., 2003). Additionally, in up to 30% of EP-NEC cases, no primary site can be identified (Kloppel et al., 1996). In the prior 2000 WHO classification, these tumours were known as poorly differentiated endocrine carcinoma (PDEC) (Solcia et al., 2000). In the 2010 WHO GI classification PDEC the nomenclature has been altered, and these tumours are now called neuroendocrine carcinoma (NEC) (Bosman et al., 2010). NEC tumours have a much higher proliferation rate than well-differentiated endocrine tumours. The terms poorly differentiated high-grade and neuroendocrine carcinoma are used synonymously and encompass mainly two histological entities: small-cell neuroendocrine carcinoma (SCNEC) and large-cell neuroendocrine carcinoma (LCNEC) (Bosman et al., 2010). LCNEC is morphologically distinguished from SCNEC by cytological features of a non–small cell carcinoma, including large cell size, low nuclear to cytoplasm volume ratio, coarse chromatin, and frequent nucleoli. They are both characterised by markers of neuroendocrine differentiation with synaptophysin, neuron-specific enolase, chromogranin and CD56 being the primary stains. They are also characterised by a high mitotic rate (defined as >10 mitotic figures per 10 high-power fields or a ki-67 > 20% in the gastrointestinal (GI) tract and other extrapulmonary sites and often with extensive necrosis. Most carcinomas in this family exhibit substantially more mitoses than these thresholds, typically in the range of 40 to 70 mitoses per high-power fields. Up to 40% of NECs contain elements of non-NECs, usually adenocarcinoma or squamous cell carcinoma. Often the diagnosis of a NEC tumor is after surgery on examination of the histological specimen. NECs are characterised by a high proclivity for metastatic dissemination even in patients with clinically localised tumours. This principle is validated by retrospective studies confirming that surgery alone is rarely curative (Brenner et al.,2004a).

In devising treatment strategies for extrapulmonary NEC, many authors refer to the extensive literature surrounding high-grade neuroendocrine carcinoma of the lung (Brenner et al., 2004a, Walenkamp et al., 2009). Several series have, however, questioned the rationale for this, and point out many differences between pulmonary small-cell carcinoma and SCNEC (Brennan et al., 2010, Brenner et al., 2004a, Brenner at al., 2007, Ku et al., 2008). Differences include aetiology (less smoking history in SCNEC), frequency of brain

metastases (less in SCNEC), overall survival (superior in SCNEC, and survival may be site specific, i.e. gynaecologic and head and neck cancers may have better outcomes than GI primaries), and molecular differences, e.g. BCl-2 overexpression is more common in lung compared with SCNEC. Guidelines for treating EP- NEC advocate the use of combination chemotherapy with a platinum-based chemotherapy combined with the etoposide (NCCN 2010). No other regimen has consistently shown a benefit over this combination. When a patient has disease limited to the lung, using an aggressive multi-modality therapy including platinum-based chemotherapy and thoracic radiotherapy has showed improved survival. Based on this treatment paradigm for limited-stage small-cell lung cancer, a course of definitive chemotherapy and local therapy (surgery or radiation) can be considered in many patients with loco-regional EP- NEC. Whereas there are no studies examining adjuvant chemotherapy in NEC, their aggressive behaviour warrants consideration of adjuvant therapy in most cases. The North American Neuroendocrine Tumor Society (NANETS) recommend 4-6 cycles of cisplatin or carboplatin and etoposide as adjuvant therapy for resected patients (Strosberg et al., 2010). The use of neoadjuvant chemotherapy has by many been advocated for these patients, as surgery or radiation often has a poor prognosis due to the frequent development of distant metastases. Recently, neoadjuvant chemotherapy for resectable gastric cancer and resectable liver metastasis from colorectal cancer has been shown to increase survival (Cunningham et al., 2006, Nordlinger et al., 2008). Potential advantages to a neoadjuvant approach include; earlier treatment of micrometastatic disease; better compliance to treatment; determination of responsiveness to chemotherapy which can be prognostic and help in planning of postoperative chemotherapy; and avoidance of unnecessary surgery for patients with early systemic disease progression. Potential disadvantages include the risk of missing the window of opportunity for resection because of disease progression. The present paper discuss available literature concerning the use of neoadjuvant chemotherapy for EP-NEC.

2. Gastrointestinal neuroendocrine carcinoma

2.1 Background

Extra-pulmonary neuroendocrine carcinomas can originate anywhere in the gastrointestinal (GI) tract, but are mainly located in the oesophagus, stomach, pancreas and colon (Brenner et al., 2004a). Few data exist about this tumor group as many have been included in the general neuroendocrine tumor group and many are frequently misdiagnosed as poorly differentiated adenocarcinoma. GI primary tumours account for 35-55% of all NEC outside the lung (Galanis et al., 1997, Lee et al., 2007). Approximately 10% of all GI neuroendocrine tumours are NEC. Most GI NEC's are metastatic at the time of diagnosis. In the SEER database, colorectal NEC has an incidence of 2/1,000,000 inhabitants/year, and distant disease at diagnosis was present in 62% of patients (Kang et al., 2007). Median survival from diagnosis in untreated patients is usually 4-6 months, indicating a very rapidly growing tumor. Among 94 GI NEC patients in the National Cancer registry of Spain, 67% presented as distant metastatic disease, median survival was 1.7 months and 39% alive at 5 year (Garcia-Carbonero et al., 2010). Morphologically GI NEC are classified in two types: a small-cell carcinoma, resembling small-cell carcinoma of the lung, and a large-cell pleomorphic carcinoma (Bosman et al., 2010) (Figure 1-2). Small-cell histological preponderance in the squamous GI tract (oesophagus and anus) and large-cell carcinomas in the glandular parts (Shia et al., 2008). Awareness of the latter is essential, as these tumours often are indistinguishable from poorly differentiated non-NET carcinomas.

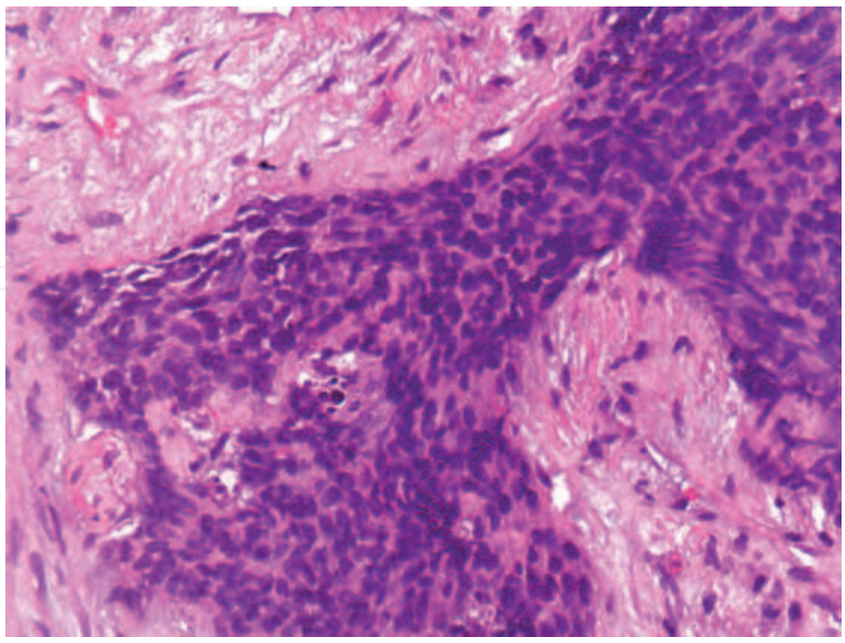

Fig. 1. Small-cell NEC from pancreas.

