New rising entities in cancer of unknown primary: Is there a real therapeutic benefit?

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\textbf{ABSTRACT}

Cancers of Unknown Primary Site (CUP) account for approximately 1–3 % of all malignant neoplasms. It represents a heterogeneous group of malignancies without a detectable primary and is characterized by aggressive clinical behavior. Patients with CUP are presumably categorized into prognostic subsets according to their clinical and pathological characteristics. The majority of these patients are chemo-resistant and treated with empiric chemotherapy regimens which yield limited survival. Recent diagnostic advances have led to the identification of a higher percentage of culprit primaries among which colorectal, lung and renal tumors. The empiric CUP regimens may be suboptimal in these patients which explain in part their poor prognosis. In the absence of prospective randomized studies to prove the benefit of site-specific therapy in these subsets, we reviewed the literature to assess whether CUP with colorectal, lung and renal - profiles should be treated similarly to the correspondent primary tumors.

1. Introduction

Cancers of unknown primary (CUP) are defined by metastatic cancer with no identifiable primary site following adequate evaluation (Fizazi et al., 2015). The standard diagnostic procedure includes a detailed history and physical examination, blood tests, expert pathological review, and imaging using computerized tomography of the chest, abdomen, and pelvis (Fizazi et al., 2015). These recommendations led to better identification of the culprit primary as manifested in the declined incidence of CUP between the historical series (3% - 5%) and the recent reports (1 %–2%) (Rassy and Pavlidis, 2019). CUP remains a deadly disease and constitutes the seventh to eighth cause of mortality in patients with cancer (Pavlidis and Pentheroudakis, 2012).

Patients with CUP are categorized into two prognostic subgroups according to their clinicopathologic characteristics (Pavlidis and Pentheroudakis, 2012). The majority of patients with CUP (80 %–85%) belong to unfavorable subsets, with a modest sensitivity to therapy and median overall survival (OS) of generally 6–10 months (Pavlidis and Pentheroudakis, 2012). In this subset, two prognostic groups are identified according to the performance status (0 or 1) and lactate dehydrogenase (LDH) level (Culine et al., 2002). The one-year survival rate is 53% for good-risk patients and 23% for poor-risk patients. The treatment of this subset consists of empiric broad-spectrum chemotherapy including carboplatin plus paclitaxel or gemcitabine plus cisplatin (Pavlidis, 2007). On the other hand, a minority of patients with CUP (15 %–20 %) harbors a chemosensitive disease and has better long term outcomes (Pavlidis and Pentheroudakis, 2012). The favorable risk cancer subgroup includes patients with neuroendocrine carcinomas of unknown primary, peritoneal adenocarcinomatosis of a serous papillary subtype, isolated axillary nodal metastases in females, squamous cell carcinoma involving nonsupraclavicular cervical lymph nodes, single metastatic deposit from unknown primary and men with blastic bone metastases and PSA expression (Fizazi et al., 2015; Pavlidis and Pentheroudakis, 2012). These patients are treated according to the

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equivalent primary guidelines for metastatic disease.

The current precision medicine era has reclassified more patients with CUP into the favorable prognostic subset, subsided the role of empiric therapy and suggested a potential role for targeted therapies (Rassy et al., 2018; Rassy and Pavlidis, 2018; Greco et al., 2013). New favorable subsets of CUP seem to emerge including colorectal, lung and renal CUP which underlies specific treatments. In this framework, we review the available literature to assess whether CUP with colorectal, lung and renal - profiles should be treated similarly to the correspondent primary tumors.

2. CUP with a colon-cancer profile

CUP with a colon-cancer profile (CUP-CCP) is increasingly being recognized as a distinct favorable subset (Fizazi et al., 2015; Pavlidis and Pantel, 2012). It consists of (1) adenocarcinoma histologically compatible with a colorectal primary site, (2) primary intra-abdominal metastases and (3) typical immunohistochemistry (IHC) tumor staining (cytokeratin [CK] 20 +, CDX2+ and CK7-). CK20 expression is seen in 70–100 % of colorectal cancer and when associated with CK7 negativity has a specificity of 97% in predicting colorectal carcinomas (Bayrak et al., 2012; Blumenfeld et al., 1999). Microsatellite-high (MSI-H) colon tumors and poorly differentiated tumors have low levels of CK20 expression (Rende et al., 2003; McGregor et al., 2004). CDX2, a nuclear transcription factor that is the product of a homeobox gene necessary for intestinal organogenesis, is expressed in almost 97% of colorectal carcinomas (Barbareschi et al., 2003). The concordance of molecular profiling and IHC is around 64.7% (Varadhachary et al., 2008b).

