Chapter 7

# Ovarian Clear Cell Carcinoma: Metastatic Pathways

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Additional information is available at the end of the chapter

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**Abstract**

Ovarian carcinoma reflects the biggest challenge among the field of gynecologic oncology. It represents the most common death cause of genital carcinomas throughout years. The major classification consists of epithelial and non-epithelial types. Due to the histologic origin, epithelial types of ovarian carcinoma are endometrioid, serous-mucinous, and clear cell types. Due to intense metastatic infiltration and rapid tumor spread, clear cell ovarian carcinoma constitutes type of lesion with the most poor prognosis, decreased overall survival, decreased free survival, and poor quality of life of the patient. The metastatic infiltration is strongly accompanied with all significant prognostic factors. All biochemical pathways at the time of the infiltration are correlated with tumor size, lymphatic spread, staging of the lesion, histologic type, and grade of differentiation of the lesion.

**Keywords:** clear cell, chemotherapy, debulking, metastasis, ovarian carcinoma

## 1. Introduction

According to current literature, ovarian cancer represents a high mortality neoplasm in gynecologic malignancy. The 2017 incidence estimates 22,400 new cases in the United States [1]. The increased mortality rate is strongly accompanied with staging of the lesion at the time of the diagnosis. Many predisposition factors influence the therapeutic mapping. Age of the patient, parity, staging, cluster of differentiation, surgical margins, and lymphatic infiltration consist the gold standard of therapeutic strategy (**Figure 1**).

The frequency of the lesion increases in ages between 55 and 65 years old. There are also studies implicating younger or older patients. The lesion is more frequent in developed countries of the Western World and less in Asian countries [2]. Ovarian neoplasms express

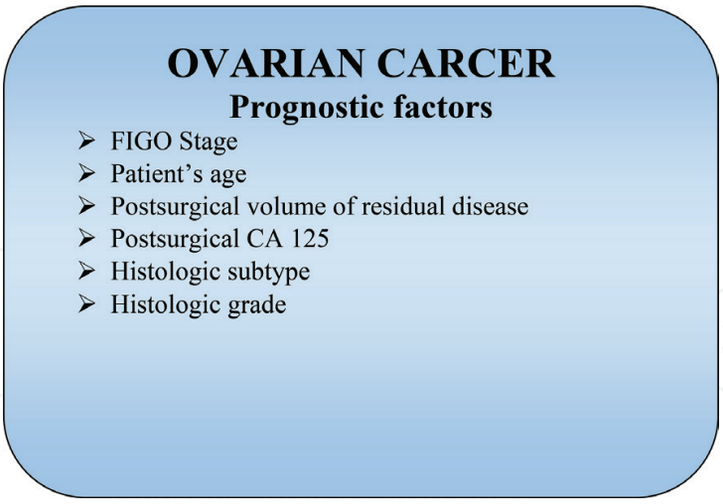


**Figure 1.** Prognostic factors in ovarian cancer. Ozols RF et al. Cancer Principles and Practice of Oncology. 5th ed. 1997;1510.

a wide variety. The most practical and useful classification depends on the histogenetic origin. Histological classification represents an autonomic entity with independent subtypes, disease-free survival, and quality of life of the patient (**Figure 2**).

On the other hand, depiction of histopathology, immunohistochemistry, and molecular genetic analysis reveal five basic types of ovarian carcinoma: high-grade serous carcinoma (HGSC 70%), endometrioid carcinoma (EC 10%), clear cell carcinoma (CCC 10%), mucinous carcinoma (MC 3%), and low-grade serous carcinoma (LGSC <5%) [3] (**Table 1**).

All recent conducted studies with classification parameter of the histogenetic origin express in 90% of cases the epithelial type as the most common type of ovarian carcinoma. Many useful tools, such as physical examination, transvaginal ultrasonography, Ca-125 levels, abdominal CT, or MRI, are mandatory in order to establish a more accurate clinical diagnosis [4]. Depending on clinical diagnosis, proper therapeutic mapping can be performed.

Among histologic subtypes of epithelial ovarian carcinoma, the most significant type with chemoresistance and poor prognosis consists clear cell ovarian carcinoma (CCC).

