Cancer of unknown primary: biological and clinical characteristics

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**Introduction**

In the early 1970s some researchers argued that a diagnosis of carcinoma of unknown primary (CUP) could only be made if the primary tumor was not found at autopsy. Today, the definition of CUP includes patients who present with histologically confirmed metastatic cancer in whom a detailed medical history, a complete physical examination, including a pelvic and rectal examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, computed tomography of abdomen and pelvis, and in certain cases mammography, fail to identify the primary site [1–2].

**Epidemiology**

Data from epidemiology surveys and large registries indicate that CUP constitutes 2.3–4.2% of all human cancers. The annual age-adjusted incidence is 7–12 cases per 100000 population per year in the USA and 18–19 cases per 100000 population per year in Australia. In The Netherlands, almost 2500 new patients are diagnosed annually giving an age-standardized incidence rate of 6.7 per 100000 for males and 5.3 per 100000 for females. Carcinoma of unknown primary therefore represents the seventh to eighth most frequent type of cancer and the fourth most common cause of cancer death in both males and females. It is considered to be more common than non-Hodgkin’s lymphoma [3–5].

**Pathology**

Cancers of unknown primary are categorized into four major subtypes by routine light microscopy criteria: (i) adenocarcinomas well–moderately differentiated; (ii) undifferentiated or poorly differentiated adenocarcinomas; (iii) squamous cell carcinomas; and (iv) undifferentiated neoplasms.

About half of the patients will be diagnosed with metastatic adenocarcinoma, 30% will have undifferentiated or poorly differentiated carcinomas, 15% squamous cell carcinomas and the remaining 10% will have undifferentiated neoplasms. With modern immunohistochemistry, most of the tumors in the latter group can be better characterized, and can include poorly differentiated carcinomas, neuroendocrine tumors, lymphomas, germ-cell tumors, melanomas, sarcomas and embryonal malignancies [6].

**Clinical presentation**

**Natural history**

Early dissemination, clinical absence of primary tumor, unpredictability of metastatic pattern and aggressiveness constitute the fundamental characteristics of these tumors. Early dissemination is reflected in the clinical absence of symptoms related to a primary tumor.

More than 50% of CUP patients present with multiple sites of involvement, while the rest have a single site, most commonly in liver, bone, lung or lymph nodes [7]. The clinicopathological entities of CUP are listed in Table 1.

**Metastatic CUP primarily to the liver or to multiple sites**

Patients with mainly liver metastases represent one of the most frequent subgroup accounting for ~25% of the total CUP population. Adenocarcinoma of moderately to poorly differentiated or undifferentiated type are the most common histological types. The prognosis of this subset is poor with a median survival of 6–9 months. However, cases with hepatic metastases carrying neuroendocrine features have better response to treatment and longer survival [6–8].

**Metastatic CUP to lymph nodes**

**Mediastinal–retroperitoneal nodal involvement**

Patients who present with CUP affecting predominantly mediastinal or retroperitoneal areas are sometimes referred to as having the ‘extragonadal germ-cell syndrome’. It affects mainly males who are <50 years of age and is clinically characterized by metastatic disease of a midline distribution, usually involving mediastinal and retroperitoneal lymph nodes and/or pulmonary lesions. Histopathologically, these patients carry a diagnosis of undifferentiated or poorly differentiated carcinoma [9].

**Isolated axillary nodal involvement**

Most patients presenting with lymph node metastases isolated to one axillary area are female and should be suspected of having stage II breast cancer. Median age is 52 years (range 21–80). Histopathological examination usually reveals an invasive ductal adenocarcinoma of grade III, while estrogen or progesterone receptors are positive in 20–30% of cases. Seventy per cent of patients have N1 disease; only 5% of cases present with disseminated disease at diagnosis [10, 11].
Cervical nodal involvement

Cervical nodal metastases from clinically undetectable primary squamous cell carcinoma accounts for 1–2% of head–neck malignancies. With locoregional treatment these patients can achieve a considerable prolongation of survival. Patients with supraclavicular lymphadenopathy, which histologically are either of squamous cell or undifferentiated carcinoma origin, have a worse prognosis. 2-[Fluorine-18]fluoro-2-deoxy-D-glucose (FDG)- positron emission tomography (PET) is sometimes useful in localizing a primary tumor in the head–neck area [12].