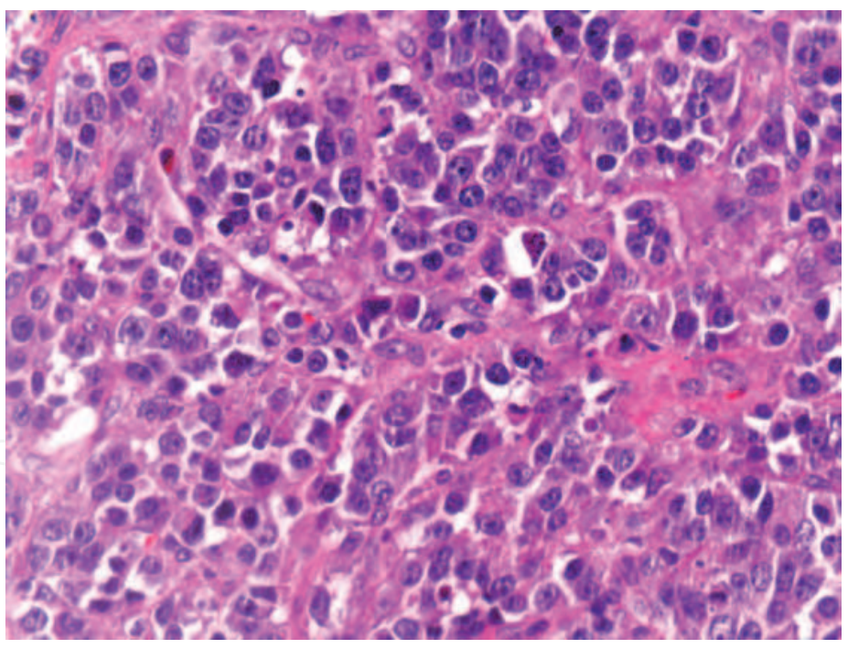

Fig. 2. Large-cell NEC from colon.

Usually synaptophysin will be positive in immunohistochemistry while staining for chromogranin A (CgA) is present at a lower level (Figure 3-4). The presence of CgA indicates a more mature tumor, and the presence of both markers is a good prognostic sign (Faggiano A et al., 2007, Welin et al., 2011). Several pathologists advocate for routine staining with synaptophysin and chromogranin for all tumours initially classified as poorly differentiated gastrointestinal adenocarcinoma.

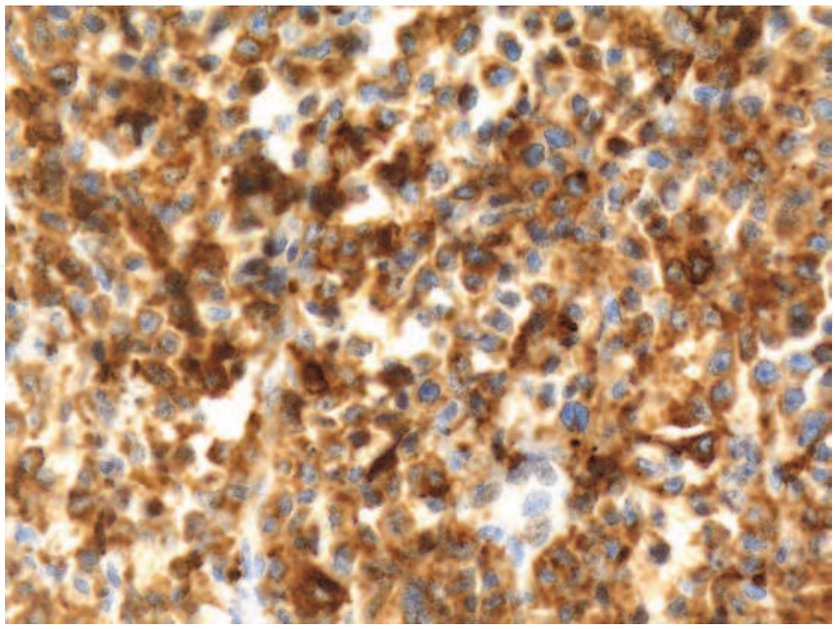

Fig. 3. Synaptophysin positive NEC.

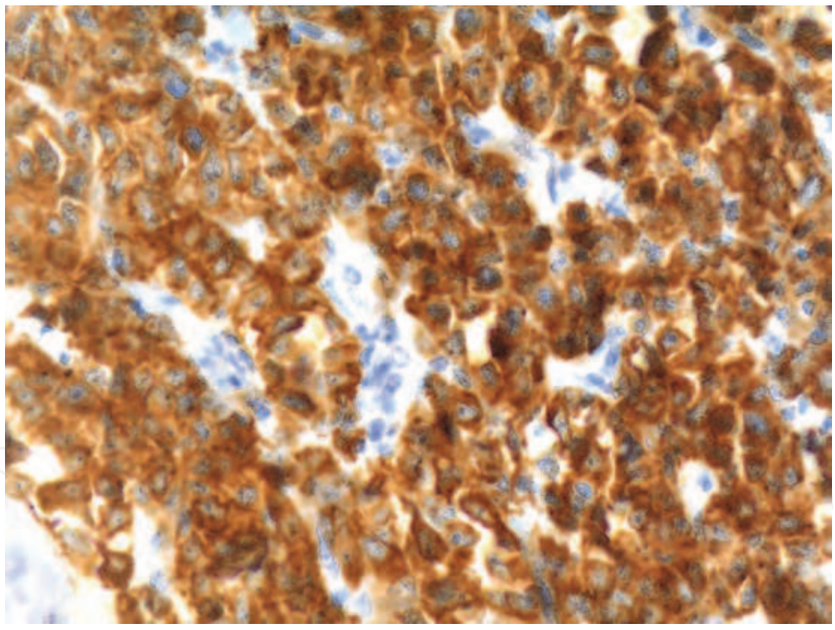

Fig. 4. Chromogranin A positive NEC.

