Fallopian tube tumors: an overview

Roland Gregor Stein, Joachim Diessner, Arnd Hönig, Jörg Wischhusen, Johannes Dietl

Wurzburg University Hospital, Department of Obstetrics and Gynecology, Josef-Schneider-Str. 4, 97080 Wurzburg, Germany (RGS, JD, AH, JW, JD)

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Identity

Introduction
This article shall give an overview of different tumors occurring in the fallopian tube.
Though being a very rare location of primary or exclusive tumor manifestation, the fallopian tube is now receiving increased attention in gynecological oncology since considerable evidence suggests that it represents the site-of-origin of many (if not most) serous pelvic carcinomas (Folkins et al., 2009; Dietl and Wischhusen, 2011; Dietl et al., 2011; Seidman et al., 2011; Vang et al., 2013).

Disease definition
A tumor is classified as primary fallopian tube tumor when it is either restricted to this anatomical structure, or when the fallopian tube is most affected whereas co-locations such as ovary and uterus show lesser involvement or a different histology (Alvarado-Cabrero et al., 2003; Folkins et al., 2009).

Classification

Note
Solid fallopian tube tumors can be subcategorized based on origin and behavior. The WHO classification distinguishes several groups of solid tumors of the fallopian tube (Alvarado-Cabrero et al., 2003) shown in Figure 1.

Classification

Staging
Malignant tumors of the fallopian tube are classified according to the “Union International contre le cancer” (UICC) and the "Fédération internationale de Gynécologie et d’Obstétrique” (FIGO, Table 1 and 2).
The TNM classification is based on clinical and pathological findings whereas the FIGO classification requires a surgical staging (UICC, 2009; AJCC, 2010). According to the TNM classification, the carcinomas of the fallopian tube approximate different stages (Table 2).
Figure 1: WHO Classification of solid tumors of the fallopian tube (Alvarado-Cabrero et al., 2003).
Table 1: TNM and FIGO Classification of carcinomas of the fallopian tube (UICC, 2009)

<table>
<thead>
<tr>
<th>TNM Category</th>
<th>FIGO Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor confined to fallopian tube(s)</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor limited to one tube, without penetrating the serosal surface</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor limited to both tubes, without penetration the serosal surface</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor limited to one or both tube(s) with extension onto or through the tubal serosa, or with malignant cells in ascites or peritoneal washing</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor involves one or both fallopian tube(s) with pelvic extension</td>
</tr>
<tr>
<td>T2a</td>
<td>Extension and/or metastasis to uterus and/or ovaries</td>
</tr>
<tr>
<td>T2b</td>
<td>Extension to other pelvic structures</td>
</tr>
<tr>
<td>T2c</td>
<td>Pelvic extension (2a or 2b) with malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T3 and/or N1</td>
<td>Tumor involves one or both fallopian tube(s) with peritoneal implants outside the pelvis and/or positive regional lymph nodes</td>
</tr>
<tr>
<td>T3a</td>
<td>Microscopic peritoneal metastasis outside the pelvis</td>
</tr>
<tr>
<td>T3b</td>
<td>Macroscopic peritoneal metastasis outside the pelvis</td>
</tr>
<tr>
<td>T3c and/or N1</td>
<td>Peritoneal metastasis more than 2 cm in greatest dimension and/or positive regional lymph nodes</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis (excludes peritoneal metastasis)</td>
</tr>
<tr>
<td>N0</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N2</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>M0</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M2</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
</tbody>
</table>

Table 1: TNM and FIGO Classification of carcinomas of the fallopian tube (UICC, 2009). Table 2: Staging of fallopian tube carcinomas (UICC, 2009).
Fallopian tube tumors: an overview

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Clinical and pathology

Etiology

The etiology of primary fallopian tube tumors is unknown. Multiparity seems to be protective (Riska et al., 2003), pregnancies and oral contraceptives decrease the risk (Inal et al., 2004). Neither age, nor weight, education level, pelvic inflammatory disease, infertility, previous hysterectomy or endometriosis show significant correlations especially with fallopian tube carcinomas (Henderson et al., 1977; Demopoulos et al., 2001; Inal et al., 2004). Demographic distribution is similar to ovarian cancer, and the highest incidence was found in white, non-Hispanic women and women aged 60-79. However, recent evidence suggests tubal cancer to be much more frequent (Stewart et al., 2007; Piek et al., 2008).

