Narrative review on serous primary peritoneal carcinoma of unknown primary site: four questions to be answered

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Abstract: Serous peritoneal papillary carcinoma (SPPC) represents a particular cancer of unknown primary (CUP) entity that arises in the peritoneal surface lining the abdomen and pelvis without a discriminative primary tumor site. In this review, we discuss the validity of SPPC as a distinct entity. Clinically, patients with SPPC are older, have higher parity and later menarche, are more often obese and probably have poorer survival compared to those with primary ovarian cancer. Pathologically, SPPC is more anaplastic and multifocal, unlike primary ovarian cancer which is commonly unifocal. Biologically, it presents a higher expression of proliferative signals and similar cell cycle and DNA repair protein expression. These differences hint towards SPPC and primary ovarian cancer being as a spectrum of disease. Patients with SPPC are traditionally managed similarly to stage III–IV ovarian cancer. The recommended approach integrates aggressive cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, and systemic chemotherapy to remove the macroscopic tumor, eradicate the microscopic residual disease, and control the microscopic metastasis. However, the available evidence lacks proper randomized or prospective studies on SPPC and is limited to retrospective series. The diligent identification of SPPC is warranted to design specific clinical trials that eventually evaluate the impact of the new therapeutics on this distinct entity.

Keywords: Serous papillary carcinoma; peritoneum; peritoneal carcinomatosis; cancer of unknown primary (CUP)

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Introduction

Cancer of unknown primary (CUP) represents a heterogeneous syndrome of metastatic tumors for which a thorough workup fails to identify the primary site (1). The diagnostic advances have let to better identification of the culprit tumor which decreased the incidence of CUP from around 3–5% in the 1990s to 1–2% in the current era. However, this did not translate into a survival benefit as the patient outcomes do not differ between empiric and site-specific therapy (2,3). To date, patients with CUP are managed according to their clinicopathologic characteristics (4). The majority of patients (80–85%) have an unfavorable prognosis with a dismal survival of 3–6 months despite aggressive chemotherapy. On the other hand, the minority of patients (15–20%) which can be assigned to potential primary tumors have a favorable prognosis with a median survival of 10–16 months (4).

Serous papillary peritoneal cancer of unknown primary (SPPC) is a particular CUP entity that arises in the peritoneal surface lining the abdomen and pelvis without a discriminative primary tumor site. Autopsy studies estimate the incidence of SPPC around 1 case per 150,000 women.
per year and recent studies show an age-adjusted incidence rate of 0.68 per 100,000 (5,6). It was first described by Swerdow seventy-years ago in a patient that presented peritoneal carcinomatosis without any evidence of a primary tumor site (7). Patients with SPPC have a similar clinical presentation, histological features, and pattern of spread to those with primary ovarian cancer (8,9). In this review, we aim to review the validity of SPPC as a single entity as well as its biology, diagnosis, and treatment.

Materials and methods

We searched PUBMED and MEDLINE for articles published in the English language using the following keywords: (serous papillary peritoneal cancer or carcinomatosis or tumor) or (extraovarian serous papillary cancer) or (serous papillary peritoneal carcinomatosis of unknown primary or unknown primary peritoneal cancer or carcinomatosis). We have also looked up “Peritoneal Neoplasms” (Mesh) published between 2010 and 2020. Relevant articles were assessed by two reviewers (ER and TA) for their title and abstract. The bibliography of the selected articles was also reviewed to identify studies that were missed in the initial database search. Data on clinical presentation, clinicopathology, molecular biology, management and outcome were extracted, summarized and tabulated.

Results

Question 1: does SPPC represent a single entity?

A delicate question is whether SPPC arises from the gynecologic tract similarly to primary ovarian cancer and tubal carcinomas. In 1982, Tobacman et al. reported the case of three women with SPPC occurring after prophylactic oophorectomy in the setting of a family history of ovarian cancer (10). Thus, the hypothesis supporting an exclusive origin of SPPC arising from the ovaries becomes arguable. Available data have shown that SPPC occurs more commonly in women undergoing prophylactic oophorectomy (8%) in comparison to those who have also had the fallopian tubes removed (5%) (11,12).