CD56 is another neuroendocrine marker, which can help to classify a tumour. Screening for CgA in serum should be done, but is usually negative and hormonal symptoms are rare (Janson et al., 2010). In most NET guidelines it is stated that somatostatin receptor scintigraphy is usually negative in NEC. A somatostatin receptor scintigraphy should however be performed if ki-67 is below 30-40%, when peptide receptor radionucleotide therapy (PRRT) is a future treatment option. Ki-67 is per definition >20% but is more likely to be between 50 and 100% (Figure 5-6).

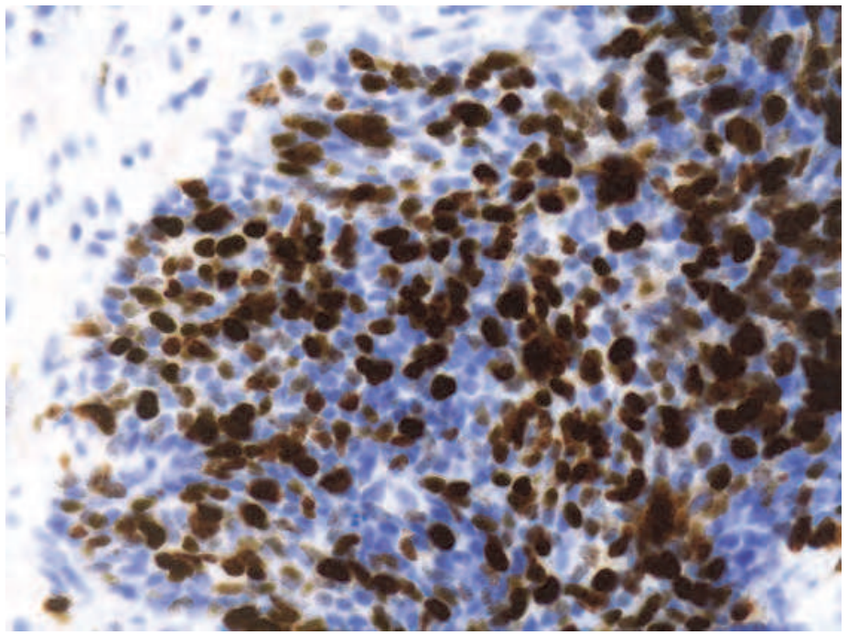

Fig. 5. SCNEC with a ki-67 index of 50%.

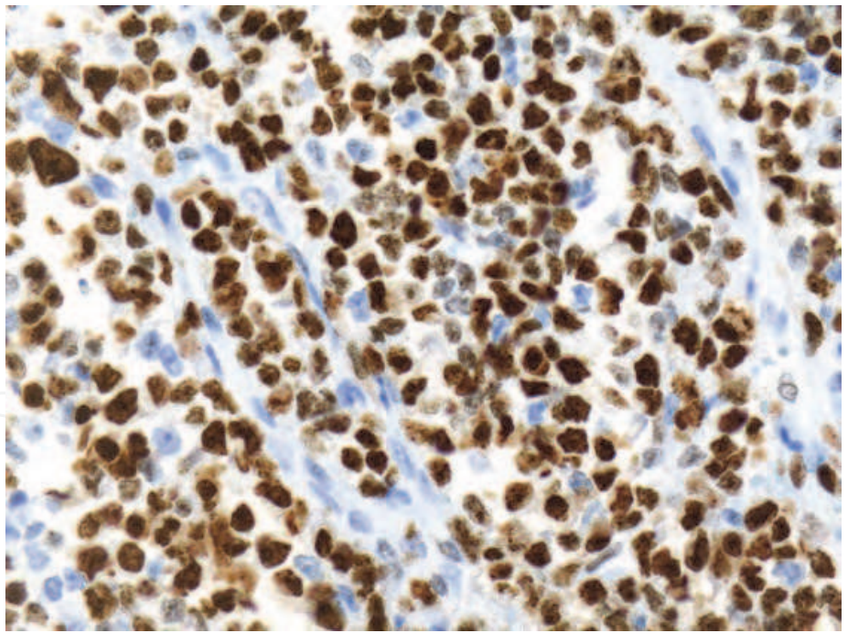

Fig. 6. LCNEC with a ki-67 index of 80-90%

In many patients, metastatic disease is present at time of diagnosis. In some instances the primary can be found, but often the primary will be of uncertain origin but usually considered GI if the metastatic load is dominating in liver and abdomen. Despite rare reports of long-term survivors, surgery alone is inadequate therapy even for apparently localised disease. Many operated patients have a rapid recurrence after surgery. Adjuvant

radiotherapy 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 multi-modality therapy including surgery and systemic chemotherapy, the median survival in colorectal SCC was six months, with only 15% of patients alive at one-year (Hung 1989). Data from Memorial Sloan Kettering Cancer Centre show a median survival of ten months for patients with colorectal SCC (Bernick et al., 2004). One-year, two-year, and three-year survival was 46%, 26%, and 13%, respectively. There are no significant differences in survival based on pathologic subtypes (Bernick et al., 2004, Shia et al., 2008). 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 (Fujii et al. 2001). In the SEER database of colorectal NEC, 5-year survival was 21% for all stages, ranging from 73% in localised disease to 6 % in distant disease (Kang et al., 2007).

2.2 Neoadjuvant chemotherapy

Extensive disease (ED) is almost invariably treated by systemic chemotherapy. In contrast, the treatment approach for limited disease (LD), a potentially curable condition, is presently neither consistent nor uniform. While some authors used only local therapies, mostly surgery and occasionally radiotherapy, others advocate the use of chemotherapy, even alone, in these patients. NEC do not respond to treatments usually applied in other neuroendocrine tumours such as somatostatin analogues and interferon (Alhmann et al., 2008, Nilson et al. 2006). For patients with disease localised within an anatomic region (limited disease), initial neoadjuvant therapy with chemotherapy or chemoradiotherapy is an option, followed by surgery if no distant metastases are identified and the locoregional disease is resectable. Usually 2-3 cycles are given before surgery (Figure 7).