Epidemiology

Epidemiological data on malignant fallopian tube tumors are adequate, even though only 0.3-1.1% of all gynecological malignancies are typically classified as primary fallopian tube carcinomas (Baekelandt et al., 2000), mostly adenocarcinomas (Schneider et al., 2000). In the U.S., the incidence is about 3.6 per million women per year (Rosenblatt et al., 1989). Stage-adjusted survival rates are generally better than for epithelial ovarian carcinoma (Kosary and Trimble, 2002). Underestimation of the real incidence might be due to fallopian tube carcinomas being mistaken for ovarian cancers (Woolas et al., 1994) which show a significantly higher prevalence. Still, Riska and colleagues reported an increasing incidence of fallopian tube carcinomas from 1.2 per million per year for 1953-1957 to 5.4 per million per year from 1993-1997 (Riska et al., 2003).

Clinics

Clinical presentation

Patients with benign tumors of the fallopian tube are often asymptomatic or report local pain. The tumors are incidentally found during operations for other indications (Etoh et al., 2012). Benign tumors can abet tubal torsions (Alvarado-Cabrero et al., 2003). Especially papillomas can obstruct the fallopian tube (Gisser, 1986). Obstruction of the fallopian tube can cause infertility (Heller et al., 1991; Heatley, 2001). Primary fallopian tube carcinomas most frequently occur between the fourth and sixth decade of life with a mean patient age of 55 years (Boutselis and Thompson, 1971; Sedlis, 1978). Stewart et al. found an incidence rate of 0.41 per 100000 women with highest incidence rates in women aged 65-69 in a study including 3051 cases of primary fallopian tube carcinomas (Stewart et al., 2007). Symptoms are very diffuse, the Latzko triad of symptoms - intermittent profuse serosanguinous vaginal discharge, colicky pain relieved by discharge, abdominal or pelvic mass - is reported in only 15% of all patients (Ajithkumar et al., 2005). 5% of the patients show a hydrops tubae profuens. Fallopian tube carcinomas are diagnosed at earlier stages than epithelial ovarian cancers (Peters et al., 1988; Rose et al., 1990; Gadducci et al., 2001; Pectasides et al., 2006). 10-36% show positive PAP smear tests with intermittent detection of abnormal, suspicious or poorly differentiated cells or glands (Ajithkumar et al., 2005). In 80% of the advanced stages, peritoneal metastases occur (Levite et al., 2001). Also haematogenous or transluminal metastases were found (Yoonessi, 1979). Bilateral tubal involvement has been described in 10-27% of fallopian tube carcinomas (Schiller and Silverberg, 1971; Hirai et al., 1989; Rose et al., 1990; Alvarado-Cabrero et al., 1999; Rosen et al., 1999; Gadducci et al., 2001). The higher rate of lymph node metastases in comparison to ovarian cancer should be considered, as staging of fallopian tube carcinomas is surgical. Compared to epithelial ovarian cancer, fallopian tube carcinomas show a higher rate of retroperitoneal and distant metastases (Yoonessi, 1979; McMurray et al., 1986; Maxson et al., 1987; Asmussen et al., 1988; Peters et al., 1988; Gadducci et al., 2001). Para-aortic lymph node metastases were detected in 33% of patients (Tamimi and Figge, 1981). Another study revealed 42-59% lymph node metastases in routine lymphadenectomy with equal involvement of para-aortic and pelvic lymph nodes (Ajithkumar et al., 2005). If routine lymphadenectomy is not performed, a surgical understaging may occur. Overall, 20-25% of patients with fallopian tube carcinomas showed FIGO stage I, 20% stage II, 45-50% stage III and 5-10% stage IV (Ajithkumar et al., 2005). Ectopic β-HCG-production was reported in two cases of serous or undifferentiated fallopian tube carcinomas (Carapeto et al., 1978; Alvarado-Cabrero et al., 1999). These tumors contained synctyiotrophoblast-like cells. Case reports about renin-producing or alpha fetoprotein (AFP)-producing tumors have been published (Aoyama et al., 1996; Zabernigg et al., 1997).