2.1. The applicability of colon-like regimens in CUP

The activity of colon-like regimens combining capecitabine, 5-fluorouracil, irinotecan, and oxaliplatin, have been addressed in multiple phase II trials enrolling patients with poor prognostic subsets of CUP (Golfinopoulos et al., 2007). These regimens yielded an ORR of 35–45% and a median OS of 15–20 months in patients with advanced colorectal cancers (Golfinopoulos et al., 2007). However, treatment-naive patients without a colon-like profile had been uniformly modest results showing an objective response rate (ORR) of 11.7–35 %, progression-free survival (PFS) of 2.5–3 months and OS of 7.5–9.5 months (Table 1). Similarly, second-line chemotherapy with 5-FU/LV or oxaliplatin plus capecitabine has no impact on survival (Table 1). Taken together, colon-like chemotherapy regimens are disappointing in the frontline and second-line treatment of patients with poor prognostic subsets of CUP.

On the other hand, patients with CUP attributed to a colorectal culprit and treated with empiric CUP regimens have suboptimal outcomes and would probably benefit from a colon-like chemotherapy regimen (Table 2).

2.2. The applicability of colon-like regimens in CUP-CCP

An accurate tissue of origin assignment is of potential clinical importance because standard regimens for advanced colon cancer differ substantially from empiric CUP regimens. The relatively site-specific colorectal chemotherapy regimens have improved the prognosis of patients with colorectal carcinoma.

The outcome of patients with CUP-CCP as defined by IHC has been initially reported by two case series. Varadhachary et al. reported on three patients that were treated with colon-like chemotherapy: two patients with metastatic disease alive at 24–40 months and one patient receiving adjuvant treatment with no recurrence at 20 months follow up (Varadhachary et al., 2008a). One patient received frontline empiric CUP regimens but received colon-like chemotherapy at progression and remains alive at 40 months (Varadhachary et al., 2008a). The largest

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### Table 1

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Regimen schema</th>
<th>Line of treatment</th>
<th>N</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxiIri</td>
<td>Oxaliplatin 80 mg/m² followed by irinotecan 100 mg/m² diluted in 500 ml saline infused over 4 hours, administered every 3 weeks</td>
<td>First-line</td>
<td>47</td>
<td>13%</td>
<td>2.7 months</td>
<td>9.5 months</td>
</tr>
<tr>
<td>FOLFOX-6</td>
<td>Oxaliplatin 100 mg/m² and leucovorin 200 mg/m² as a 2-h infusion followed by bolus administration of 5-fluorouracil 400 mg/m² and continuous infusion of 5-fluorouracil 2400 mg/m² over 2 weeks</td>
<td>First-line</td>
<td>23</td>
<td>35%</td>
<td>3 months</td>
<td>9.5 months</td>
</tr>
<tr>
<td>CapOx</td>
<td>Capecitabine 1000 mg/m² twice daily orally for 2 weeks and oxaliplatin 130 mg/m² intravenously day 1, repeated every three weeks at a maximum of 6 cycles</td>
<td>First-line</td>
<td>51</td>
<td>11.7%</td>
<td>3.7 months</td>
<td>9.7 months</td>
</tr>
<tr>
<td>CapOxa</td>
<td>Capecitabine 1000 mg/m² twice daily orally for 2 weeks and oxaliplatin 130 mg/m² intravenously day 1, repeated every three weeks at a maximum of 6 cycles</td>
<td>Second-line</td>
<td>48</td>
<td>13%</td>
<td>3.9 months</td>
<td>9.7 months</td>
</tr>
<tr>
<td>5FU/LV</td>
<td>Leucovorin 200 mg/m² as a 2 h infusion followed by bolus 5-FU 400 mg/m² and a continuous infusion of 5-fluorouracil 1200 mg/m² every 2 weeks</td>
<td>Second-line</td>
<td>36</td>
<td>0%</td>
<td>Not reported</td>
<td>3 months</td>
</tr>
</tbody>
</table>

* 76% of the patients had a histopathological assessment favoring a gastrointestinal primary.