Clear cell carcinoma represents a distinct entity of epithelial ovarian carcinoma with an incidence less than 5% of all ovarian lesions [5]. Gold standard concerning therapeutic strategy of epithelial ovarian cancer and, respectively, of clear cell carcinoma is based on abdominal total hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy with peritoneal sampling, and lymphadenectomy, adding cytoreductive surgery in advanced cases.

In many cases, surgical mapping for clear cell carcinoma remains a controversial issue. Many studies underline the decreased impact of adjuvant chemotherapy in patients with stage I clear cell carcinoma and the relation of the lesion with overall survival [6]. The ultimate scope of cytoreductive surgery in patients with clear cell carcinoma reflects the acknowledgment of high-risk patients correlated with recurrence of the lesion.

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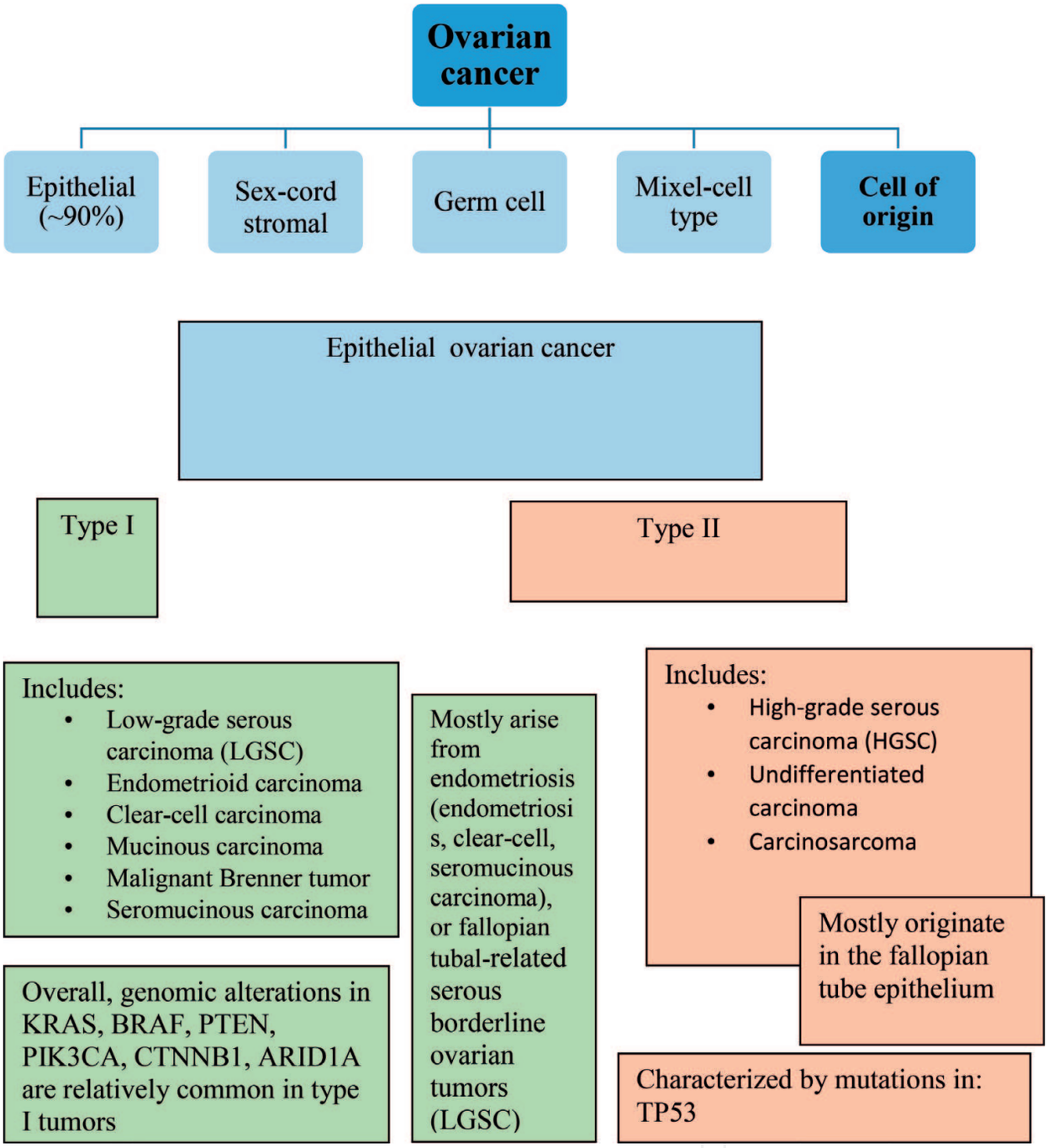