Fallopian tube carcinomas show frequent expression of CA-125 (Pals et al., 1993). Hence, >80% of the patients show elevated CA-125 serum levels (McMurray et al., 1986; Ajithkumar et al., 2005) that correlate significantly with disease-free and overall survival (Rosen et al., 1999; Ajithkumar et al., 2005). Adenomyomas can also cause elevated CA-125 levels and small volumes of serous ascites. With some limitations, CA-125 may thus be considered as suitable tumor marker for use in cancers of the fallopian tube (Baekelandt et al., 2000).
Figure 2: Histology of an invasive serous-papillary adenocarcinoma of the fallopian tube. a: Tumor formation in the tubal wall. b shows 200 fold magnification with gland formation (*). c: Metastasis in adipous tissue. d: Immunohistochemistry for Ki67 with nuclear positivity. e and f: Immunohistochemistry for p53 also with nuclear positivity.
Figure 3: a: In this H&E staining, the STIC cells show polymorphic nuclei and a multilayer epithelium (arrowheads) compared with normal tubal epithelium (arrows). b: Distinct transition from normal tubal epithelium to p53 positive STIC (p53 immunohistochemistry). c: Invasive fallopian tube carcinoma (arrowheads) next to STIC formation (arrows, H&E).

The average lead time of increasing CA-125 levels versus clinical or radiological diagnosis of recurrence is three months with a range from 0.5 to 7 months (Ajithkumar et al., 2005).

Fallopian tube carcinomas can cause paraneoplastic symptoms. For example, a paraneoplastic cerebellar degeneration (PCD) with Anti-Yo antibodies is associated with fallopian tube carcinomas (Levite et al., 2001; Tanaka et al., 2005; Selby et al., 2011).

Pathology

Benign tumors

Benign tumors are often solid and clearly delimited. They arise at the intraluminal or serosal surface of the fallopian tube.

Papillomas show fibrovascular stacks with epithelial lining. They can obstruct the fallopian tube (Gisser, 1986).

Adenofibromas and cystadenofibromas occur between the third and eighth decade. They remain asymptomatic and are diagnosed incidentally during other operations (Zheng et al., 1996). Macroscopically, these tumors grow to 0.5-3cm and can be intraluminal or at the serosa surface as well as at the fimbriae. They show a stromal and a papillary structured fraction (Alvarado-Cabrero et al., 2003). In fallopian tubes resected post partum, few metaplastic papillary tumors were detected (Saffos et al., 1980; Keeney and Thrasher, 1988; Bartnik et al., 1989). These tumors consist of papillae lined by epithelium displaying patterns of a serous borderline tumor. The cells can be positive for intracellular mucin (Alvarado-Cabrero et al., 2003). Adenomyomas consist of bundle-like growing leiomyoma cells and sometimes endometrial tissue remnants.

Endometrioid polyps occur in the interstitial part of the tube attached to the intratubal epithelium and sometimes cause infertility (Heller et al., 1991; Heatley, 2001).

Cystadenofibromas can show vimentin-cytokeratin-coexpression. Further, diffuse apical epithelial membrane antigen (EMA) immunoreactivity occurs. Gürbüz et al. suggest that tumors are derived from embryonic remnants of the Mullerian duct (Gürbüz and Ozkara, 2003).

Borderline tumors of the fallopian tube occur very rarely and can show serous, mucinous or endometrioid differentiations. Histological features resemble those in borderline tumors of the ovary (Alvarado-Cabrero et al., 1997). Mucinous tumors of the fallopian tube can
be associated with pseudomyxoma peritonei (McCarthy and Aga, 1988), other mucinous lesions or Peutz-Jeghers-Syndrome (Seidman, 1994). There are also reports about adenofibroma with borderline malignancy. The prognosis seems to be favorable (Zheng et al., 1996; Alvarado-Cabrero et al., 1997).

**Precursor lesions: Intraepithelial carcinoma**

Non-invasive carcinomas of the fallopian tube were formerly known as "carcinoma in situ". This term should be abandoned as it implies restricted local tumor formation. Intraepithelial carcinoma cells can, however, form implants on the ovarian surface and the peritoneum. Recent publications highlight the fallopian tube as likely site-of-origin of primary pelvic serous carcinomas detected in the fallopian tube, the ovary or the peritoneum (Folkins et al., 2009; Dietl and Wischhusen, 2011; Dietl et al., 2011; Seidman et al., 2011; Vang et al., 2013). Serous tubal intraepithelial carcinomas (STIC) as well as endometrioid intraepithelial carcinomas (EIC) are thus considered as precursor lesions (Ambros et al., 1995; Carlson et al., 2008). This hypothesis is supported by findings from Colgan et al. who found a high frequency of pre-cancerous lesions in fallopian tubes from patients with BRCA gene mutations (Colgan, 2003). Lee and colleagues could detect mutant p53-signatures predominantly in epithelial cells at the fimbriated ends of fallopian tubes from patients with BRCA1 and 2 mutations. Moreover, the same signatures were also found in corresponding ovarian cancer tissues (Lee et al., 2007). Interestingly, Li-Fraumeni-Syndrome - which is associated with p53 mutations and generally increased risk for serous carcinomas - does not correlate with a higher incidence of PPSC, especially fallopian tube carcinomas. Thus, it seems that other mutations e.g. those affecting BRCA are required to drive PPSC development (Xian et al., 2010). Kim and colleagues could prove by histology that serous epithelial cancers develop in the fallopian tubes of Dicer-PTEN-double-knockout mice. By histology and pathological behavior these tumors showed characteristic traits of serous epithelial ovarian cancer, even though oophorectomy was not protective. Instead, tumor development could be prevented by salpingectomy (Kim et al., 2012). Furthermore, in prophyphactic salpingo-oophorectomy specimen, occult carcinomas are more frequent in the fallopian tube than the ovary (Vang, 2011). While carrying the potential of invasiveness, the STIC cells grow sparing the tubal stroma. Figure 3 focusses on the STIC with its distinct cellular alterations such as polymorphic nuclei, multilayer epithelium and atypic mitoses. Figure 3d also shows an invasive fallopian tube carcinoma with an adjoining STIC.