Primary ovarian cancer and SPPC are commonly approached as a single disease and the lack of a culprit tumor is attributed to incomplete diagnostics and uncertainty in classifying a lesion as either primary or metastasis. CUP experts do not fare better with this approach and consider primary ovarian cancer and SPPC as two separate entities. Fifteen percent of patients considered to have primary ovarian cancer in truth suffer instead of SPPC (8,9). The histopathological classification of high-grade serous carcinoma corresponding to the gene expression subtypes identified categorized primary ovarian tumors into mesenchymal transition in 34%, immune reactive in 32%, solid and proliferative in 25%, and papilla-glandular in 9%. On the other hand, SPPC is commonly assigned to the mesenchymal transition type in 75% and lack immune reactive patterns (13).

As reviewed by Sørensen et al., patients with SPPC typically share subtle clinical features that differ from those with primary ovarian cancer. Patients with SPPC may be older, have higher parity, later menarche and are more often obese (14,15). Its metastatic spread is intriguingly distinct with a high frequency of multifocal metastatic sites with diffuse micronodular involvement of the upper abdomen and diaphragmatic surfaces. The underlying different patterns of allelic loss, p53 gene mutation, and X-chromosome inactivation at different metastatic sites within the same patient support the multifocality of SPPC (16-18).

New insights into the differences in the molecular biology of SPPC and primary ovarian cancer may be accounted for the distinct natural history of the two entities. In comparison to primary ovarian cancer, SPPC has higher expression of HER2 (34–59% vs. 9–36%) (19-21) which parallels a higher proliferation index Ki-67 (38% vs. 28%) (20). It presents a lower expression of estrogen receptors (31% vs. 73%) and progesterone receptors (46% vs. 91%) (20) as well as a lower frequency of loss of heterozygosity (22). Last, it presents a similar expression level of p53 and BCL2 expression as well as microvessel density (19-21,23) and microRNA profiles (24). As such, according to this molecular pattern, SPPC and primary ovarian cancer appear to display two entities of a spectrum of disease rather than being completely distinct cancers.

Question 2: is the biology of SPPC different from that of primary ovarian cancer?

The carcinogenesis of CUP implies a clonal proliferation of normal cells acquiring multiple interdependent alterations in the cellular pathways (Table 1). Two hypotheses underlying differences in the origin and the genetic/epigenetic alterations harbored by the malignant clone are suggested to explain the carcinogenesis of SPPC.
Multifocal SPPC seems to arise from any structure that embryologically derives from the Müllerian ducts, which are in close proximity to the peritoneum (29). On the other hand, unifocal SPPC supposes that the coelomic epithelium undergoes Müllerian metaplasia, namely serous tubal intraepithelial carcinoma which is encountered in 45–56% of SPPC (30-32), low grade and borderline tumors (33), as a necessary precursor step to malignant transformation. Thereafter, tumor cells migrate to the peritoneum either via the sloughed tubal cancer cells which disseminate into the peritoneal cavity or hematogenous spread with a predilection for implantation in the omentum (34). This dissemination may occur before local tumor growth according to two scenarios (35). In the first scenario which is characterized by independent genetic alterations between the primary tumor and metastatic sites (36), tumor cells alter their microenvironment and metastasize before generating a detectable tumor (37,38). In the second scenario which considers a clonal relationship between the primary and metastatic sites (39), the tumor microenvironment selectively abrogates the clonal proliferation at the primary site and favors the outgrowth of tumor cells at the metastatic sites (40,41).