N: number of patients; ORR: objective response rate; OS: overall survival; PFS: progression free survival.
Table 2

<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-up</th>
<th>CO/PAL/CRC</th>
<th>First-line treatment</th>
<th>N2</th>
<th>ORR1</th>
<th>Second-line treatment</th>
<th>N2</th>
<th>ORR2</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varadhachary et al. (2008a)</td>
<td>Retrospective</td>
<td>Colon-like chemotherapy</td>
<td>3</td>
<td>100%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Alive at 20-36 months</td>
<td></td>
</tr>
<tr>
<td>Varadhachary et al. (2008b)</td>
<td>Prospective</td>
<td>Empiric CUP regimens</td>
<td>12</td>
<td>16.7%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.5-29 months</td>
<td></td>
</tr>
<tr>
<td>Greco et al. (2012)</td>
<td>Prospective</td>
<td>Colon-like chemotherapy</td>
<td>10</td>
<td>50%</td>
<td>Colon-like chemotherapy</td>
<td>5</td>
<td>80%</td>
<td>3-60 months</td>
<td></td>
</tr>
<tr>
<td>Hainsworth et al. (2012)</td>
<td>Retrospective</td>
<td>Colon-like chemotherapy</td>
<td>24</td>
<td>50%</td>
<td>Colon-like chemotherapy</td>
<td>8</td>
<td>50%</td>
<td>20-36 months</td>
<td></td>
</tr>
</tbody>
</table>

CUP-CCP: cancer of unknown primary with colorectal cancer profile; N1: number of patients in the first-line setting; N2: number of patients in the second-line setting; ORR1: objective response rate of the first-line treatment; ORR2: objective response rate of the second-line treatment; OS: overall survival; PFS: progression-free survival.

In a smaller series, 23 patients were included among which 6 were treated with colon-like chemotherapy. The ORR was 100% and the OS ranged between 9 and 31 months (Varadhachary et al., 2008b). Among the 17 patients treated with empiric CUP regimens, the ORR was 17.6% and the OS range varied between 0.5 and 38 months. The three patients that received second-line treatment achieved partial responses when salvaged with colon-like regimens (Varadhachary et al., 2014).

A prospective trial from the Sarah Cannon Research Institute has reported on the site-specific treatment of 289 patients with CUP among which 28 were considered to have a colorectal primary according to a 92-gene reverse transcriptase-polymerase chain reaction cancer classification assay (Hainsworth et al., 2013). Patients treated with FOLFOX or FOLFIRI plus bevacizumab achieved a median OS of 12.5 months (Hainsworth et al., 2013).

Lung cancer is the most common primary culprit in the autopsy series of patients with CUP (Pentheroudakis et al., 2007). CUP patients with a lung-cancer profile (CUP-LCP) often present with adrenal, liver and cerebral metastases. It consists of non-small cell lung cancer subtype including squamous cell carcinoma and predominantly adenocarcinoma. The typical IHC pattern of adenocarcinoma stains positively for TTF1 and CK7, and negatively for CK20 but can also be encountered in thyroid and neuroendocrine cancers (Fizazi et al., 2015). TTF1 is a master regulatory transcription factor for tissue-specific genes that is expressed physiologically in the normal lung as it plays a decisive role in the maintenance of the functions of terminal respiratory unit cells. Its expression is a highly specific marker for primary lung adenocarcinomas and is reported in 70–80% of lung adenocarcinomas (Kim et al., 2018). The combination of TTF1 and CK7 has a sensitivity of 96% and a specificity of 73% in predicting lung adenocarcinoma (Gurda et al., 2015). Several molecular profiling has also been evaluated (Hainsworth et al., 2013; Varadhachary et al., 2008b) with one series reporting an agreement rate of 74% between molecular profiling and IHC in lung cancer (Greco et al., 2013). Among patients with CUP in whom a latent lung cancer was identified, the primary was correctly identified by IHC in 40% and molecular profiling in 50% (Greco et al., 2013).
3.1. The applicability of lung-like regimens in CUP

The CUP-LCP entity is categorized among the poor prognosis CUP subsets and treated with empiric CUP regimens. The commonly recommended options include carboplatin plus paclitaxel or gemcitabine plus cisplatin which are historically considered the standard of care in the treatment of metastatic lung cancer (Fizazi et al., 2015). These regimens achieved an ORR ranging between 18–55%, PFS of 3.3–5 months and OS of 6.5–11 months (Table 3). Similarly, before the era of immunotherapy patients with advanced lung cancer had an ORR of 30–45% and a median OS of 8–11 months (Baggstrom et al., 2007). To the best of our knowledge, the antitumor activity of pemetrexed was not assessed in patients with CUP.