In clinical studies, a frequent coexistence of pelvic serous carcinoma and tubal intraepithelial carcinomas was found in unselected (Przybycin et al., 2010) and BRCA mutated patients (Kindelberger et al., 2007). Shortening of telomeres is another early event in PPSC development and already detectable in the STIC (Kuhn et al., 2010).

As the post-reproductive fallopian tube lacks physiological functions and also causes complications such as hydrosalpinx, Dietl et al. suggested combined hysterosalpingectomy instead of simple hysterectomy or salpingectomy as a recommendable method for sterilization in clinical routine (Dietl and Wischhusen, 2011; Dietl et al., 2011).

**Invasive carcinoma**

All tumor subtypes in the ovaries are also known in the fallopian tube, with serous carcinomas being most frequent. In a series of 105 fallopian tube carcinomas Alvarado-Cabrero et al. found the following distribution of different histologies: About 50% were serous, 25% endometrioid, 20% transitional cell or undifferentiated carcinomas and 5% were of other subtypes (Alvarado-Cabrero et al., 1999).

Serous adenocarcinomas are generally invasive with 50% G3 tumors (Alvarado-Cabrero et al., 1999). Sometimes immune cell invasion disguises the tumor as salpingitis (Cheung et al., 1994). Mucinous adenocarcinomas, a very rare entity, are often associated with other mucinous carcinomas of the female genital tract or the appendix (Seidman, 1994). Endometrioid adenocarcinomas are very often non-invasive or superficially invasive and show a favorable prognosis (Navani et al., 1996). A part of those tumors displays characteristics of the wolffian adnexal tumor (Daya et al., 1992; Navani et al., 1996). Clear cell adenocarcinomas account for 2-10% of all fallopian tube carcinomas (Voet and Lifshitz, 1982; Hellstrom et al., 1994; Alvarado-Cabrero et al., 1999). Transitional cell carcinomas are rare in the genital tract. Still, the frequency between 11 and 43% of all fallopian tube carcinomas makes it an important locus-specific entity (Uehira et al., 1993; Alvarado-Cabrero et al., 1999).

Undifferentiated carcinomas lack any patterns of squamous cells or glandular cells but instead contain multinuclear giant cells (Alvarado-Cabrero et al., 1999). Lacy et al. reported immunohistochemical positivity for c-erbB-2 (HER-2/neu) overexpression in 26% and p53 positivity in 61% of all cases in a cohort of 43 patients with fallopian tube carcinoma. There was not significant correlation with survival (Lacy et al., 1995). Ovarian cancer in comparison also shows c-erbB-2 (HER-2/neu) positivity in about 29% of all cases (Lanitis et al., 2012). Others, in contrast, described a correlation between p53 immunohistochemical positivity and shorter survival (Zheng et al., 1997; Rosen et al., 2000). FIGO stages, however, did not correlate with survival in this same cohort of 63 patients (Rosen et al., 2000). Zheng et al. investigated the correlating immunohistochemistry and polymerase chain reaction-single-strand conformation polymorphism (PCR-SSCP) for p53 in 52 cases of fallopian tube carcinoma and 10 normal fallopian tubes.
and found that p53 alterations already occur at early stages suggesting a role in early tumor progression (Zheng et al., 1997). Chung and colleagues found that survival neither correlated with immunohistochemical p53 positivity nor with cMyc overexpression (which occurred in 61%). However, the statistical power of this study was limited by the small cohort of 18 patients (Chung et al., 2000). Hence, it did not challenge larger studies which proposed that p53 might have an important role especially in familial BRCA-associated cases of fallopian tube carcinomas. Figure 2 shows different pathohistological aspects of a serious adenocarcinoma of the fallopian tube.