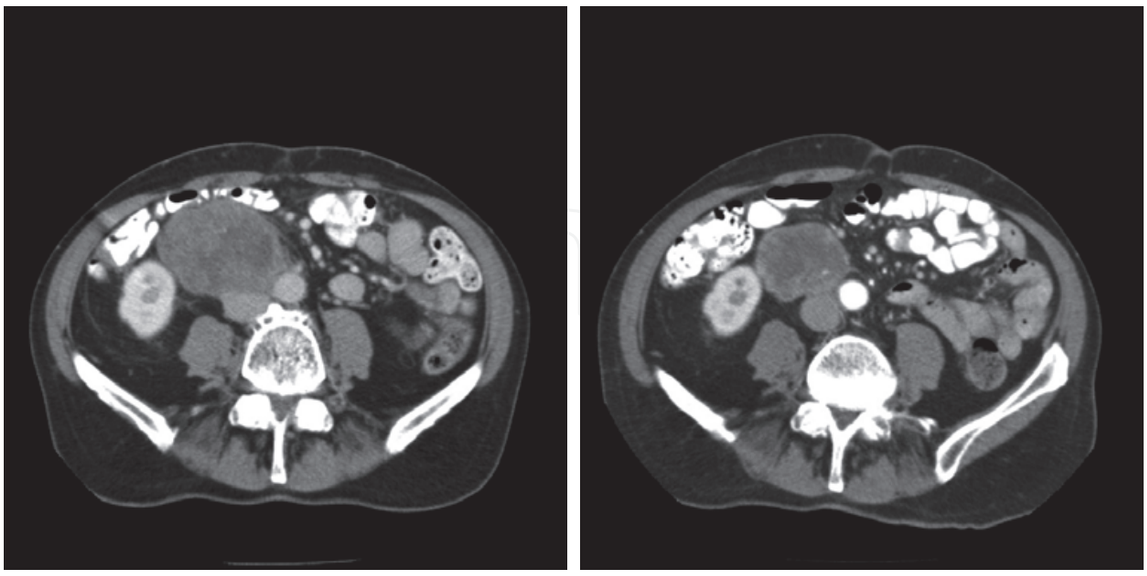

Fig. 7. Partial response after 4 cycles of neoadjuvant cisplatin/etoposide before radical surgery in a patient with unknown primary NEC.

No convincing data exist concerning adjuvant postoperative chemotherapy, but most recommend postoperative chemotherapy with the same drugs for 3-4 months as part of the neoadjuvant approach. Adjuvant or neoadjuvant chemotherapy is based on the effect in a metastatic setting, and is usually given with cisplatin /carboplatin and etoposide with response rates between 41- 67% (Mitry et al., 1999, Moertel et al., 1991). Casas and colleagues highlighted the role of systemic chemotherapy and local treatment in small-cell carcinomas of the oesophagus. In a retrospective series of 199 patients, improved median survival from 5 to 20 months was reported in patients with localised disease who received multi-modal therapy, i.e. surgery, radiation therapy, and systemic treatment (Casas et al., 1997). A prognostic factor analysis found that local therapy only (e.g. surgery alone) was the single most powerful predictor of poor prognosis. In the prognostic factor analysis, chemotherapy was found to be strongly associated with improved survival, both in LD and ED. Recent data from Memorial Sloan Kettering Cancer Centre support the use of induction chemotherapy followed by consolidative chemoradiation for patients with limited disease oesophageal SCNEC (Ku et al., 2008). Median survival was 20 months in this single institute retrospective study of 25 oesophageal SCNEC patients, with two limited disease patients alive and free of disease after five years follow-up. The authors concluded that surgery might not be necessary as part of initial therapy if a clinical complete response is achieved after chemoradiation, and that surgery may be reserved for salvage after documented local failure. In 64 patients with GI NEC seen at Memorial Sloan Kettering Cancer Center between 1980 and 2002,the most common primary tumour locations were in the large bowel and oesophagus (Brenner et al., 2004b). Sixteen patients with LD received chemotherapy, 12 of whom received it in conjunction with either surgery or radiotherapy. Of these, two remained alive with no evidence of disease for at least 64 and 94 months and one expired with no evidence of recurrence after almost 9 years. The authors suggests a potential role for surgery for LD; half of the operated patients retained locoregional control, and four of the six long-term survivors had surgery; two of them with no other treatment. The authors also state that this study supports the effectiveness of chemotherapy on survival in this disease; three of the long-term survivors received chemotherapy and six patients were treated by a combination of surgery and chemotherapy. Two of these had no evidence of disease for over 7 years and locoregional control was preserved in three. At present, in the absence of data derived from prospective clinical trials, they recommend to treat patients with LD with pre- or postoperative chemotherapy.

In contrast to metastatic neuroendocrine tumours with a low ki-67, debulking surgery and surgery for liver metastasis is generally not recommended in NEC patients due to the high ki-67 level. In some patients, however, this may still be an option. In one of our patients, surgery for extensive metastatic disease after neoadjuvant chemotherapy resulted in long time survival (Figure 8) (Sorbye et al., 2007). Similar case reports of neoadjuvant chemotherapy before locoregional treatment of metastatic NEC lesions have been reported (Power et al., 2010).

Altogether, most data support that in patients presenting with limited disease NEC of the gastrointestinal tract, a combination of systemic platinum-based chemotherapy combined with local treatment consisting of radiotherapy, surgery or both offer the best chance for long-term survival. Based on the high rate of micrometastatic disease presentation, several authors suggest that a sequence of neoadjuvant chemotherapy followed by definitive surgery seems appropriate, although the reverse sequence of surgery followed by adjuvant chemotherapy can not be excluded (Brenner et al., 2007).

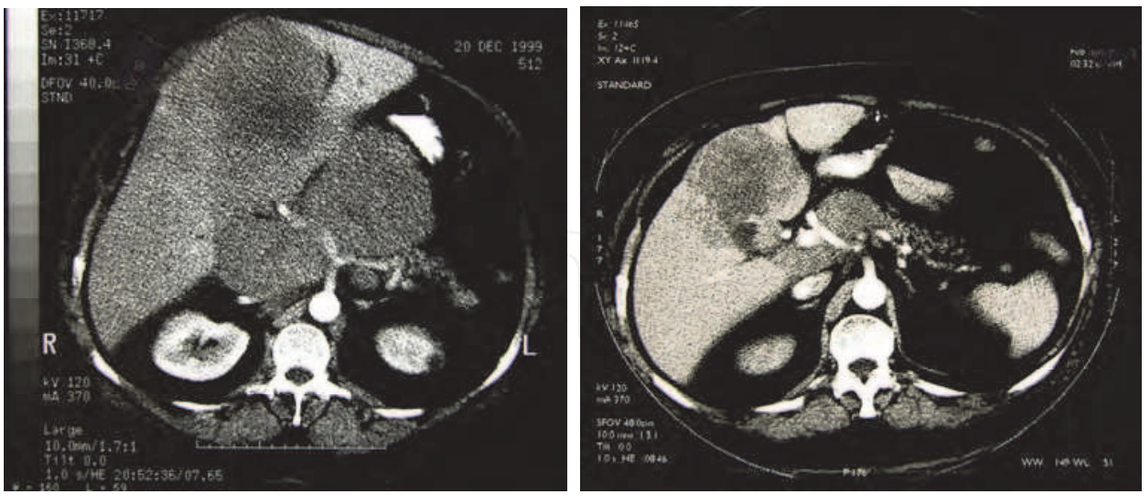

Fig. 8. Partial response of liver metastases and lymph node metastases after 4 cycles of neoadjuvant chemotherapy with cisplatin/etoposide before radical surgery and long-term survival.