**Figure 2.** (A) Histological subtypes of ovarian cancer and (B) widely accepted epithelial ovarian cancer classification paradigm based on clinic, pathologic, and molecular evidence that type I and type II tumors develop through different pathways. *Indicates rare tumor. †Mucinous and malignant Brenner tumors are considered to be possible exceptions that may arise from transitional cells at or close to the junction of the fallopian tube and the peritoneum. Kurman RJ, Shih Ie M. The dualistic model of ovarian carcinogenesis: Revisited, revised, and expanded. Am. J. Pathol. 2016, 186, 733–747.

The significant role to metastatic pathways of clear cell carcinoma and the therapeutic mapping reflects the histologic configuration of the lesion. Histologic figures of clear cell carcinomas express clear cytoplasm with large nuclei and prominent nucleoli and a partial hobnail appearance (**Figure 3**).

| | HGSC | LGSC | MC | EC | CCC |
|---|---|---|---|---|---|
| Risk factors | BRCA1/BRCA2 | ? | ? | HNPCC[2] | ? |
| Precursor lesions | Tubal intraepithelial carcinoma | Serous borderline tumor | Cystadenoma/ borderline tumor? | Atypical endometriosis | Atypical endometriosis |
| Pattern of spread | Very early transcoelomic spread | Transcoelomic spread | Usually confined to the ovary | Usually confined to the pelvis | Usually confined to the pelvis |
| Molecular abnormalities | BRCA, p53 | BRAF, KRAS | KRAS, HER2 | PTEN, ARIDIA | HNF1, ARIDIA |
| Chemosensitivity | High | Intermediate | Low | High | Low |
| Prognosis | Poor | Intermediate | Favorable | Favorable | Intermediate |

Rat J. New insights into ovarian cancer pathology. Annals of Oncology 23 (Supplement 10): x111-x117, 2012.

HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma; EC, endometrioid carcinoma; CCC, clear cell carcinoma. [a]Hereditary nonpolyposis colorectal carcinoma.