**Mixed epithelial-mesenchymal tumors**
The least common site for malignant Müllerian mixed tumor (carcinosarcoma, metaplastic carcinoma) is the fallopian tube accounting for only 4% of all cases. The prognosis of these mostly postmenopausal patients is poor (Hanjani et al., 1980). In the literature, only one adenosarcoma has been described in the fallopian tube (Gollard et al., 1995).

**Soft tissue tumors**
Leiomyosarcomas are very rare as only 37 cases have been reported in 100 years (Jacoby et al., 1993).

**Mesothelial tumors**
Adenomatoid tumors mostly occur in middle-aged or elderly women (Inoue et al., 2001). In most cases, they remain asymptomatic but can also obstruct the lumen. Often, they show gland-like structures with a lining of flat to cuboidal cells (Stephenson and Mills, 1986).

**Germ cell tumors**
Until 2003, 50 cases of mature or immature teratoma were reported (Alvarado-Cabrero et al., 2003). For malignant mixed germ cell tumors of the fallopian tube, only one single case was published (Li et al., 1999).

**Trophoblastic tumors**
Only about 4% of choriocarcinomas occur in the fallopian tube (Dekel et al., 1986). About 40% of these go along with adnexal tumors (Ober and Maier, 1981). In the fallopian tube, hydatidiform moles can histologically correspond to a complete, partial or invasive mole (Alvarado-Cabrero et al., 2003). Placental site nodules as non-neoplastic proliferation of intermediate trophoblast can occur (Alvarado-Cabrero et al., 2003). Intermediate trophoblast tumors can be either benign or malignant (Kurman et al., 1976). Only one case of malignant placental site trophoblastic tumor has been reported in the fallopian tube (Su et al., 1999).

**Lymphoid and haematopoietic tumors**
Malignant lymphoma and leukemia mostly show an involvement of the ipsilateral ovary (Osborne and Robboy, 1983). 25% of patients with ovary lymphomas had a Burkitt-lymphoma or Burkitt-like lymphoma or a diffuse large-cell lymphoma.

**Metastatic tumors**
For 89% of secondary tumors in the fallopian tube, the primary tumor was assigned to be of ovarian origin (Woodruff and Julian, 1969). Considering the ongoing paradigm shift which proposes that serous ovarian carcinomas likely originate from the fallopian tube, these figures have to be reconsidered. Many of these tumors may have originated from the fimbriated end of the fallopian tube with a secondary manifestation in the ovary.

**Treatment**

**Surgical therapy:** For fallopian tube tumors and especially for carcinomas, surgical removal is the first line treatment. Whereas benign tumors can usually be resected completely, the approach for fallopian tube carcinomas should be the same as for epithelial ovarian cancer with the aim of complete resection or at least maximum tumor debulking.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA-B, optimal surgical staging, no pre-or intraoperative rupture</td>
<td>No further treatment</td>
</tr>
<tr>
<td>IA-B, suboptimal surgical staging, pre- or intraoperative rupture</td>
<td>Carboplatin (AUC6) plus Paclitaxel (175 mg/m²) every 3 weeks for 3-6 cycles</td>
</tr>
<tr>
<td>IC-IIIA</td>
<td>Carboplatin (AUC6) plus Paclitaxel (175 mg/m²) every 3 weeks for 6 cycles</td>
</tr>
<tr>
<td>IIb-IV</td>
<td>Carboplatin (AUC5-6) plus Paclitaxel (175 mg/m²) every 3 weeks for 6 cycles</td>
</tr>
</tbody>
</table>

Table 3: Postoperative treatment of fallopian tube carcinoma (Pectasides et al., 2006)
Special focus should be placed on para-aortic and pelvic lymphadenectomy in regard to the higher rate of lymph node metastases (Yoonessi, 1979; McMurray et al., 1986; Maxson et al., 1987; Asmussen et al., 1988; Peters et al., 1988; Gadducci et al., 2001). Klein and colleagues found a significantly reduced median survival of 21 months versus 43 months in patients who had not undergone lymphadenectomy (Klein et al., 1999).