3. Neuroendocrine cancer of the uterine cervix

3.1 Background

Neuroendocrine tumours of the uterine cervix represent 1–2% of cervical cancers and are the 2nd most common extra-pulmonary location of the primary tumor for NEC (Crowder et al., 2007). They are classified as typical carcinoid tumours, atypical carcinoid tumours, small-cell neuroendocrine carcinomas (SCNEC) and large-cell neuroendocrine carcinomas (Figure 9). Small-cell neuroendocrine carcinoma is the most common, and is aggressive with a high chance of distant metastasis and poor prognosis, even with combinations of treatments.

The natural history of this disease differs from the more commonly seen squamous cell or adenocarcinoma of the cervix. Patients diagnosed with SCNEC are more likely to have lymph node metastases and lymphovascular space invasion, and their clinical course is frequently marked by local and distant failure. Five-year survival rates vary from 31-36% for early disease and 0-14% for advanced disease (Chen et al., 2008). Long-term survival can be achieved only in patients with limited stage disease. Limited stage disease, which is defined as disease that can be encompassed within a radiation field, is treated with curative intent with combined modality therapy, with approximately 30% of patients achieving a cure (Figure 10). Patients with extensive stage disease – defined as disease outside of these confines – have a dismal prognosis with few surviving beyond two years. Clear treatment recommendations for SCNEC have not been defined. Due to the rarity of this disease it has been difficult to conduct prospective trials. Based on retrospective studies and treatment paradigms established for small-cell lung carcinoma, many clinicians favour the use of combined modality therapy for limited stage disease, definitive chemoradiation therapy for locoregional advanced disease and palliative chemotherapy for metastatic disease. It is not known if these treatment modalities ultimately improve survival. Often, the diagnosis of small-cell is not made until receipt of the final pathology on a radical hysterectomy; once the

diagnosis is made, prompt initiation of combined modality therapy should follow post-operatively. The role of surgery for SCNEC is not well studied. It is unclear which patients, if any should undergo radical hysterectomy as opposed to primary combined chemotherapy and radiation therapy. If small cell histology is known, it is probably most appropriate to proceed with chemotherapy followed by surgery and postoperative chemotherapy or postoperative chemoradiation.