**Table 1.** Ovarian carcinoma: clinical and molecular features of the five most common types.

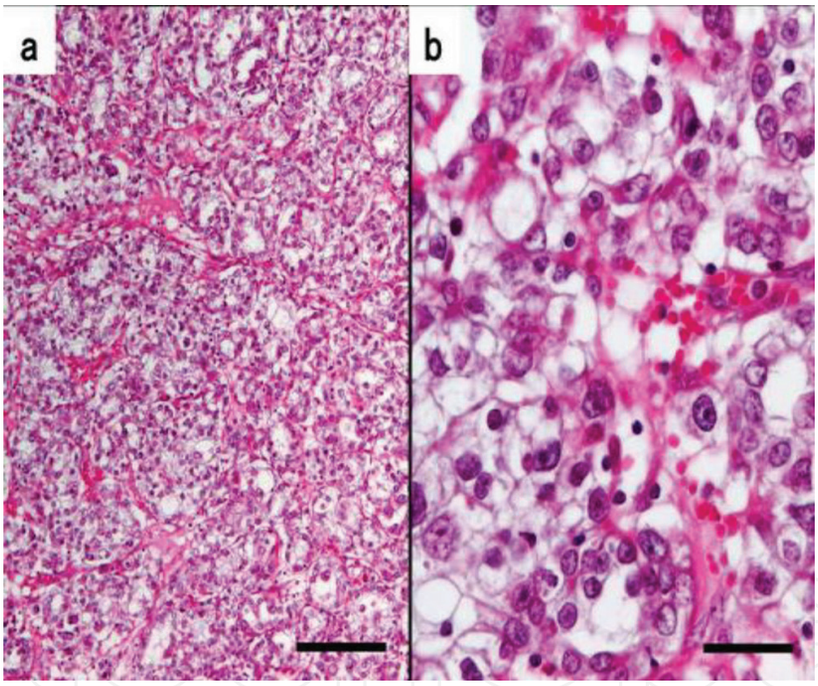


**Figure 3.** Histology of the original tumor. The left ovarian tumor is a clear cell carcinoma, with cells harboring clear cytoplasm and a partial hobnail appearance, as shown by hematoxylin and eosin (HE) staining ((a) bar = 200 μm; (b) bar = 50 μm). Yamada T et al. Characterization of a Novel Cell Line (HCH-3) Derived from a Human Ovarian Clear Cell Carcinoma. Yamada et al., J Carcinogene Mutagene 2017.

## 2. Discussion

Despite poor prognosis, overall survival, and quality of life of the patient, all conducted studies are focusing on the pathologic and metastatic pathways of the lesion. This issue remains controversial.

Szubert et al. described the correlation of endometriosis and clear cell ovarian carcinoma [7]. All the efforts lead to correlate the risk factors of endometriosis and clear cell carcinoma. We must never forget the role of endometriosis as trigger point and prominent risk factor of ovarian cancer. On the other point, many conducted studies depict the opposite statistic conclusion, gaining the impression of controversial issue. Zafrakas et al. correlated all the current data without an informative meta-analysis [8]. More conducted studies were mandatory in order to establish such a hypothesis.

Critical points of clear cell ovarian carcinoma remain the understanding of carcinogenesis, the genetic changes of the lesion, and most of all the mechanisms of target therapy.

Mabuchi et al. described and correlated all the critical genetic changes in clear cell carcinoma [9] (**Table 2**). Focusing on gene mutation, pathway bridge, and following tumor implications, we can explain the carcinogenesis of clear cell carcinoma.

Focusing on tumor angiogenesis, many conducted studies described targeted antibodies as therapeutic shield toward the production of tumor vessels [10]. Classical examples of target therapy consist monoclonal antibodies against vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (PDGF), and angiopoietin/Tie2 receptor complex [11]. Therapeutic philosophy depends on adjunction of monoclonal antibodies with growth factors, in order to prohibit tumor angiogenesis and infiltration. The emphasis in this procedure reflects the significant chemoresistance and poor prognosis of the lesion. The results of this target therapy remain controversial, justifying the significance of therapeutic strategy (**Figure 4**).

All therapeutic strategies consisted of overall survival, patient's quality of life and, in young ages with early stage lesion, the fertility-sparing surgery [12]. There are extreme selected indications, performing this surgical dissection.

Nasioudis et al. using the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database managed to perform the safety of fertility-sparing surgery in stages IA and IC of ovarian clear cell carcinoma [13]. The comparison, in patients with stage I ovarian clear cell carcinoma with preservation of the uterus and ovaries with general survival outcome, did not lead to statistical conclusion. However, further conducted studies are mandatory, in order to establish this type of surgical strategy in young female patients with stage IA or IC ovarian clear cell carcinoma.

Besides understanding the carcinogenesis of the lesion, the biochemical pathways, and the effort of fertility-sparing surgery in young female patients, we must mention the advanced metastatic opportunity of the lesion.

Lymphatic, hematogenic, and endoperitoneal infiltration of the lesion can lead to advanced metastatic possibilities. First of all, the lesion can penetrate the local anatomic organs: the salpinx, round ligament, uterus, peritoneal wall, colon, or even the omentum [14].