The advances in targeted therapies and immunotherapy have transformed the treatment arsenal of non-small cell lung cancer where driver alterations and PDL-1 expression are key factors in treatment decisions (Planchard et al., 2018; Rassy et al., 2019a). Driver alterations known in lung adenocarcinomas have been reported in CUP such as EGFR alterations in 1–6 %, BRAF mutations in 3–6 % and ALK re-arrangements in 0.7–1 % (Rassy and Pavlidis, 2018; Löfler et al., 2016; Ross et al., 2015a; Varghese et al., 2017). Multiple case reports showed a potential activity for targeted therapy in CUP (Table 4). Two phase II trials have also been conducted in this regard (Table 5) but did not report on the percentage of driver alterations namely EGFR mutations (Hainsworth et al., 2007, Hainsworth et al., 2009). The largest includes 60 patients with CUP (adenocarcinoma, poorly differentiated carcinoma, and poorly differentiated squamous carcinoma) treated with a combination of bevacizumab plus erlotinib with paclitaxel plus carboplatin for four cycles followed by bevacizumab plus erlotinib maintenance (Hainsworth et al., 2009). The ORR was 53%, the median PFS was 8 months and OS was 12.6 months (John D. Hainsworth et al., 2009). A smaller series of 51 patients with CUP (adenocarcinoma, poorly differentiated carcinoma, and poorly differentiated squamous carcinoma) treated with bevacizumab plus erlotinib yielded an ORR of 10%, median PFS of 3.9 months and OS of 7.4 months (Hainsworth et al., 2007).

Immune checkpoint inhibitors have improved the OS in the first- and second-line setting of patients with non-small cell lung cancer that lack targetable driver alterations (Rassy et al., 2019a). Unfortunately, the published experience of immune checkpoint inhibitors in patients with CUP is limited to case reports (Gröschel et al., 2016; Kato et al., 2017; Röe and Wahl, 2017) although CUP constitutes a group of highly heterogeneous tumors which renders immunotherapy a very attractive option. The currently ongoing trials are evaluating pembrolizumab monotherapy in poor-prognosis CUP (NCT03391973) as well as pembrolizumab and concurrent radiation in patients with previously treated CUP (NCT03396471). Some studies evaluated the biomarkers of CUP in regards to immune therapy: tumor PD-L1 expression was detected in 22% (SP142 antibody threshold for positivity 5% in cancer cells), TML-high in 11.8%, and MSI-high in 1.8% (Gatalica et al., 2018).

3.2. The applicability of lung-like regimens in CUP-LCP

The CUP-LCP is increasingly being recognized as a distinct entity with several studies trying to report on the outcome of these patients especially that platinum-based doublets are no longer the standard treatment for all non-small cell lung cancer patients (Planchard et al., 2018). The prospective trial from the Sarah Cannon Research Institute enrolled 27 patients with CUP that were considered to have a lung primary their gene expression profile (Hainsworth et al., 2013). These patients were treated with platinum-based doublets plus bevacizumab which achieved a median OS of 15.9 months (Hainsworth et al., 2013). A smaller series of 18 patients with lung profile according to a 10-gene reverse transcriptase-polymerase chain reaction assay has also been reported (Varadhachary et al., 2008b). The carboplatin-based regimens (13 patients received paclitaxel, carboplatin, and etoposide) yielded an...
ORR of 38.9% and median OS of 9 months (Varadhachary et al., 2008b).

4. CUP with a renal-cancer profile

CUP with a renal cell carcinoma profile (CUP-RCC) is described in 5% of patients with CUP syndrome in autopsy series (Pentheroudakis et al., 2007). Patients present heterogeneous clinical manifestations with metastatic sites involving the lungs, bones, lymph nodes, liver, adrenal glands, and brain. Uncommon metastatic sites have been reported in the nose and soft tissues (Bhatia et al., 2010; Walton et al., 2019). Ectopic kidney localizations complicates the identification of the primary tumor culprit (Terada, 2012). Tissue examination shows morphological features of renal cell carcinoma, mostly clear-cell, papillary and chromophobe which can be associated with rhabdoid and sarcomatoid components (Greco and Hainsworth, 2018). Poorly differentiated carcinomas or adenoacarcinomas can also be encountered but in the absence of clinical suspicion for renal cell carcinoma, CUP-RCC can be missed as specific IHC are not routinely performed (Greco and Hainsworth, 2018).