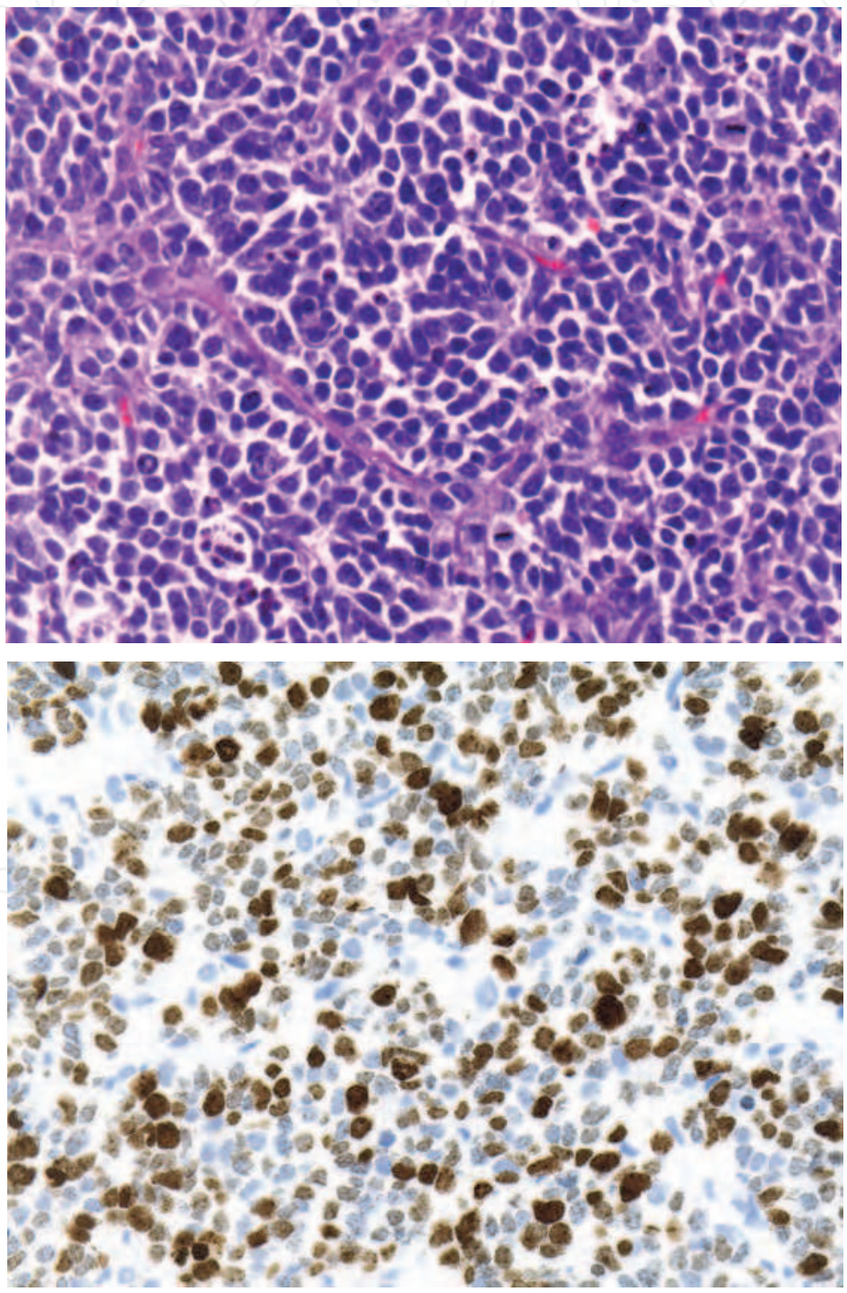

Fig. 9. Small-cell neuroendocrine cancer of uterine cervix, ki-67 about 60%

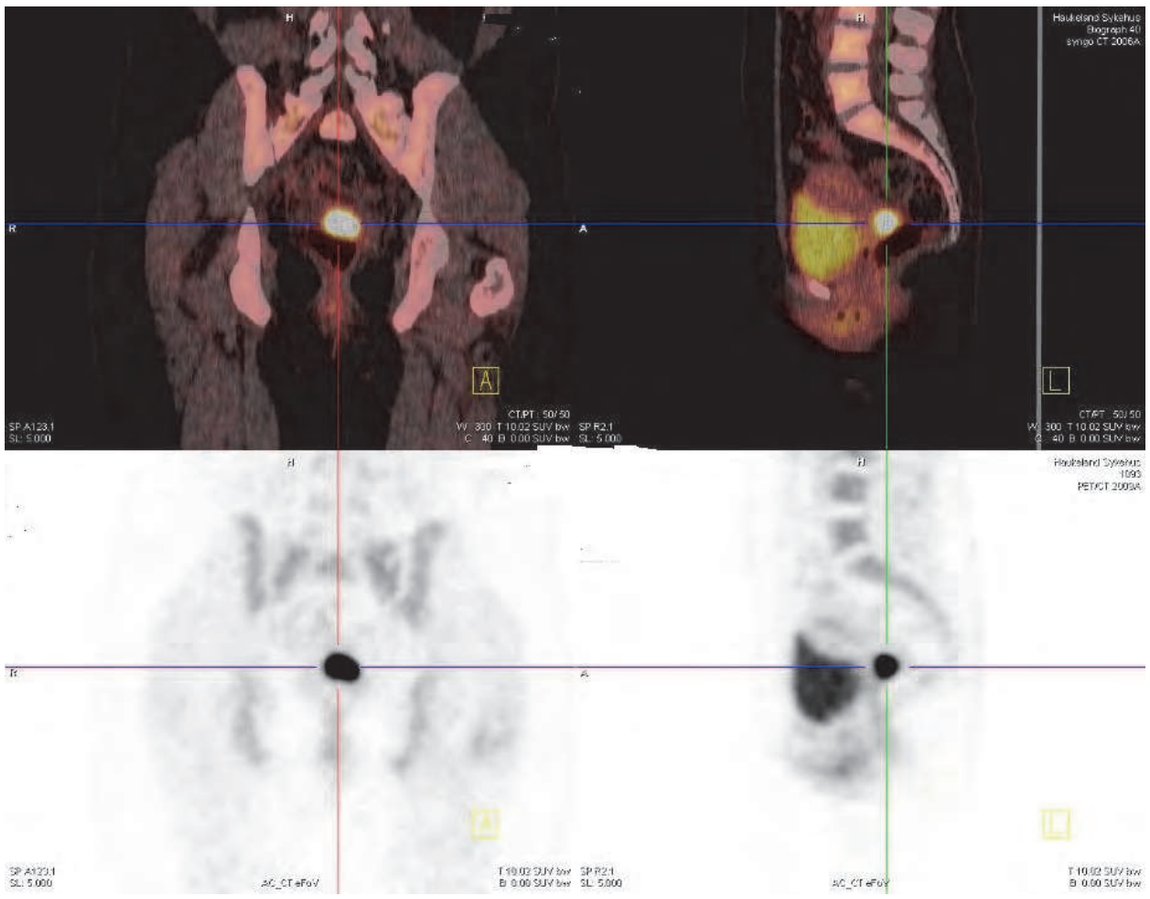

Fig. 10. PET/CT and MRI of a localised uterine cervix NEC before initiation of neoadjuvant chemotherapy.

3.2 Neoadjuvant chemotherapy

In a retrospective review of 188 patients of small-cell carcinoma of the uterine cervix, 135 patients had stages I-IIA, 45 stages IIB-IVA, and 8 stage IVB disease (Cohen et al., 2010). Adjuvant chemotherapy or chemoradiation was associated with improved survival in patients with stages IIB-IVA disease compared with those who did not receive chemotherapy (17.8% vs 6.0%; P = .04). On multivariable analysis, early-stage disease and use of chemotherapy or chemoradiation were independent prognostic factors for improved survival. Hoskins et al. reported 31 patients who were treated with protocols using etoposide, cisplatin and radiation therapy with concurrent chemotherapy with or without the addition of carboplatin and paclitaxel (Hoskins et al., 2003). The 3-year failure-free rate of the patients with early stage disease (stage I and II) was 80%. Chang et al. analysed 40 cases of small-cell uterine cervical carcinoma treated with primary hysterectomy followed by adjuvant chemotherapy containing a combination of vincristine, doxorubicin and cyclophosphamide or cisplatin and etoposide (Chang et al., 1998). Median survival was 47 months, signifying the importance of adjuvant chemotherapy for early stage small-cell cervical carcinoma after radical hysterectomy. A recent study from Korea retrospectively reviewed 68 patients (Lee et al., 2008). 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 worse prognosis than those who did not receive neoadjuvant chemotherapy, but the patients who received neoadjuvant therapy had worse baseline prognostic factors. Adjuvant chemoradiation did not improve survival compared with adjuvant chemotherapy alone. In a study with 17 patients with SCNEC in uterine cervix, all 5 patients with early stage disease without chemotherapy as part of their initial treatment developed distant metastases within 2 years from the diagnosis (Zivanovic et al., 2009). This was in contrast to the 6 patients who were treated with adjuvant platinum- and etoposide-based combination therapy. In this group, only 1 patient developed systemic disease. In a retrospective analyses of 62 patients with large-cell NEC of the uterine cervix, median age was 37 and FIGO stage was: 58% stage I, 16% stage II, 2% stage III and 8% stage IV disease (Embry et al., 2011). Median overall survival for stage I, II, III, and IV cancers was 19, 17, 3, and 1.5 months, respectively. Thirty-seven women (60%) received chemotherapy as part of their initial treatment plan. In a multivariate analysis, earlier stage and the addition of chemotherapy were associated with improved survival. Both platinum agents and platinum and etoposide together were associated with improved survival.

Among 20 patients with neuroendocrine cervical carcinoma, patients with stage Ib_2 or greater received neoadjuvant chemotherapy with vincristine, bleomycin, and platinum (Bermudez et al., 2001). The response was <50% in 2/13 cases (15%), >50% in 9/13 (69%), and complete in 2/13 (15%), and resection was successfully performed in all 13 patients. Patients with initial tumor volume less than 4 cm had no recurrences and 5-year survival was 76%, whereas 75% recurred and 5-year survival was only 18% when initial tumor volume was over 4 cm (Figure 11).