Inguinal nodal involvement

This is an uncommon subset, and the most common histology is that of undifferentiated (anaplastic) carcinoma. Squamous carcinoma or mixed squamous/adenocarcinoma can also be found. Examination of the anorectal region, a meticulous gynecological examination and probably cystoscopy are necessary investigations for these patients. Lymphomas and metastatic or amelanotic melanomas of unknown primary site should also be ruled out [13].

Metastatic CUP of peritoneal cavity

Peritoneal carcinomatosis in females

These are usually female patients with a median age of 60 years, who present with ascites and peritoneal masses and with no evidence of a primary tumor in the ovaries. This syndrome has also been termed ‘multifocal extraovarian serous carcinoma’ or ‘peritoneal papillary serous carcinoma’. Diagnosis is usually made by exploratory laparotomy. Biopsies from peritoneal deposits frequently show papillary serous adenocarcinoma with or without psammoma bodies. Serum CA 125 levels are usually elevated [14].

Some patients have non-papillary tumors, and are as likely to be male as female. In those with mucin-producing adenocarcinoma often with signet ring cells, a gastrointestinal origin should be suspected. The tumors in these patients in general are not as responsive to chemotherapy as the papillary serous adenocarcinomas [15].

Metastatic CUP to the lungs

Parenchymal metastases (pulmonary nodules)

These patients present with multiple bilateral lung lesions and with a histological diagnosis of adenocarcinoma of various differentiation. The prognosis is poor for most patients. Young male patients with possible extragonadal germ-cell cancer should be carefully distinguished from this group of patients [1, 6, 7].

Isolated malignant pleural effusion

Malignant pleural effusion is not uncommon in patients with CUP; however, in a small group it can be the only area of demonstrable involvement. The primary cancer remains unknown in about 7% of all cases of metastatic carcinomatous pleurisy. Adenocarcinoma is the main histopathological type; primary sites in the lung, breast or ovary should be excluded. Mesothelioma should also be included in the differential diagnosis. In general, the outcome of this subset carries a poor prognosis [1, 6, 7].
Metastatic CUP to the bones

Almost one-quarter of CUP patients present with bone symptoms due to metastases, although bone scintigraphy is positive in >50% of these patients. Bony metastases may manifest as multiple lesions or as a single metastatic site. Adenocarcinoma is the most frequent histological diagnosis. Prostate cancer and breast cancer should be suspected in male and female patients, respectively [16].

Metastatic CUP to the brain

This subset is diagnosed with either a solitary lesion or with multiple metastases. Up to 15% of all patients with CNS metastases will have no clearly identified primary site despite an intensive investigation. These patients primarily present with neurological dysfunction. Histopathologically, they are most frequently metastatic adenocarcinoma or metastatic squamous cell carcinoma. Patients with solitary lesions are candidates for surgery and have a better survival [17].

Metastatic neuroendocrine carcinomas of unknown primary

Three different clinicopathological subsets of neuroendocrine tumors have been described: (i) low-grade neuroendocrine carcinomas (e.g. metastatic well-differentiated carcinoid or islet-cell tumors), which usually involve the liver; (ii) small cell anaplastic carcinoma, with histological appearance and clinical behaviour similar to small-cell lung cancer or extrapulmonary small cell carcinoma; and (iii) the 'poorly differentiated carcinomas' or 'poorly differentiated adenocarcinomas' of unknown primary with neuroendocrine features [1, 6, 7, 18].

Diagnostic evaluation

Role of the pathologist

Light microscopy

Light microscopic examination is rarely successful in identifying the site of origin in patients with CUP. Light microscopy can basically characterize cell morphology and tumor differentiation.

Immunohistochemistry

Immunohistochemical studies sometimes result in the identification of tumor origin, especially if the metastases are poorly differentiated by light microscopy. Several cell components can be identified by a series of monoclonal or polyclonal immunoperoxidase antibodies including enzymes, structural tissue components, hormonal receptors, hormones, oncofetal antigens or other substances [6] (Table 2).

The development of monoclonal antibodies against various cytokeratin (CK) polypeptides has opened new avenues in investigating the normal and cancerous epithelial cells. Among them, CK7 and CK20 have been extensively studied in solid tumors. CK20 appears to be very useful in diagnosing gastrointestinal adenocarcinomas, while CK7 is more common in respiratory or gynecological malignancies [1].

Electron microscopy

Electron microscopy is not widely available, is relatively expensive and can only be recommended for the evaluation of certain poorly differentiated neoplasms. It could be useful in distinguishing lymphoma from carcinoma, adenocarcinoma from squamous cell carcinoma (desmosomes, prekeratin filaments) and in identifying neuroendocrine tumors (neurosecretory granules), melanomas (premelanosomes) or poorly differentiated sarcomas [6].