**Radiotherapy:** Although radiotherapy for fallopian tube carcinomas could be considered, it is inferior to adjuvant platin compounds containing chemotherapy. Neither irradiation nor intraperitoneal instillation of radioisotopes could prevent relapse (Asmussen et al., 1988). A second look operation with pathological complete remission (pCR) is a predictor for longer survival. 50% of patients with surgical complete remission will ultimately relapse. Thus, second-look operations are not generally beneficial and hence no routine treatment (Takeshima and Hasumi, 2000).

**Adjuvant chemotherapy:** Baekelandt et al. found a 70% response rate to adjuvant platinum-containing chemotherapy in platinum-naïve patients with median response duration of 12.5 months. They further suggested to refrain from postoperative radiation therapy due to its low efficacy and high rate of complications (Baekelandt et al., 2000). Kosary et al. gave the general recommendation to treat women with fallopian tube carcinomas like women with epithelial ovarian cancer, i.e., by surgical staging and debulking followed by adjuvant chemotherapy (Kosary and Trimble, 2002). In addition to platinum-based chemotherapy, also paclitaxel is becoming more and more important in the treatment of advanced fallopian tube tumors (Takeshima and Hasumi, 2000). Patients with early stages as IA and IB might not need adjuvant chemotherapy. For all higher stages, adjuvant combined chemotherapy is requested. Two randomized controlled trials (International Collaborative Ovarian Neoplasm 1 (ICON1) and Adjuvant Chemotherapy In Ovarian Neoplasm (ACTION)) compared platinum based adjuvant chemotherapy and mere observation after early stage ovarian cancer surgery and reported 5 year overall survival rates of 74% without and 82% with adjuvant platinum based chemotherapy (Trimbos et al., 2003). This could hint at a survival benefit being associated with adjuvant chemotherapy also for early stage fallopian tube carcinomas. Cisplatin based chemotherapy yielded response rates between 53 and 92 % (Deppe et al., 1980; Raju et al., 1981; McMurray et al., 1986; Maxson et al., 1987; Peters et al., 1988; King et al., 1989; Muntz et al., 1989; Barakat et al., 1993; Pectasides et al., 1994). Several studies also included Paclitaxel in the first line therapy (McMurray et al., 1986; Maxson et al., 1987; Muntz et al., 1991; Ben-Hur et al., 1999; Gennimi et al., 2001). For relapse therapy, data from epithelial ovarian cancer in platinum-pretreated patients also highlights the role of Paclitaxel (Treskusos et al., 1995; Baekelandt et al., 2000; Ichikawa et al., 2000; Gadducci et al., 2001). After review of the literature and according to the U.S. guidelines, Pectasides and colleagues suggested an adjuvant standard treatment shown in table 3 (Pectasides et al., 2006).

For the treatment of relapse, platinum-sensitive tumors (relapse after more than 6 months) receive a reintroduction with platinum with or without Paclitaxel, whereas patients with platinum-refractory (relapse during therapy) or platinum-resistant tumors (relapse ≤6 months) receive Topotecan or liposomal Doxorubicin (Pectasides et al., 2006). In epithelial ovarian cancer, Bookman and colleagues as well as Hoskins et al. treated patients with relapse after platinum- and Paclitaxel-based chemotherapy with Topotecan (Bookman et al., 1998; Hoskins et al., 1998). Also liposomal Doxorubicin can achieve response rates of 17-26% in patients who have relapsed after platinum- and Paclitaxel based chemotherapy (Muggia et al., 1997; Gordon et al., 2000). Recent data from the OCEANS trial revealed that addition of Bevacizumab to the combination of carboplatin/gemcitabine increases the response rate and prolongs progression-free survival in patients with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer. Overall survival, however, remained unchanged (Aghajanian et al., 2012).

Likewise, the CALYPSO trial which tested the combination of pegylated liposomal doxorubicin (PLD)/carboplatin with paclitaxel in platinum-sensitive ovarian cancer patients found a prolonged time to progression along with reduced side effects of PLD as compared to paclitaxel. Again, however, there was no effect on overall survival (Wagner et al., 2012). Still, an intermediate report from the AURELIA trial suggests that supplementation of chemotherapy with Bevacizumab might be highly beneficial for patients with platinum-resistant ovarian cancer (Pujade-Lauraine et al., 2012).