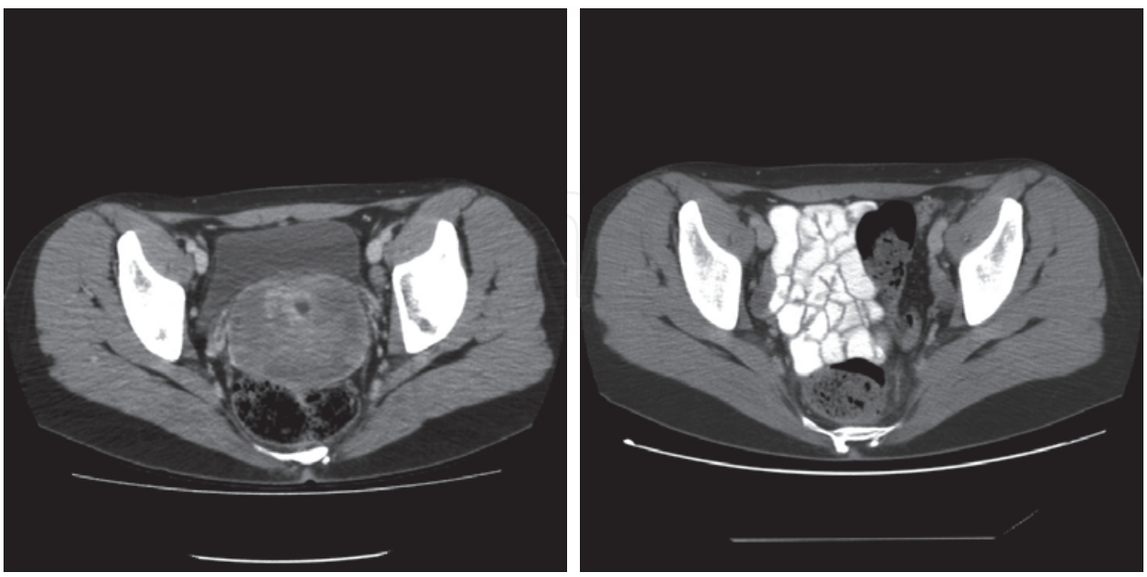

Fig. 11. Complete response of small-cell NEC of uterine cervix after 2 cycles of neoadjuvant chemotherapy with cisplatin and etoposide preceding planned surgery.

Although the comparison between different series is problematic due to selection bias and different treatment strategies, data support that in patients with early stage disease NEC of the uterine cervix, the addition of systemic platinum-based chemotherapy appears to have a protective effect on the development of distant metastases. The association between chemotherapy and local therapy (surgery/radiation) seems to obtain the best results in terms of survival. However, the sequence at which both therapeutic modalities should be used has not been proven yet.

4. Neuroendocrine carcinoma of the bladder

4.1 Background

In the urinary system, the majority of cases have been observed in the bladder and prostate. Small-cell neuroendocrine carcinoma accounts for less than 1% of all bladder tumours, whereas large-cell neuroendocrine carcinoma is even rarer. Like small-cell carcinoma of the lung, small-cell carcinoma of the bladder has a propensity for early metastases. Only about one third (14–44%) of the patients present with limited disease. Given the lack of evidence to the contrary, a radical cystectomy has been considered the "de facto" standard for patients without evidence of metastatic disease. However, the lack of efficacy of this approach is readily apparent; even in recently published series, most patients die within 2 years of cystectomy (Cheng et al., 2004, Quek et al., 2005). Management ranges from cystectomy alone, with or without adjuvant radiation therapy or adjuvant chemotherapy. Recent retrospective reviews suggest better survival with initial chemotherapy followed by local consolidation with cystectomy or radiation (Church & Bahl 2006). The use of preoperative chemotherapy follows from the frequent observation of rapid growth rates and typical upstaging on initial surgery, not uncommonly leading to aborted cystectomy. The benefits of incorporating neoadjuvant chemotherapy can be multifold. Whereas it may take time to schedule an operation or for patients in this age group to complete preoperative clearance, systemic chemotherapy can be initiated quickly, providing timely control of this rapidly growing chemotherapy-sensitive tumor. Tumor can frequently be downstaged, resulting in a surgery that is more likely to achieve negative margins and the pathologic stage after preoperative chemotherapy may provide valuable prognostic information.

4.2 Neoadjuvant chemotherapy

In a retrospective review of 25 patients with neuroendocrine tumor of the bladder, Quek and associates reported significant improvement in recurrence-free and overall survival (OS) in those receiving neoadjuvant or adjuvant chemotherapy with radical cystectomy as compared with radical cystectomy alone (Quek et al., 2005). Walther et al observed that five of seven patients were alive and cancer free at 36 months, most as a result of preoperative chemotherapy (Walther et al., 2002). A study from M.D. Anderson Cancer Centre reported similar results with regard to neoadjuvant chemotherapy but not with adjuvant chemotherapy (Siefker-Radtke et al., 2004). Of the 88 patients 46 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 5 years. For patients receiving preoperative chemotherapy median CSS had not been reached, although CSS at 5-years was 78% with no

cancer related deaths observed beyond 2 years. Notably 7 of 25 patients treated with initial cystectomy received chemotherapy after surgery, but their survival was no better than those treated with cystectomy alone. As others have observed, the pathological stage was higher than clinically appreciated for 56% of patients treated with initial cystectomy. There were no cancer related deaths among patients with disease that was downstaged to pT2 or less. Other studies, however, have shown no survival benefit between cystectomy and multi-modal therapy. Cheng et al. reported no survival benefit in 64 cases of SCC in those undergoing cystectomy alone compared with multi-modal treatment (Cheng et al., 2004). 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 retrospective report from the Mayo Clinic advocates surgery alone in patients with surgically resectable tumours, especially for those with muscle-invasive tumours (pT2N0M0) (Choong et al., 2005). Although it is not clear how many patients were upstaged at surgery, of 12 patients with pT2N0M0 small-cell urothelial cancer, the 3-year OS rate was 63.6%. However, half of these patients experienced relapse. The Mayo Clinic results are also in marked contrast to another retrospective study that suggests an approximately 25% 3-year survival rate in 30 patients with organ-confined disease (≤ pT2N0M0). In a study of 106 cases of SCC bladder cancer, only cisplatin chemotherapy predicted survival on multivariate analysis (Mackay et al., 1998). Initial stage was not independently associated with survival, which strongly suggests that micrometastatic disease is usually present at presentation in clinically localised tumours and systemic metastases are the major cause of mortality. In the most recent study, 4 cycles of neoadjuvant chemotherapy were given to small-cell urothelial cancer in a phase II trial (Sifker-Radtke 2009). 18 patients with surgical resectable cancer received neoadjuvant treatment with a median survival of 58 months, 13 are still cancer free and alive. Pathologic downstaging was quite frequent, with an improved survival in those downstaged to ≤ pT2N0M0. The largest impact on survival seemed to be in patients with muscle-invasive bladder cancer.

In the absence of a large comparative trial, definitive conclusions cannot be drawn regarding the best multi-modality strategy for the treatment of neuroendocrine carcinoma of the bladder. Currently available literature suggests that local therapy with surgery or radiotherapy alone is not optimal, and that integrating chemotherapy can improve long-term disease control. Recent results suggest that neoadjuvant chemotherapy followed by localised therapy to the pelvis may be the optimal strategy. Whether radiation or cystectomy provides optimal local consolidation is not currently known.