**Question 3: what are the diagnostic criteria in favor of SPPC?**

Patients with SPPC are commonly women with a median age of 55–65 years at the time of diagnosis (42). BRCA1/2 germline mutations have been reported in 15.8–40.9% (42-46) and are commonly associated with a higher prevalence of a multifocal tumor (18). For patients with germline BRCA mutations, the lifetime risk of SPPC is 1.3% (44,47). Prophylactic bilateral salpingo-oophorectomy does not seem to reduce the risk of SPPC which may occur at intervals reaching 12–84 months (44,47). Patients commonly present symptoms of peritoneal carcinomatosis such as abdominal distention and non-specific abdominal pain. It is often associated with visceral metastases that vary according to the primary tumor, disease stage, and histology (8). Sixty percent of patients with peritoneal carcinomatosis present deposits of serous papillary or poorly differentiated adenocarcinomatous histology which constitute the majority of malignant tumors arising from the ovary or fallopian tube (48). Table 2 summarizes the different diagnostic criteria suggested for the diagnosis of SPPC. The criteria of the Gynecologic Oncology Group published in 1993 are the most widely accepted and have not been revisited in the modern era (51,54). Patients with SPPC usually undergo an extensive diagnostic workup that exceeds the minimum requirements of the ESMO recommendations which consist of basic blood tests and computed tomography scans of thorax, abdomen, and pelvis (1,4). The serum level of CA-125 does not have any significant predictive or prognostic value but can be used if the levels are initially elevated (55). Gastroscopies, colonoscopies and PET-CT scans are almost routinely performed in every single patient although they are not even recommended in the ESMO guidelines. Notably, PET-CT scan usually reveals ascites, peritoneal nodules, and omental thickening, nodularity and caking, but seldom identifies the origin of the tumor (56).

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### Table 1: Summary of the published literature reporting on the hallmarks of SPPC.

<table>
<thead>
<tr>
<th>Hallmarks of SPPC</th>
<th>Gene and protein expression</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-sufficiency in growth signals</td>
<td>HER2 overexpression 34–59% (19,20)</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Evasion of apoptosis</td>
<td>BCL2 overexpression 9.4% (21)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Limitless replicative potential</td>
<td>p53 overexpression 38–81% (19-21,25,26)</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td></td>
<td>WT1 expression 51% (27)</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Sustained angiogenesis</td>
<td>Thymidine phosphorylase expression 43% (23)</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Evasion of immune destruction</td>
<td>Microsatellite instability 7%* (22)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Chromosomal alterations</td>
<td>Loss of heterozygosity of chromosomes 6q, 9p, 17p, 17q, and Xq (16,22)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*, microsatellite instability has been assessed using 22 primers from 9 different chromosomes to screen for loss of heterozygosity and compared between BRCA1-related peritoneal cancer and BRCA1-ovarian carcinomas. This method is not the commonly used technique that requires an instability (insertion/deletion mutations) in two or more of the five markers including two mononucleotide repeats (Bat-25 and Bat-26) and three dinucleotide repeats (D2S123, DSS346 and D17S250) (28). SPPC, serous peritoneal papillary carcinoma.
Table 2 Summary of the diagnostic criteria suggested for SPPC

<table>
<thead>
<tr>
<th>Authors</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mills et al. 1988 (49)</td>
<td>Ovaries should be less than 3 cm in diameter and show no invasion or microinvasion</td>
</tr>
<tr>
<td>Fromm et al. 1990 (50)</td>
<td>The maximum diameter of normal ovaries should be less than 4 cm</td>
</tr>
<tr>
<td>Bloss et al. 1993 (51)</td>
<td>Both ovaries have a normal size or are enlarged by a benign process and involvement of extraovarian sites must be greater than on the ovarian surface. The ovarian component must be nonexistent microscopically or confined to the ovarian surface epithelium with no evidence of cortical invasion or involving the ovarian epithelium and/or the underlying stroma by less than 5 mm × 5 mm in depth and extent</td>
</tr>
<tr>
<td>Mulhollan et al. 1994 (52)</td>
<td>The diameter of the ovary should be 3 cm or less and the surface of the ovarian tumor size should be less than 5 mm into the ovarian parenchymal microinvasion was less than 3 mm</td>
</tr>
<tr>
<td>NCCN Guidelines version 1. 2020 (53)</td>
<td>SPPC is usually diagnosed postoperatively if there is no major involvement of the ovary or preoperatively if there is a biopsy and the patient has already had a bilateral oophorectomy</td>
</tr>
</tbody>
</table>

SPPC, serous peritoneal papillary carcinoma.