**Prognosis**

Prognostic factors for early stage I carcinomas are depth of invasion into the tubal wall and tumor rupture during surgery. Even early stages tend to metastasize to the peritoneum (Baekelandt et al., 2000). The surgical stage is an independent prognostic factor (Alvarado-Cabrero et al., 1999; Baekelandt et al., 2000). Carcinomas of the fimbriae region are afflicted by a worse prognosis than carcinomas of the isthmic region (Alvarado-Cabrero et al., 1997). There are different results concerning the histological grading: Vaughan et al. found a significant correlation between grading and survival (Vaughan et al., 1998). Gadducci et al. could also find this in univariate but not
in multivariate analysis (Gadducci et al., 2001). Grading further correlates with lymphogenous metastases (Klein et al., 1999). Lymphocytic infiltration of the tumor correlates with favorable outcome (Rosen et al., 1993). The role of DNA-ploidy is thought to be negligible (Klein et al., 2002).

Fallopian tube carcinoma patients show an overall survival of 30-50% which is slightly better than the reported 25-40% for epithelial ovarian cancer (Momtazee and Kempson, 1968; Baekelandt et al., 1993; Barakat et al., 1993; Woolas et al., 1994; Alvarado-Cabrero et al., 1999; Piura and Rabinovich, 2000).

The general 5-year survival rate is about 65% (Sedlis, 1978; Deppe et al., 1980; Inal et al., 2004). Kosary and colleagues found in a cohort of 416 women with fallopian tube carcinoma 5 year-survival rates of 95% for stage I (n=102), 75% for stage II (n=29), 69% for stage III (n=52) and 45% for stage IV (n=151) (Kosary and Trimble, 2002).

Genetics

Note
Fallopian tube carcinomas can manifest as a consequence of the hereditary breast-ovarian cancer syndrome. They are associated with BRCA1 and BRCA2 mutations. In a cohort of 44 cases of fallopian tube carcinoma, 11% of the patients were positive for BRCA1 mutation and 5% were positive for BRCA2 mutations. Of the patients who received their diagnosis before the age of 55 years, 28% (5/18) were BRCA positive. First degree relatives of fallopian tube cancer patients show an increased risk for early breast and ovarian cancer (Aziz et al., 2001).

A BRCA1-carrier patient undergoing prophylactic salpingo-oophorectomy showed a fallopian tube cancer (Hartley et al., 2000). A positive family history of fallopian tube carcinoma was predictive for BRCA1 mutation in 26 Canadian breast-ovarian cancer families (Tonin et al., 1995). Friedman et al. reported fallopian tube carcinomas in 2 of 12 families with BRCA1 mutations (Friedman et al., 1995). Tonin et al. found BRCA1 mutations in four Ashkenazi Jewish breast-ovarian cancer families with fallopian tube carcinoma (Tonin et al., 1996). Zweemer and colleagues detected fallopian tube carcinomas in 2 of 23 families with known BRCA1 mutations (Zweemer et al., 2000).

Thus, genetic evaluation should become part of the diagnostics for patients with fallopian tube carcinomas. In risk patients, prophylactic oophorectomy should be accompanied by salpingectomy (Aziz et al., 2001). And whether salpingectomy without oophorectomy is sufficient treatment will be analyzed in the clinical trials yet to come. Jongsma and colleagues reported frequent loss of heterozygosity (LOH) on chromosome 13 in BRCA1-associated cases of fallopian tube carcinomas indicating that these areas may contain putative tumor suppressor genes (Jongsma et al., 2002).

Different authors (see above) found that immunohistochemical or PCR-based positivity for p53 alterations correlates with shorter survival (Hellstrom et al., 1994; Zheng et al., 1997; Rosen et al., 2000).

Cytogenetics

Note
In BRCA1-related cases of ovarian and fallopian tube carcinoma, loss of heterozygosity (LOH) studies revealed high LOH frequencies on chromosome 13q11, 13q14, 13q21, 13q22-23, 13q32 and 13q32-4 that were independent of type of BRCA1 mutation, stage and grade.

The authors suggested the long arm of chromosome 13 to contain putative tumor suppressor genes (Jongsma et al., 2002).

Genes involved and proteins

**BRCA1 (breast cancer 1, early onset)**

Location
17q21

DNA / RNA
6 different mRNA variants that undergo alternative splicing. Splicing influences intracellular function and location. According to ENTREZ Gene, BRCA1 starts at NC_000017.10 (41196312..41277500, complement), Spidey (mRNA to genomic sequence alignment tool, http://www.ncbi.nlm.nih.gov/spidey) finds 24 exons. The mRNA consists of ~81.2kb.

Protein
The encoded protein functions as intracellular tumor suppressor with E3-ubiquitin ligase- and phosphopeptide binding activity. As a transcription factor, it is a DNA damage sensor forming (together with other proteins) the BRCA1-associated genome surveillance complex (BASC). Germline mutations lead to the familiar breast and ovarian cancer syndrome with highly increased risk for cancer development. Working together with RNA polymerase II, the protein has an important role in transcription, DNA repair of double-stranded breaks, and recombination. There are five different protein isoforms. Isoform 1 is the biggest with 1863 amino acids and 220 kDa. The highest expression of BRCA1 is found in the ovaries, thymus and testes.