5. Neuroendocrine carcinoma of the prostate

5.1 Background

Prostate cancer is one of the most common types of extra-pulmonary small-cell carcinoma, accounting for 10% of all EP-NEC (Asmis et al., 2006). Pure SCC is rare at initial presentation, accounting for less than two percent of all prostate malignancies. Small cell carcinoma prostatic disease has a worse prognosis than SCC bladder disease (Mackey et al., 1998). Three patterns of small-cell carcinoma are known: one third present as pure small-cell carcinoma; one fifth of cases present with combined adenocarcinoma; and approximately half present as recurrence of small-cell carcinoma from conventional adenocarcinoma. Many

prostatic adenocarcinomas show areas of focal neuroendocrine differentiation, and many extrapulmonary small-cell carcinomas of the prostate are associated with an adenocarcinoma component. In patients with mixed prostate cancer that has metastasised, it is often unclear whether the metastatic disease is of the adenocarcinoma component, the SCC component or both since biopsies of metastatic lesions are typically not done. Because this type of prostate cancer essentially has two tumor types, it may be beneficial to biopsy any atypical metastatic lesion. Clinically, prostate cancer with SCC component act differently from pure adenocarcinoma. Typical features of a mixed tumor type include; elevated neuroendocrine markers such as serum chromogranin A, low to normal PSA, early disease progression, resistance to androgen deprivation and high-grade disease. Small-cell carcinomas of the prostate do not express androgen receptors. These features warrant aggressive multi-modal therapy. Small-cell neuroendocrine carcinoma of the prostate is a highly aggressive tumor, presenting early metastasis to soft tissues and bone without a commensurate with serum PSA level.

5.2 Neoadjuvant chemotherapy

For patients with mixed adenocarcinoma/SCC prostate cancer, the standard treatment regimen includes hormonal therapy in combination with systemic etoposide/cisplatin chemotherapy. Whether chemotherapy is effective for long term survival for patients with small cell prostate carcinoma is controversial. Vinblastine, doxorubicin, and cyclophosphamide, or platinum (cisplatin or carboplatin) compound-based regimens combined with etoposide, or etoposide and doxorubicin, are recommended for the initial treatment. Therapy usually results in a 60% response rate, median survival is approximately one-year whereas long-term survival is rare (Amato et al., 1992, Palmgren et al., 2007). Immediate chemotherapy with or without hormonal therapy for both pure SCC and mixed adenocarcinoma of the prostate resulted in longer clinical remissions in retrospective study, although none survived (Moore et al., 1992). In a single centre study performed at M.D. Anderson Cancer Centre with 83 patients, 26 had no evidence of metastatic disease at the time of diagnosis (Spiess et al., 2007). 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 (6 patients) or with surgery and ADT (3 patients). The use of systemic chemotherapy was not found to be a predictor of PFS and disease-free survival in this study, because the majority of patients (92%) received it as initial therapy. In a retrospective study of 60 SCC prostate cancer patients, primary surgical therapy was the only parameter that predicted survival on univariate analysis (Mackey et al., 1998). In contrast to bladder SCC, no benefit of chemotherapy was found for prostate primary tumours. Within the framework of the Rare Cancer Network Study, 30 patients suffering from small-cell neuroendocrine prostate cancer were examined, either in an early/localised or an advanced/metastatic stage (Stein et al., 2008). Patients were treated with cisplatin-based chemotherapy, with or without pelvic radiotherapy. Two patients with early disease achieved complete remission for a duration of 19 and 22 months. Twenty-five patients succumbed to massive local and/or distant failure. Despite initial response, the common cisplatin-based chemotherapy plus radiotherapy failed to improve outcome markedly.

In conclusion, for localised non-metastatic small-cell neuroendocrine prostate, initial therapy with platinum-based chemotherapy is usually recommended, but the long term benefit is uncertain.

6. Neuroendocrine carcinoma of the breast

6.1 Background

Neuroendocrine carcinoma of the breast is one of the least common types of breast cancer with data consisting of only case reports in the literature. All the tumours described showed morphological and immunohistochemical similarities to the breast metastases of pulmonary small cell carcinoma, the most distinguishing feature are the absence of primary small-cell cancer elsewhere. In 2003, the World Health Organization (WHO) recommended classification of these tumours into three histologic types: solid, small-cell, and large-cell neuroendocrine carcinoma (Tavassoli et al., 2003). Seventy-four patients with NEC of the breast who were treated at M. D. Anderson Cancer Center were recently analysed. NEC showed a more aggressive course than invasive ductal carcinoma, with a higher propensity for local and distant recurrence and poorer overall survival (Wei et al., 2010). No standard treatment protocol has been defined with certainty due to the small number of cases. Modified radical mastectomy with axillary lymph node dissection seems to be the treatment of choice, with adjuvant radiation, chemotherapy or both, based on the clinical stage and presence of metastasis. Data suggest using different chemotherapy schedules than ordinary used in breast cancer treatment. Most studies show that the SCNEC of breast is a very aggressive neoplasm and has in general a worse prognosis than the usual ductal types, but may have a good prognosis depending on the initial stage of the disease (Wei et al., 2010).

6.2 Neoadjuvant chemotherapy

There are case reports on the use of neoadjuvant chemotherapy for SCC of the breast and one patient with a complete response after cisplatin and etoposide treatment (Mirza & Shahab, 2007). Treatment and outcome information for 60 patients with NEC of the breast at M. D. Anderson Cancer Center show that among 14 patients who received cisplatin-based neoadjuvant chemotherapy only 1 patient had recurrence of disease (Wei et al., 2010). Among the other 46 patients where 38 received postoperative chemotherapy, 18 patients had a recurrence of disease indicating that neoadjuvant chemotherapy might be superior to postoperative treatment.

7. Conclusion

In the absence of large comparative trials, definitive conclusions cannot be drawn regarding the best multi-modality strategy for the treatment of EP-NEC. Currently available literature suggests that local therapy with surgery or radiotherapy alone is not optimal and that integrating platinum-based chemotherapy can improve long-term disease control and survival. Most data support that patients presenting with limited disease EP-NEC of the GI, bladder, breast and uterine cervix should be treated with systemic platinum based chemotherapy combined with local treatment consisting of radiotherapy, surgery or both. The sequence at which both therapeutic modalities should be used has not been proven yet, but recent results for NEC in bladder and breast indicate that neoadjuvant chemotherapy

might be superior to postoperative treatment. Secondary surgery can be considered after neoadjuvant chemotherapy in highly selected patients with metastatic disease.

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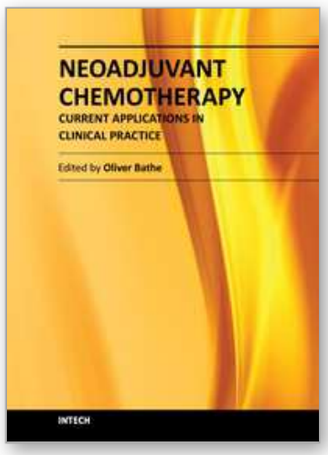

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