The most common, premature, and characteristic route of infiltration consists of the endoperitoneal [15]. All neoplasmatic cells are deafened, entering the peritoneal cavity. Through respiratory movements, endoperitoneal fluid with neoplasmatic cells finally reaches all epithelial

| Gene | Gene type | Change | Pathways affected | Roles in tumor development |
|---|---|---|---|---|
| ARID1A | Tumor suppressor | Mutation in ~50% | SWI/SNF chromatin complex | Modulate accessibility of transcription factors to promoters |
| PIKECA | Oncogenic | Mutation in ~40% | PI3K/AKT/mTOR | Proliferation/survival |
| PPP2R1A | Oncogenic | Mutation in 7% | AKT/MAPK | Proliferation/survival |
| KRAS | Oncogenic | Mutation in 5% | AKT/MAPK | Proliferation/survival |
| BRCA1/BRCA2 | Tumor suppressor | Mutation in 6% | DNA repair | Genomic instability |
| PTEN | Tumor suppressor | Mutation in 5% | PI3K/AKT/mTOR | Proliferation/survival |
| CDKN2A/CDKN2B | Tumor suppressor | Deletion in 9% | CDK inhibitors (p15/p16) | Cell cycle progression |
| ZNF217 | Oncogenic | Amplification in 36% | ZNF217 | Antiapoptosis |
| PPM1D | Oncogenic | Amplification in 10% | P53-mediated apoptosis | Antiapoptosis |
| AKT2 | Oncogenic | Amplification in 14% | AKT/mTOR | Proliferation/survival |
| MET | Oncogenic | Amplification in 37% | AKT/MARK | Proliferation/survival |

ARID1A, AT-rich interactive domain 1A; BRCA, breast cancer; CDK, cyclin-dependent kinase; CDKN, cyclin-dependent kinase inhibitor; MAPK, mitogen-activated protein kinases; mTOR, mammalian target of rapamycin; PIK3CA, phosphatidylinositol-45-bisphosphate 3-kinase catalytic subunit alpha; PI3K, phosphatidylinositol 3-kinase; PPM1D, protein phosphatase 1D; PPP2R1A, protein phosphatase 2 regulatory subunits 1A; PTEN, phosphatase and tensin homolog; SWI/SNF, SWItch/sucrose non-fermentable; ZNF217, zinc finger protein 217.

**Table 2.** Mabuchi S, Sugiyama T, Kimura T. Clear cell carcinoma of the ovary: molecular insights and future therapeutic perspectives. J Gynecol Oncol. 2016May; 27(3); e31.

areas and especially the hemidiaphragms. Final result, building of metastatic lesions as metastatic plaque or in advanced lesion as neoplasmatic "cake" (**Figure 5**). Through the right hemidiaphragm, the lesion can be spread in the pleura area, provoking hydrothorax or reaching the subclavian lymph nodes.

Usual distant organs with signs of infiltration are liver, lungs, and lymph nodes beyond the pelvic and para-aortic chains. Lymphatic spread of this lesion is common. The spread route follows the lymphatic vessels of ligamentum teres uteri or the lymphatic vessels of the right hemidiaphragm. The most common areas are pelvic lymph nodes with less frequent inguinal, axillary, or subclavian lymph nodes.

Hematogenic infiltration is strongly connected with advanced stages of the lesion. In these cases, the most common is liver and lung infiltration. In extreme advanced stages of the lesion, there are cases of skin or brain infiltration.

Nam et al. reported skin metastases in ovarian clear cell carcinoma as severe advanced metastatic area of the lesion [16]. Infiltration of these organs reflects severe decrease of disease-free survival, overall survival, and quality of life of the patient.