Despite these diagnostic efforts, surgical diagnosis and staging remain the standard reference (57). The updated International Federation of Gynecology and Obstetrics (FIGO) classification of 2014 has uniformly classified SPPC as stage III–IV tumors depending on the disease extent and localization (57).

A pathology review of a good quality tissue sample is also required (1). SPPC resembles a papillary serous ovarian cancer being composed of complex papillary or glandular architecture (58). It presents frequent and abundant psammoma bodies (59). An initial assessment of cytokeratin 7 and 20 is the first step in identifying the culprit tumor in adenocarcinomas. The immunophenotype stains are typically positive for CK7, CD15, S-100, P53, WT-1, ER, and PAX-8 in most cases and negative for calretinin (59-63). These tumors need to be distinguished from peritoneal mesotheliomas which are negative for Ber-EP4 and MOC-31 and positive for calretinin and D2-40 (64).

**Question 4: is the treatment of SPPC different from that of primary ovarian cancer?**

In the absence of an identifiable primary tumor, both oncologists and patients find it hard to accept the cancer diagnosis which often delays treatment initiation. SPPC is traditionally managed according to a comprehensive treatment strategy that integrates aggressive cytoreductive surgery (CRS) to remove the macroscopic tumor, hyperthermic intraperitoneal chemotherapy (HIPEC) to eradicate the microscopic residual disease, and systemic chemotherapy to control the microscopic metastasis. The supportive evidence is limited to retrospective series in the absence of proper randomized or prospective studies on SPPC (Tables 3,4).

The confinement of the metastatic spread of SPPC to the peritoneal cavity, the pelvic and para-aortic lymph nodes constitutes a robust rationale for aggressive local control (97). A total peritonectomy (residual tumor <1–2 cm) is feasible in 13–79% of patients and should be performed to remove precursor sites and microscopic residual disease (98). Complete resection sorts out one of the most important prognostic factors affecting survival as residual tumors are reported in 60% of grossly normal-appearing peritoneum (99-101). The rates of lymph node involvement are similar between SPPC and primary ovarian tumor however the approach for lymph node dissection is different between the two entities. Systematic lymph node dissection is no longer routinely recommended in patients with primary ovarian cancer, however, it is favored in patients with SPPC (102). This discrepancy is due to the differences in the carcinogenesis of each tumor and to the workup (98). Neoadjuvant chemotherapy has been recommended to optimize local control (14,103). In a subset of 17 patients undergoing CRS following chemotherapy, the median progression-free survival was 25 months and the median OS was 48 months (82). It can be argued that patients with complete response to neoadjuvant chemotherapy and no residual disease do not require surgical intervention. Connolly et al. reported on the outcomes of 44 patients with SPPC treated with neoadjuvant chemotherapy of whom only 17 underwent CRS (82). The surgical group achieved lower recurrence rates (65% vs. 93%) and longer median progression-free survival (25 vs. 9 months; P=0.001) and
Table 3 Summary of the outcomes reported in the SPPC series