The IHC patterns vary between the different RCC subsets as CK20 and CK7 stain positively for clear-cell RCC whereas CK7 stains negatively for papillary and chromophobe RCC (Bahrami et al., 2008; Shen et al., 2012). RCC marker, CD10, and PAX8 are useful markers for CUP-RCC diagnosis work-up (Fizazi et al., 2015; Shen et al., 2012). RCC marker is a normal human proximal tubular brush border glycoprotein that stains positively in 85% of clear-cell RCC and more than 95% of papillary RCC (Avery et al., 2000; McGregor et al., 2001). CD10 stains positively in 90% of RCC with a diffuse cytoplasmic or membranous pattern (Chu and Arber, 2000). PAX 8 and vimentin usually stain positively in clear-cell and papillary RCC (Shen et al., 2012).

Molecular alterations can also help to the diagnosis of CUP-RCC. For example, SETD2 BAP1 and PBRM1 are frequently altered in clear-cell and papillary RCCs (Linehan et al., 2016; The Cancer Genome Atlas Research Network, 2013), VHL inactivation is found in more than 80% of clear-cell RCC (Nickerson et al., 2008) and MET amplification is present in more than 80% of type 1 papillary RCC (Albiges et al., 2014). Molecular profiling using a 92-gene molecular cancer classifier assay performed in a series of 539 CUP patients classified 24 tumors as CUP-RCC whereas standard pathologic examination only identified 5 CUP-RCC cases (Greco and Hainsworth, 2018).

4.1. The applicability of renal-like regimens in CUP

The available data reporting on the efficacy of renal-like regimens such as tyrosine kinase inhibitors, mTOR inhibitors, and immune checkpoint inhibitors in CUP are very sparse. An observational study of 286 patients has reported on the outcome of 92 patients with CUP treated with sunitinib which achieved a median OS of 11.9 months (Ma et al., 2016). A phase II trial has evaluated the efficacy of a standard CUP regimen, carboplatin plus paclitaxel, in addition to everolimus in patients with CUP (Yoon et al., 2016). Forty-six patients with a majority having distant metastases to the liver, lung, or bone and tumors exhibiting poor/anaplastic differentiation were included. The ORR was 36% and the median PFS and OS were 4.1 and 10.1 months respectively (Yoon et al., 2016). As discussed previously, the evidence supporting the efficacy of immune checkpoint inhibitor-based regimens in CUP is weak but trials are currently ongoing in this regard.

4.2. The applicability of renal-like regimens in CUP-RCC

The identification of patients with CUP-RCC is essential to optimize their management because the treatment options for advanced RCC do not overlap with the empiric chemotherapy regimens used usually for CUP (Escudier et al., 2019; Fizazi et al., 2015). Patients with CUP-RCC treated with CUP-like regimens usually do not achieve any response
The first subset includes patients with CUP-CCP which are classified as poor prognostic CUP and treated with empiric CUP regimens. However, the tailored treatment seemed to be associated with a better outcome compared to the site-specific therapy and empiric chemotherapy (Fizazi et al., 2019). The efficacy outcomes PFS (HR = 0.95; 95% CI 0.72–1.25) and OS (HR = 0.92; 95% CI 0.69–1.23) did not differ between the two arms although prediction of the original site was not reported. Overall, 20 of the 24 patients received renal-like regimens and had a median OS of 16 months (range 2-43 + months) (Greco and Hainsworth, 2018).

The smaller series include 10 patients (6 males and 4 females) diagnosed with CUP-RCC according to pathological criteria (clear cell in 30%, papillary type II in 20%, and unclassified in 50%) and clinical examination (Overby et al., 2019). Renal-like regimens (pazopanib in 6 patients, sunitinib in 2 patients and sorafenib in 1 patient) were administered in nine patients. The ORR was 40%, median PFS and OS were 2.5 months and 5.7 months, respectively. The survival analysis according to the International Metastatic Renal Cell Carcinoma Database Consortium showed an OS of 18.6 months in patients with an intermediate-risk score (n = 7) and 2.3 months in a poor-risk score (n = 3) (Overby et al., 2019).