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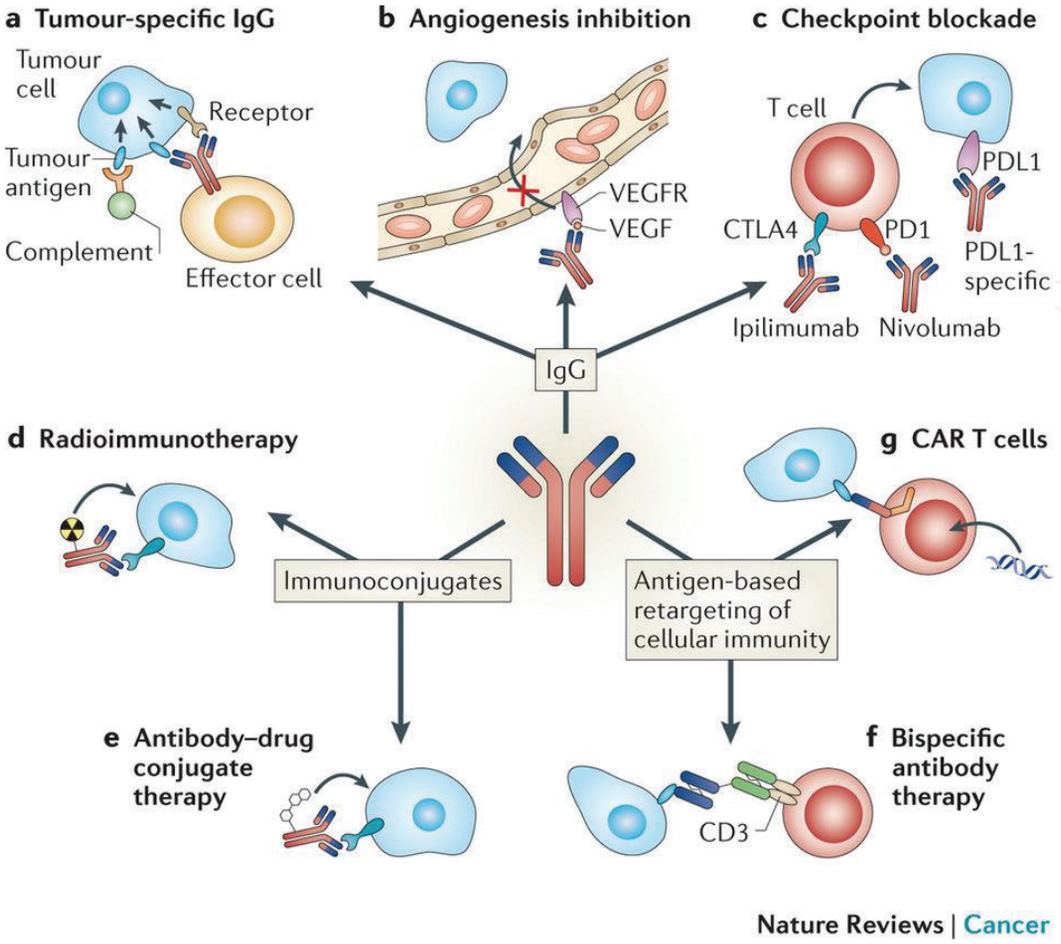


**Figure 4.** Weiner Building better monoclonal antibody-based therapeutics. Nature Reviews Cancer 15,361–370 (2015).

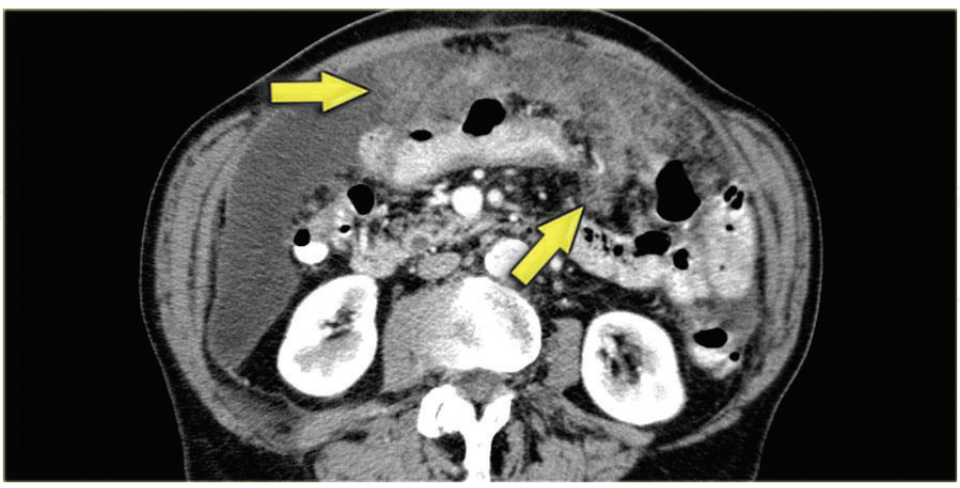

**Figure 5.** Omental cake (arrows) and ascites in a patient with peritoneal metastases derived from ovarian cancer. Levy Angela. Chief Gastrointestinal Radiology, Department of Radiologic Pathology, Armed Forces Institute of Pathology, Washington DC, Associate Professor of Radiology, Uniformed Services University of the Health Sciences, Bethesda, MD.