Molecular diagnostics

Conventional or molecular cytogenetics are of limited use in identifying the origin of the primary tumor, since only a few tumor-specific chromosomal abnormalities have been identified. An isochromosome of the short arm of chromosome 12 i(12p) or a deletion in 12p is an abnormality characteristic of testicular carcinoma and other germ-cell tumors. Other chromosomal abnormalities have been found in several carcinomas, lymphomas or sarcomas such as translocation t[11; 22] [q24; q12] in PNET and Ewing’s sarcoma, t[8; 14] [q24; q32] in non-Hodgkin’s lymphomas, t[3; 13] in alveolar rhabdomyosarcoma or 3p deletion in small-cell lung carcinoma [19].

Role of the radiologist

Conventional radiology

A routine chest radiograph has always been a part of the initial evaluation of the patient with CUP. However, based on autopsy studies, chest X-rays were able to differentiate between primary and secondary malignancy in the lungs in only one third of cases. Barium enemas are of very limited value and therefore are not recommended at all [20].
Computed tomography

Computed tomographic scanning of the abdomen and pelvis results in the detection of a primary site in 30–35% of patients. Computed tomography of the chest has not been adequately evaluated. Computed tomography can also determine the extent of metastatic disease and may provide guidance in selecting the optimal site for biopsy [21].

Mammography and other breast imaging tests

Mammography has been proposed in women with metastatic adenocarcinoma involving axillary lymph nodes, although its sensitivity is still around 20%. In a case of strong suspicion of a primary breast tumor and if mammogram and/or ultrasound are not contributory, a magnetic resonance imaging (MRI) scan may be requested [22, 23].

Role of the endoscopist

Endoscopic examination should be used to evaluate CUP patients with specific clinical presentations. Therefore, ENT endoscopy is recommended in patients with isolated cervical node involvement, fiberoptic bronchoscopy is advisable in patients with thoracic indications or pulmonary symptoms, gastrointestinal endoscopies in patients with abdominal symptoms or occult blood in the stool, and proctoscopy and/or colposcopy in patients with inguinal lymph node involvement [1, 7].

Serum tumor markers

Patients with CUP should have serum human chorionic gonadotropin β (β-HCG), α-fetoprotein (AFP) and prostate-specific antigen (PSA) tested (in men) to exclude treatable extragonadal germ-cell tumors and to identify metastatic prostate cancer amenable to endocrine treatment. High levels of serum thyroglobulin in CUP patients with bone metastases suggest an occult thyroid cancer. Serum CA 15-3 and CA 125 could be of some help, i.e. in isolated axillary node adenocarcinomas and in peritoneal papillary adenocarcinomatosis, respectively. In all other cases, routine evaluation of commonly used epithelial serum tumor markers [carcinoembryonic antigen (CEA), CA 19-9, CA 15-3, CA 125] has no proven prognostic or diagnostic value, and non-specific elevations of multiple markers occurs in the majority of CUP patients [25, 26].

How often can the primary site be identified?

Even with an extensive diagnostic work-up using modern pathological and imaging procedures, the frequency of detection of the primary tumor site remains low. Less than 20% of patients have a primary site identified antemortem, while from necropsy data it was found that almost 70% of autopsied cases remained undiagnosed. Post-mortem detection of a primary site may be higher in patients with well-differentiated adenocarcinomas [1, 7].

Ultimately, primary sites are most frequently detected in the lung and pancreas, followed by other gastrointestinal and gynecological malignancies.

Prognostic and predictive factors

In general, it appears that patients with CUP have a limited life expectancy with a median survival of ~6–9 months. However, some subsets have a better prognosis and enjoy longer survival. Analyses of prognostic and predictive factors in CUP have examined several clinicopathological parameters. Several positive and negative prognostic and predictive factors were detected, which helped to define several favorable and unfavorable groups of CUP patients. The proposed favorable and unfavorable subsets are listed in Table 3.

Therapeutic management

The oncologist should recognize whether the patient belongs to any of the favorable or unfavorable groups prior to recommending the appropriate therapy. During the last 40 years almost all cytotoxic drugs have been used either as single agents or in combination regimens.

Tables 4 and 5 summarize the results of the major prospective studies using platinum-based or taxane/platinum-containing regimens.