5. Discussion

CUP is a heterogeneous group of metastatic tumors with a distinct natural history that mainly depends on clinicopathological criteria. We have previously reported on new clinical CUP entities that emerge as CUP of adolescents and young adults as well as pathologic entities such as HPV-related squamous cell CUP of the head and neck and HPV-related CUP of the abdomen, pelvis and retroperitoneum (Rassy et al., 2019b; Pavlidis et al., 2019; Rassy et al., 2019c). This review reports on three rising subsets of CUP including colorectal, lung and renal subsets.

The first subset includes patients with CUP-CCP which are classified in the good prognosis subsets of CUP. The survival of patients with CUP-CCP is significantly longer than it is expected for patients with CUP (Tables 1 and 2). Moreover, the ORR seems of prognostic value (Hayashi et al., 2019). Similarly, the phase III trial, GEFCAP 04 (NCT01540058), has randomized patients into site-specific therapy and empiric chemotherapy (Fizazi et al., 2019). The efficacy outcomes PFS (HR = 0.95; 95% CI 0.72–1.25) and OS (HR = 0.92; 95% CI 0.69–1.23) did not differ between the two arms of the study. The subgroup analysis did not identify a statistically significant difference between the two arms although prediction of the original site was not reported. Between the two arms of the study, patients who are unlikely to respond to empiric CUP regimens. It is noteworthy that 15–20% of patients had a pancreaticobiliary cancer profile. Therefore, treatment for the site-specific arm did not differ from the empiric regimen. However, the tailored treatment seemed to be associated with better outcomes in certain subgroups notably renal cell and colorectal carcinoma (Fizazi et al., 2019). The CUPISCO (NCT03498521) trial may bring useful data on this matter especially by categorizing patients according to these subsets where the molecular advances have transformed the corresponding treatment landscape.

6. Conclusion

Patients diagnosed with CUP - colorectal, lung and renal profiles
Table 6
Case reports of patients with CUP-RCC treated with renal-like CUP.