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>SPPC extension</th>
<th>Age (years)</th>
<th>N</th>
<th>Surgical debulking (%)</th>
<th>Chemotherapy regimen</th>
<th>ORR (%)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lele et al. 1988 (65)</td>
<td>Retrospective</td>
<td>Diaphragm, omentum</td>
<td>NA</td>
<td>23</td>
<td>NA</td>
<td>Platinum (cisplatin) + alkylators</td>
<td>65</td>
<td>NA</td>
</tr>
<tr>
<td>Strnad et al. 1989 (66)</td>
<td>Retrospective</td>
<td>None</td>
<td>62</td>
<td>18</td>
<td>50</td>
<td>Platinum (cisplatin) + alkylators</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>Ransom et al. 1990 (67)</td>
<td>Retrospective</td>
<td>Diaphragm, lymph nodes, ovaries</td>
<td>NA</td>
<td>33</td>
<td>69</td>
<td>Platinum (Cisplatin) + Alkylators or doxorubicin</td>
<td>NA</td>
<td>17</td>
</tr>
<tr>
<td>Truong et al. 1990 (68)</td>
<td>Retrospective</td>
<td>Omentum, lymph nodes, ovaries, liver</td>
<td>56</td>
<td>22</td>
<td>NA</td>
<td>Platinum (cisplatin) + alkylators</td>
<td>90</td>
<td>14.8</td>
</tr>
<tr>
<td>Zhou et al. 1995 (69)</td>
<td>Retrospective</td>
<td>Omentum, ovaries, upper abdomen</td>
<td>56.5</td>
<td>10</td>
<td>60</td>
<td>CAP</td>
<td>NA</td>
<td>27</td>
</tr>
<tr>
<td>Liapis et al. 1996 (70)</td>
<td>Retrospective</td>
<td>Omentum</td>
<td>58</td>
<td>10</td>
<td>NA</td>
<td>Platinum (cisplatin) + alkylators</td>
<td>NA</td>
<td>15</td>
</tr>
<tr>
<td>Taus et al. 1997 (71)</td>
<td>Retrospective</td>
<td>Diaphragm</td>
<td>NA</td>
<td>18</td>
<td>33</td>
<td>Platinum (cisplatin) + alkylators</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Piver et al. 1997 (72)</td>
<td>Prospective Phase 2 (2 cohorts)</td>
<td>Omentum, ovaries</td>
<td>62</td>
<td>46</td>
<td>70</td>
<td>Platinum + taxanes or CAP</td>
<td>62.5–70</td>
<td>21.5–24</td>
</tr>
<tr>
<td>Kennedy et al. 1998 (73)</td>
<td>Retrospective</td>
<td>Upper abdomen</td>
<td>62</td>
<td>38</td>
<td>34</td>
<td>Platinum + taxanes</td>
<td>87</td>
<td>40</td>
</tr>
<tr>
<td>Morita et al. 2004 (74)</td>
<td>Retrospective</td>
<td>Omentum</td>
<td>59</td>
<td>11</td>
<td>45</td>
<td>Platinum + taxane or CAP</td>
<td>NR</td>
<td>22</td>
</tr>
<tr>
<td>Pentheroudakis et al. 2005 (75)</td>
<td>Retrospective</td>
<td>Pelvis</td>
<td>62</td>
<td>47</td>
<td>35</td>
<td>Platinum + taxanes</td>
<td>53</td>
<td>15</td>
</tr>
<tr>
<td>Choi et al. 2007 (76)</td>
<td>Retrospective</td>
<td>Omentum, mesentery</td>
<td>52</td>
<td>20</td>
<td>55</td>
<td>Platinum + taxanes</td>
<td>100</td>
<td>Not reached</td>
</tr>
<tr>
<td>Zhang et al. 2008 (77)</td>
<td>Retrospective</td>
<td>NA</td>
<td>59</td>
<td>24</td>
<td>13</td>
<td>Platinum + taxanes or CAP</td>
<td>80</td>
<td>42</td>
</tr>
<tr>
<td>Roh et al. 2007 (78)</td>
<td>Retrospective</td>
<td>NA</td>
<td>62</td>
<td>22</td>
<td>77</td>
<td>Platinum-based</td>
<td>79</td>
<td>23</td>
</tr>
<tr>
<td>Iavazzo et al. 2008 (55)</td>
<td>Retrospective</td>
<td>NR</td>
<td>63</td>
<td>9</td>
<td>33</td>
<td>Platinum + taxane</td>
<td>NR</td>
<td>30</td>
</tr>
<tr>
<td>Liu et al. 2011 (59)</td>
<td>Retrospective</td>
<td>NR</td>
<td>56</td>
<td>22</td>
<td>82</td>
<td>Platinum-based</td>
<td>NR</td>
<td>21</td>
</tr>
<tr>
<td>Bakkar et al. 2014 (79)</td>
<td>Retrospective</td>
<td>Lymph nodes, omentum</td>
<td>53</td>
<td>13</td>
<td>100</td>
<td>Platinum + taxane</td>
<td>NR</td>
<td>117</td>
</tr>
<tr>
<td>Usach et al. 2015 (80)</td>
<td>Retrospective</td>
<td>NR</td>
<td>67</td>
<td>1037</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5-y OS: 26%</td>
</tr>
<tr>
<td>Sun et al. 2016 (81)</td>
<td>Retrospective</td>
<td>NR</td>
<td>61</td>
<td>22</td>
<td>100 (+ HIPEC)</td>
<td>Platinum + taxane</td>
<td>NR</td>
<td>31</td>
</tr>
<tr>
<td>Conolly et al. 2016 (82)</td>
<td>Retrospective</td>
<td>NR</td>
<td>68</td>
<td>17</td>
<td>100</td>
<td>Platinum (carboplatinum)-based</td>
<td>94</td>
<td>48</td>
</tr>
<tr>
<td>Dahm-Kähler et al. 2017 (15)</td>
<td>Retrospective</td>
<td>NR</td>
<td>73</td>
<td>269</td>
<td>42</td>
<td>Platinum-based (in 95%) or other (5%)</td>
<td>NR</td>
<td>5-y OS: 13%</td>
</tr>
</tbody>
</table>