Table 3. Favorable and unfavorable subsets of cancer of unknown primary (CUP)

<table>
<thead>
<tr>
<th>Favorable subsets</th>
<th>Unfavorable subsets</th>
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<tbody>
<tr>
<td>Poorly differentiated carcinoma with midline distribution (extragonadal germ-cell syndrome)</td>
<td>Adenocarcinoma metastatic to the liver or other organs</td>
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<tr>
<td>Women with papillary adenocarcinoma of peritoneal cavity</td>
<td>Non-papillary malignant ascites (adenocarcinoma)</td>
</tr>
<tr>
<td>Women with adenocarcinoma involving only axillary lymph nodes</td>
<td>Multiple cerebral metastases (adeno or squamous carcinoma)</td>
</tr>
<tr>
<td>Squamous cell carcinoma involving cervical lymph nodes</td>
<td>Multiple lung/pleural metastases (adenocarcinoma)</td>
</tr>
<tr>
<td>Isolated inguinal adenopathy (squamous carcinoma)</td>
<td>Multiple metastatic bone disease (adenocarcinoma)</td>
</tr>
<tr>
<td>Poorly differentiated neuroendocrine carcinomas</td>
<td>Men with blastic bone metastases and elevated PSA (adenocarcinoma)</td>
</tr>
<tr>
<td>Patients with a single, small, potentially resectable tumor</td>
<td>PSA, prostate-specific antigen.</td>
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Treatment of favorable subsets

Poorly differentiated carcinoma with midline distribution (extra gonadal germ-cell syndrome)

This subset of CUP should be treated according to guidelines for poor prognosis germ-cell tumors, using platinum-based combination chemotherapy. Overall response rates are >50%, with 15–25% complete responders and around 10–15% long-term disease-free survivors [28, 31].

Women with adenocarcinoma involving only axillary lymph nodes

Generally, the management of these patients resembles that of stage II or III breast cancer patients. Patients with N1 disease should undergo axillary clearance followed by either simple mastectomy or breast irradiation. Adjuvant chemotherapy in premenopausal women followed by tamoxifen administration in estrogen receptor-positive patients is suggested. No adequate information is available for adjuvant chemotherapy in postmenopausal patients apart from tamoxifen treatment in estrogen receptor-positive cases. However, it seems reasonable in these patients to follow guidelines for adjuvant treatment of stage II breast cancer. In patients with N2 disease preoperative chemotherapy is recommended, following guidelines for stage III breast cancer. However, in non-responding tumors or in elderly patients radical irradiation should be the treatment of choice. Estrogen receptor-positive patients should continue with tamoxifen treatment. The 5-year and 10-year overall survival rates are 75% and 60%, respectively [10, 11].

Table 4. Prospective studies in cancer of unknown primary (CUP) patients using platinum-based chemotherapy

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Regimen</th>
<th>No. of patients</th>
<th>Response rate (%)</th>
<th>Survival [median (months)]</th>
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<tr>
<td>Platinum-based combinations</td>
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<tr>
<td>Jadeja et al., 1983 [27]</td>
<td>FACP</td>
<td>23</td>
<td>17</td>
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<td>Greco et al., 1986 [28]</td>
<td>PVeB</td>
<td>56</td>
<td>57</td>
<td>16*</td>
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<tr>
<td>Milliken et al., 1987 [29]</td>
<td>PVeB</td>
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<td>5</td>
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<tr>
<td>Van der Gaast et al., 1990 [31]</td>
<td>PEB</td>
<td>34</td>
<td>79</td>
<td>8*</td>
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<tr>
<td>Raber et al., 1991 [32]</td>
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<td>36</td>
<td>22</td>
<td>11</td>
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<tr>
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<td>25</td>
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<tr>
<td>Gill et al., 1991 [34]</td>
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<td>16</td>
<td>19</td>
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<tr>
<td>Wagener et al., 1991 [35]</td>
<td>P</td>
<td>21</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Falkson and Cohen, 1998 [36]</td>
<td>PMiEp</td>
<td>40</td>
<td>50</td>
<td>9.4</td>
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<tr>
<td>Warner et al., 1998 [37]</td>
<td>CbE</td>
<td>26</td>
<td>23</td>
<td>5.6</td>
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<tr>
<td>Briassouli et al., 1998 [38]</td>
<td>CbEpE</td>
<td>62</td>
<td>37</td>
<td>10</td>
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<tr>
<td>Lofts et al., 1999 [39]</td>
<td>PF</td>
<td>44</td>
<td>27</td>
<td>–</td>
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<tr>
<td>Voog et al., 2000 [40]</td>
<td>PE</td>
<td>23</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>Guardiola et al., 2001 [41]</td>
<td>PAC</td>
<td>22</td>
<td>50</td>
<td>10.7</td>
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<tr>
<td>Saghatchian et al., 2001 [42]</td>
<td>PE→BI</td>
<td>30</td>
<td>40</td>
<td>9.4</td>
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<tr>
<td>Macdonald et al., 2002 [43]</td>
<td>PMiF</td>
<td>18</td>
<td>44</td>
<td>16.1*</td>
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<tr>
<td>Lortholary et al., 2002 [44]</td>
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<td>27</td>
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<tr>
<td>Voog et al., 2000 [40]</td>
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<tr>
<td>Lortholary et al., 2002 [44]</td>
<td>PG</td>
<td>31</td>
<td>27</td>
<td>7.7</td>
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*Poorly differentiated carcinoma (PDC) midline distribution; b1-year survival.
A, adriamycin; B, bleomycin; C, cyclophosphamide; Cb, carboplatin; E, etoposide; Ep, epirubicin; F, fluorouracil; G, gemcitabine; H, hexamethylenamine; L, leucovorin; M, mitomycin C; I, ifosfamide; Ig, interferon-α; Ig, irinotecan; P, cisplatinum; Ve, vinblastine; PDC, poorly differentiated carcinoma.
Squamous cell carcinoma involving cervical lymph nodes