Postoperative treatment of clear cell ovarian carcinoma deviates, representing a distinct entity from other epithelial ovarian carcinomas. Reflecting a chemoresistant phenotype, the final prognosis of the lesion is poor, decreasing the quality of life of the patient. In cases of clear cell

carcinoma, gold standard combination with paclitaxel and carboplatin consists a not promising therapeutic strategy. Irinotecan hydrochloride, a topoisomerase I inhibitor, reflects an alternative solution regarding the postoperative treatment of clear cell carcinoma [17] (first-line chemotherapy for clear cell carcinoma) (**Table 3**).

Many conducted studies managed to express the synergic effects of the combined therapeutic strategy of irinotecan and cisplatin (**Table 4**).

In cases of recurrent clear cell carcinoma, therapeutic mapping is very disappointed. Even in cases of sensitive platinum disease, the use of antineoplasmatic agents offers a response rate not up to 10% [18] (second-line chemotherapy for clear cell carcinoma).

| Regimen | Author | Year | Response/number of patient, response rate |
|---|---|---|---|
| Conventional platinum based | Goff (28) | 1996 | 1/6, 17% |
| | Sugiyama (29) | 2000 | 3/27, 11% |
| | Ho (30) | 2004 | 4/15, 27% |
| | Takano (9) | 2006 | 5/30, 17% |
| Taxane-platinum | Ecomoto (31) | 2003 | 2/9, 22% |
| | Ho (30) | 2004 | 9/16, 56% |
| | Utsunomiya (32) | 2006 | 8/15, 53% |
| | Takano (9) | 2006 | 9/28, 32% |
| Irinotecan-cisplatin | Takano (9) | 2006 | 3/10, 30% |

Takano et al. Clear cell carcinoma of the ovary: Is there a role of histology-specific treatment? Journal of Experimental & Clinical Cancer Research 2012, 31:53

**Table 3.** Response rates of primary chemotherapy for clear cell carcinoma.

| Regimen | Author | Year | Response/number of patient, response rate |
|---|---|---|---|
| Megestrol acetate | Malailak (45) | 2001 | 2/10, 20% |
| Cyclophosphamide + cisplatin | Takano (46) | 2008 | 1/9, 11% |
| Irinotecan + platinum | Sugiyama (29) | 1998 | 1/3, 33% |
| | Takano (46) | 2008 | 2/15, 13% |
| Etoposide + platinum | Takano (46) | 2008 | 2/13, 15% |
| Paclitaxel + carboplatin | Utsunomiya (32) | 2006 | 3/13, 23% |
| | Crotzer (43) | 2007 | 2/7, 29% |
| Gemcitabine | Crotzer (43) | 2007 | 1/9, 11% |
| | Yoshino (47) | 2012 | 1/5, 20% |
| Docetaxel + irinotecan | Yoshino (47) | 2012 | 1/11, 9% |
| Temsirolimus | Takano (46) | 2011 | 1/5, 20% |

Takano et al. Clear cell carcinoma of the ovary: Is there a role of histology-specific treatment? Journal of Experimental & Clinical Cancer Research 2012, 31:53.

**Table 4.** Response rates of salvage chemotherapy for recurrent or refractory clear cell carcinoma.

The main objective of the previous study was the presentation and implementation of an epithelial-type ovarian carcinoma with specific metastatic pathways, prohibiting especially episodes of target therapy. New scientific keys, in the near future, will unlock unknown biochemical mechanisms and give answers to many questions, concerning the understanding of carcinogenesis of this lesion.

## 3. Conclusion

Ovarian clear cell carcinoma represents a rare histological entity with extreme chemoresistance and poor prognosis in correlation with overall survival and quality of life of the patient. Better understanding of metastatic and biochemical pathways of the lesion could schedule a proper therapeutic mapping. Further conducted studies are needed, in order to establish such strategy.

## Conflict of interest

The author declares any financial interest with respect to this manuscript.

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