SPPC, serous peritoneal papillary carcinoma; N, number of patients; NA, not available; ORR, objective response rates; OS, overall survival.
### Table 4

**Summary of the outcomes reported in the SPPC series in comparison to primary ovarian cancer**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>SPPC extension</th>
<th>Age (years)</th>
<th>N</th>
<th>Surgical debulking (%)</th>
<th>Chemotherapy regimen</th>
<th>ORR (%)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mills et al.</td>
<td>Retrospective</td>
<td>Lymph nodes, ovaries</td>
<td>64.5 vs. 54.5</td>
<td>10 vs. 16</td>
<td>50 vs. 25</td>
<td>Platinum (cisplatin) + alkylators 80 vs. 100, P=NS ± doxorubicin</td>
<td>12 vs. 24, P=0.04</td>
<td></td>
</tr>
<tr>
<td>Dalrymple et al.</td>
<td>Retrospective</td>
<td>Omentum, lymph nodes, ovaries, visceral</td>
<td>59 vs. 61</td>
<td>31 vs. 135</td>
<td>64.5 vs. 64</td>
<td>Cisplatin + chlorambucil</td>
<td>32 vs. NA, P=NA</td>
<td>11.3 vs. 13.5, P=NS</td>
</tr>
<tr>
<td>Wick et al.</td>
<td>Retrospective</td>
<td>Omentum, ovaries</td>
<td>65 vs. 63</td>
<td>13 vs. 31</td>
<td>NA</td>
<td>Alkylating agents combinations</td>
<td>48 vs. NA, P=NA</td>
<td></td>
</tr>
<tr>
<td>Fromm et al.</td>
<td>Retrospective</td>
<td>Diaphragm, omentum, lymph nodes, ovaries</td>
<td>57.4 vs. 55</td>
<td>74 vs. 743</td>
<td>41</td>
<td>Platinum + alkylators</td>
<td>68 vs. NA, P=NA</td>
<td>24 vs. 27, P=NS</td>
</tr>
<tr>
<td>Killackey et al.</td>
<td>Retrospective</td>
<td>Diaphragm, omentum</td>
<td>69.5 vs. 66.4</td>
<td>29 vs. 27</td>
<td>65 vs. 79</td>
<td>Platinum (cisplatin) + alkylators NA ± doxorubicin</td>
<td>19 vs. 31, P=NA</td>
<td></td>
</tr>
<tr>
<td>Bloss et al.</td>
<td>Retrospective</td>
<td>Extraperitoneal disease</td>
<td>62 vs. 63</td>
<td>33 vs. 33</td>
<td>33 vs. 36</td>
<td>Platinum + alkylators (cisplatin + CP)</td>
<td>63 vs. 82, P=NS</td>
<td>20 vs. 28, P=NS</td>
</tr>
<tr>
<td>Fowler et al.</td>
<td>Retrospective</td>
<td>Omentum, ovaries</td>
<td>61.4 vs. 57</td>
<td>34 vs. 70</td>
<td>44</td>
<td>Platinum (cisplatin) + alkylators NA (cyclophosphamide)</td>
<td>18 vs. 22, P=NS</td>
<td></td>
</tr>
<tr>
<td>Ben-Baruch et al.</td>
<td>Retrospective</td>
<td>Pelvis</td>
<td>61.1 vs. 59.1</td>
<td>25 vs. 71</td>
<td>28 vs. 22</td>
<td>Platinum (cisplatin) + alkylators NA ± doxorubicin</td>
<td>21 vs. 26, P=NS</td>
<td></td>
</tr>
<tr>
<td>Piura et al.</td>
<td>Retrospective</td>