**BRCA2 (breast cancer 2, early onset)**

Location
13q12.3

DNA / RNA
According to Spidey, BRCA2 has 27 exons. The mRNA spans about 84.2 kb. In exon 11, the BRC repeats are encoded.
Protein
Also BRCA2 is involved in DNA stability, especially the double strand repair.
The several BRC motifs in the protein bind the RAD51 recombinase and thus enable DNA repair. The protein consists of 3418 amino acids with a weight of 384 kDa.

STK11 (serine/threonine kinase 11)
Location
19p13.3
Note
Mutation of this tumor suppressor gene causes the autosomal dominant Peutz-Jeghers-Syndrome which is characterized by intestinal polyposis and pigmented naevi as well as increased tumor risk (Jeghers et al., 1949; Giardiello et al., 1987). The protein is regulated by androgens and estrogen in adipocytes (McInnes et al., 2012).

DNA / RNA
The gene consists of 10 exons which encompass 23 kb.

Protein
The protein regulates cell polarity and functions as a tumor suppressor. It consists of 433 amino acids with a weight of 48.6 kDa.

ERBB2 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian))
Location
17q12
Note
Other names: HER-2/neu, c-erbB-2.

DNA / RNA
31 exons, 2 mRNA variants encoding 2 proteins: isoform a and b.

Protein
This protein is a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases. It forms heterodimers with other EGFRs that (unlike ErbB-2) have a ligand binding domain and can thus initiate intracellular signaling leading to activation of pathways such as mTOR or PI3K. Overexpression is known for several cancers such as breast and ovarian but also fallopian tube carcinomas.
Based on a cohort of 43 patients with fallopian tube carcinoma, Lacy et al. found immunohistochemical positivity for c-erbB-2 (HER-2/neu) overexpression in 26% and p53 positivity in 61% of these tumors, but no significant correlation with survival (Lacy et al., 1995). Others, however, described p53 immunohistochemical positivity to be associated with shorter survival (Zheng et al., 1997; Rosen et al., 2000) whereas FIGO stages were not predictive for the outcome in this cohort of 63 patients (Rosen et al., 2000).
Using 52 cases of fallopian tube carcinoma and 10 normal fallopian tubes, Zheng et al. investigated the p53 status based on immunohistochemistry and polymerase chain reaction-single-strand conformation polymorphisms (PCR-SSCP) and suggested that p53 alterations play a role in early tumor progression as they are not restricted to late stages (Zheng et al., 1997).
Chung and colleagues found that survival neither correlated with immunohistochemical p53 positivity nor with C-Myc overexpression (which occurred in 61%). However, the statistical power of this study was limited by the small cohort of 18 patients (Chung et al., 2000).

MYC (v-myc myelocytomatosis viral oncogene homolog (avian))
Location
8q24
DNA / RNA
3 exons, 1 variant, 1 isoform.

Protein
The protein plays a role in cell cycle and apoptosis. It functions as transcription factor. Overexpression is known in several cancers especially leukaemias and...
Lymphomas like Burkitt’s lymphoma. Chung and colleagues found that survival neither correlated with immunohistochemical p53 positivity nor with cMyc overexpression (which occurred in 61%). However, the statistical power of this study was limited by the small cohort of 18 patients (Chung et al., 2000).

To be noted

Note
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References


Voet RL, Lifshitz S. Primary clear cell adenocarcinoma of the fallopian tube: light microscopic and ultrastructural findings. Int J Gynecol Pathol. 1982;1(3):292-8


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Jacoby AF, Fuller AF Jr, Thor AD, Muntz HG. Primary leiomyosarcoma of the fallopian tube. Gynecol Oncol. 1993 Dec;51(3):404-7


Alvarado-Cabrero I, Navani SS, Young RH, Scully RE. Tumors of the fimbriated end of the fallopian tube: a clinicopathologic analysis of 20 cases, including nine carcinomas. Int J Gynecol Pathol. 1997 Jul;16(3):189-96


Alvarado-Cabrero I, Young RH, Vamvakas EC, Scully RE. Carcinoma of the fallopian tube: a clinicopathological study of 105 cases with observations on staging and prognostic factors. Gynecol Oncol. 1999 Mar;72(3):367-79


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