The treatment of this subset of patients should follow guidelines for locally advanced head and neck cancer. Locoregional management is the primary recommended treatment. The 5-year survival rates range from 35% to 50%, with documented long-term disease-free survivors. Although experience remains limited in this CUP subset, the emerging superiority of concurrent chemotherapy/radiation for patients with locally advanced head/neck tumors suggests a benefit for this strategy, particularly in patients with N2 or N3 adenopathy [12].

Isolated inguinal lymphadenopathy from squamous cell carcinoma

Inguinal node dissection with or without local radiotherapy is the recommended treatment for this subset of patients. Long-term survival following definitive local therapy has been reported in a minority of patients [6, 13]. The role of systemic chemotherapy has not been evaluated in these patients.

Poorly differentiated neuroendocrine carcinomas

Many poorly differentiated neuroendocrine carcinomas are highly sensitive to chemotherapy. In recent studies, the response rates to platinum-based or to paclitaxel/carboplatin-based chemotherapy were reported as high as 50–70%, with >25% complete responses and 10–15% long-term survivors [6, 9, 18].

Men with blastic bone metastases and elevated PSA from an adenocarcinoma

It has been reported that endocrine treatment often produces responses in this subset of CUP patients. Therefore, these patients should be considered as having metastatic prostate cancer and hormonal therapy should be recommended as the initial treatment of choice [6].

Table 5. Prospective studies in cancer of unknown primary (CUP) patients using taxane/platinum-based chemotherapy

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Regimen</th>
<th>No. of patients</th>
<th>Response rate (%)</th>
<th>Survival [median (months)]</th>
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<td>Paclitaxel-based</td>
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<tr>
<td>Greco et al., 2000 [45]</td>
<td>P₃C₆E</td>
<td>71</td>
<td>48</td>
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<tr>
<td>Briasoulis et al., 2000 [46]</td>
<td>P₃C₆b</td>
<td>77</td>
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<td>Dowell et al., 2001 [47]</td>
<td>C₆E</td>
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<tr>
<td></td>
<td>P₃FL</td>
<td></td>
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<td>6.4</td>
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<tr>
<td>Greco et al., 2002 [48]</td>
<td>P₃C₆G</td>
<td>120</td>
<td>25</td>
<td>9</td>
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<tr>
<td>Gothelf et al., 2002 [49]</td>
<td>P₃PG</td>
<td>29</td>
<td>50</td>
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<tr>
<td>Docetaxel-based</td>
<td></td>
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<tr>
<td>Greco et al., 2002 [50]</td>
<td>D₅P</td>
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<tr>
<td></td>
<td>D₅Cb</td>
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<td>22</td>
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<tr>
<td>Darby et al., 2001 [52]</td>
<td>D₅</td>
<td>29</td>
<td>7</td>
<td>6</td>
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</table>

C₆, carboplatin; D₅, docetaxel; F, fluorouracil; G, gemcitabine; L, leucovorin; P, cisplatinum; P₃, paclitaxel.
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