<td>Omentum, diaphragm, ovaries</td>
<td>62 vs. 55.6</td>
<td>15 vs. 52</td>
<td>62 vs. 57</td>
<td>Platinum + taxanes</td>
<td>80 vs. 79, P=NS</td>
<td>36 vs. 30, P=NS</td>
</tr>
<tr>
<td>Schorge et al.</td>
<td>Retrospective</td>
<td>Na</td>
<td>64 vs. 55</td>
<td>38 vs. 38</td>
<td>79 vs. 76</td>
<td>Platinum + taxanes</td>
<td>NA</td>
<td>40 vs. 34, P=NS</td>
</tr>
<tr>
<td>Halperin et al.</td>
<td>Retrospective</td>
<td>Diaphragm, omentum</td>
<td>59.8 vs. 59</td>
<td>28 vs. 34</td>
<td>39 vs. 60</td>
<td>Platinum + taxanes</td>
<td>NA</td>
<td>17 vs. 40, P=0.02</td>
</tr>
<tr>
<td>Bloss et al.</td>
<td>Prospective</td>
<td>Phase 2</td>
<td>NA</td>
<td>36 vs. 130</td>
<td>0</td>
<td>Platinum (cisplatin) + alkylators (cisplatin + CP)</td>
<td>65 vs. 59; P=NS</td>
<td>22 vs. 27, P=NS</td>
</tr>
<tr>
<td>Dubernard et al.</td>
<td>Retrospective</td>
<td>NA</td>
<td>Age matched</td>
<td>37 vs. 37</td>
<td>89.2</td>
<td>Platinum + taxanes</td>
<td>NA</td>
<td>5-y OS: 54% vs. 29%, P=NA</td>
</tr>
<tr>
<td>Khalife et al.</td>
<td>Retrospective</td>
<td>NA</td>
<td>64.5 vs. 61</td>
<td>29 vs. 96</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>23.6 vs. 35.3, P=NS</td>
</tr>
<tr>
<td>Ayhan et al.</td>
<td>Retrospective</td>
<td>Lymph nodes</td>
<td>60 vs. 52</td>
<td>32 vs. 43</td>
<td>66 vs. 72</td>
<td>Platinum + taxanes</td>
<td>45 vs. 51, P=NS</td>
<td>30 vs. 28, P=NS</td>
</tr>
</tbody>
</table>

Table 4 (continued)
HIPEC is a therapeutic strategy that has developed over the past two decades and consists of delivering chemotherapy directly into the peritoneum, making it a good option for local control of peritoneal carcinomatosis (104,105). One case series of 32 patients with SPPC treated with CRS followed by HIPEC showed a 1, 3 and 5-year overall survival of 93.6%, 71.5%, and 57.4%, respectively (106). A smaller case series of 22 patients with primary SPPC (n=12) or recurrent SPPC (n=10) treated locally with CRS + HIPEC procedures yielded a 1-, 3-, and 5-year overall survival of 100%, 45.5%, and 27.3%, respectively. A peritoneal cancer index below 16 was the only prognostic predictor (81). Another case series of 22 patients with primary SPPC treated locally with CRS plus HIPEC showed a median disease-free survival of 32.9 months, 5-year disease-free-survival of 33.2% and 5-year overall survival of 64.9%. Serious adverse events were described in 18% of patients but there was no postoperative mortality (98).