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (years) / gender</th>
<th>Pathology</th>
<th>Renal cell carcinoma profile assignment</th>
<th>Tumor sites</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akkad et al. (2008)</td>
<td>34 / male</td>
<td>Clear cell RCC / sarcomatoid differentiation</td>
<td>IHC</td>
<td>Lung and pleural; suspicious changes in the left kidney</td>
<td>Resection of left kidney followed by adjuvant immunotherapy</td>
<td>Died after several weeks of progressive disease</td>
</tr>
<tr>
<td>Bhatia et al. (2010)</td>
<td>63 / male</td>
<td>Clear cell RCC</td>
<td>IHC</td>
<td>Isolated mass</td>
<td>Resection of CUP-RCC</td>
<td>Alive at 12 months; no recurrence</td>
</tr>
<tr>
<td>Wayne et al. (2010)</td>
<td>61 / female</td>
<td>Clear cell RCC</td>
<td>IHC</td>
<td>Parotid, pancreas</td>
<td>Parotidectomy and pancreatectomy</td>
<td>Not available</td>
</tr>
<tr>
<td>Terada (2012)</td>
<td>61 / male</td>
<td>Clear cell RCC</td>
<td>IHC</td>
<td>Isolated retroperitoneal mass</td>
<td>Resection of CUP-RCC</td>
<td>Alive at 6 months; no recurrence</td>
</tr>
<tr>
<td>Choi et al. (2012)</td>
<td>69 / male</td>
<td>Clear cell RCC</td>
<td>IHC</td>
<td>One LN involvement</td>
<td>Radiotherapy followed by sunitinib</td>
<td>Alive at 20 months no evidence of progression</td>
</tr>
<tr>
<td>Sorscher and Greco (2012)</td>
<td>53 / male</td>
<td>Papillary RCC</td>
<td>IHC and MP</td>
<td>Diffuse LN involvement</td>
<td>Everolimus / first line</td>
<td>Alive at 11 months; no evidence of progression</td>
</tr>
<tr>
<td>Johnson et al. (2012)</td>
<td>71 / male</td>
<td>RCC not specified</td>
<td>IHC</td>
<td>Adrenal gland</td>
<td>Resection of the adrenal gland</td>
<td>Alive at 36 months; no evidence of recurrence</td>
</tr>
<tr>
<td>Thamcharoen and Chaiwiriyawong (2013)</td>
<td>37 / male</td>
<td>Papillary RCC</td>
<td>IHC</td>
<td>LN, soft tissue and intraabdominal mass</td>
<td>Sunitinib / third line</td>
<td>Alive at 22.5 months; no evidence of disease progression</td>
</tr>
<tr>
<td>Heary et al. (2014)</td>
<td>54 / male</td>
<td>RCC not specified</td>
<td>IHC</td>
<td>T2-4 spine</td>
<td>Initial resection followed by a second surgery 6 months later for recurrence</td>
<td>Alive at 12 months; no evidence of progression</td>
</tr>
<tr>
<td>Kumar et al. (2014)</td>
<td>70 / male</td>
<td>Clear cell RCC</td>
<td>IHC</td>
<td>Bone and lung</td>
<td>Sunitinib / first line</td>
<td>Alive at 18 months; no evidence of progression</td>
</tr>
<tr>
<td>Honda et al. (2014)</td>
<td>69 / female</td>
<td>Clear cell RCC</td>
<td>IHC</td>
<td>The synovium of knee and lung</td>
<td>Sunitinib / third line</td>
<td>Died at 8 months of progression</td>
</tr>
<tr>
<td></td>
<td>47 / male</td>
<td>Clear cell RCC</td>
<td>IHC</td>
<td>Bone</td>
<td>Sunitinib / third line followed by everolimus and axitinib</td>
<td>Not available</td>
</tr>
<tr>
<td>Wei et al. (2015)</td>
<td>43 / male</td>
<td>Clear cell RCC</td>
<td>IHC and MP</td>
<td>Bone and lung</td>
<td>Temsirolimus followed by axitinib then everolimus</td>
<td>Died at 9 months</td>
</tr>
<tr>
<td></td>
<td>55 / female</td>
<td>Clear cell RCC</td>
<td>IHC and MP</td>
<td>LN and lung</td>
<td>Sunitinib followed by temsirolimus</td>
<td>Alive at 16 months; no evidence of progression</td>
</tr>
<tr>
<td>Costantino et al. (2016)</td>
<td>68 / male</td>
<td>High-grade RCC</td>
<td>IHC and MP</td>
<td>Adrenal glands, liver, diffuse LN involvement</td>
<td>Resection of the adrenals and nephrectomy and retroperitoneal LN dissection followed by sunitinib at metastasis</td>
<td>Alive at 6 months; no evidence of progression</td>
</tr>
<tr>
<td>Nagasaka et al. (2017)</td>
<td>41 / male</td>
<td>Papillary RCC</td>
<td>IHC and MP</td>
<td>Diffuse LN involvement, bone</td>
<td>Palliative radiotherapy followed by Pazopanib</td>
<td>Alive at 6 months; no evidence of progression</td>
</tr>
<tr>
<td>Fayaz et al. (2017)</td>
<td>79 / male</td>
<td>Papillary RCC</td>
<td>IHC and MP</td>
<td>Diffuse LN involvement, bone</td>
<td>Sunitinib / second line</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>77 / male</td>
<td>RCC not specified</td>
<td>IHC and MP</td>
<td>Diffuse LN</td>
<td>Pazopanib / first line</td>
<td>Alive at 15 months; no evidence of progression</td>
</tr>
<tr>
<td>Walton et al. (2019)</td>
<td>52 / male</td>
<td>Clear cell RCC</td>
<td>IHC</td>
<td>Isolated mass in the soft tissue of the forearm</td>
<td>Resection of CUP-RCC</td>
<td>Alive at 27 months; no recurrence</td>
</tr>
</tbody>
</table>

seem to belong to the good prognostic subsets of CUP. Based on the available data, the treatment of these patients similarly to the corresponding primary tumors seems promising. However, the absence of defining/validated diagnostic criteria for CUP with lung and renal profiles limits the interpretation of the treatment outcomes. Moreover, the available evidence is limited to small number of patients reported in case reports and case series. Questions concerning the identification of these subsets, namely the diagnostic role of gene molecular profiling, and the effectiveness of the new treatment options available in the corresponding primaries need to be answered.

Declaration of Competing Interest

Dr Baciarello: Advisory boards and symposia: Amgen, Janssen Oncology, Sanofi, Astellas-Pharma, Roche. Travel accommodations, expenses: Amgen, Astellas-Pharma, Astra Zeneca, Ipsen, Janssen Oncology, Sanofi, Roche. None declared for the remaining authors.

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References


Chu, P., Arber, D.A., 2000. Paraffin-section detection of CD10 in 505 nonhematopoietic...