In 2012, Pentheroudakis and Pavlidis reviewed the published series of SPPC between 1980 and 2008 and concluded to three time periods (4). Before 1990, the standard treatment which consisted of platinum- plus alkylator-based chemotherapy yielded an objective response rate of 32–80% and a median overall survival of 11–23 months. Between 1990 and 1995, platinum combinations before the taxane era achieved an objective response rate of 63–90% and a median overall survival of 14.7–25 months. After 1995, the combination of platinum/taxane yielded an objective response rate of 53–100% and a median overall survival of 15–42 months (Tables 3-4).

Today, the treatment arsenal of SPPC is reinforced with bevacizumab and PARP inhibitors that were FDA approved in 2014 and 2018 respectively. These two treatment options add two milestones to the natural history of SPPC. Unfortunately, the pivotal trials as well as the retrospective case series consider primary ovarian cancers, fallopian cancers and SPPC as a single entity and do not stratify the patients’ characteristics or outcomes accordingly (107-109).

**Conclusions**

SPPC is almost indistinguishable from primary ovarian tumors as they share similar clinical presentation, histological features, and pattern of spread. However, it has subtle differences that render SPPC and primary ovarian cancer two entities of a spectrum of disease rather than being completely distinct cancers. The current

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**Table 4** (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>SPPC extension</th>
<th>Chemotherapy regimen</th>
<th>ORR (%)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eisenhaur et al. 2008 (93)</td>
<td>Retrospective</td>
<td>NA</td>
<td>Platinum + taxanes</td>
<td>90% vs. 90, P=0.001</td>
<td>5-y OS 37% vs. 62%</td>
</tr>
<tr>
<td>Usach et al. 2015 (80)</td>
<td>Retrospective</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Chao et al. 2013 (94)</td>
<td>Retrospective</td>
<td>NA</td>
<td>Platinum + taxanes</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Schnak et al. 2014 (14)</td>
<td>Retrospective</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fukuda et al. 2015 (95)</td>
<td>Retrospective</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gao et al. 2016 (96)</td>
<td>Retrospective</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

SPPC, serous peritoneal papillary carcinoma; N, number of patients; NA, not available; NS, not significant; ORR, objective response rates; OS, overall survival.

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diagnostic criteria require mainly normal-sized ovaries and extragranary site involvement that exceeds the ovarian surface. The radiological and molecular advances have generally improved the identification rate of the primary tumor sites in patients with CUP. Namely, molecular gene profiling yielded an identification rate of 77–94% using second-generation microRNA-based assays, gene expression profiling-based microarrays tests or quantitative-PCR low-density arrays in comparison to the clinicopathologic suggestions (35). Nevertheless, these tools are not validated in patients with SPPC and require further assessments before clinical applicability.

Patients with SPPC are traditionally managed similarly to patients with stage III–IV primary ovarian cancer although they tend to have inferior outcomes. The published literature supports optimal local control in addition to systemic chemotherapy combining platinum and taxanes. In the absence of proper prospective trials, the supportive evidence is limited to retrospective series from single institutions experience in peritoneal malignancies. Whether HIPEC is of benefit or CRS can be omitted should be addressed in specifically designed trials. SPPC is not commonly distinguished as a distinct clinical entity for clinical trial inclusion and has been enrolled in ovarian cancer trials. The better understanding of the biology of SPPC permits a strict disease definition that creates a common standard diagnostic workup and a homogeneous patient population. This, in turn, will lead to more effective treatment strategies, and should also lead to the identification of novel therapeutic targets.

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Footnote

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