Review Cancer of the fallopian tube

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Primary cancer of the fallopian tube is a rare malignancy of the female genital tract. The majority are papillary serous adenocarcinomas. Malignant epithelial lesions of the fallopian tube behave in a similar way to malignant epithelial ovarian tumours. Diagnosis of primary fallopian tube malignancies is difficult, especially in the earlier stages. Careful surgical and pathological staging is important. The management of fallopian tube cancer is similar to that of ovarian cancer. Although the overall survival at five years of women with epithelial tubal cancer is higher than for those with ovarian cancer, when compared stage for stage, women with early fallopian tube cancer may have a poorer prognosis. Further clinical research is needed to define definite aetiological, diagnostic and prognostic markers and to compare management modalities.

Keywords chemotherapy / laparotomy / papillary serous adenocarcinoma / primary fallopian tube cancer / surgical pathological staging

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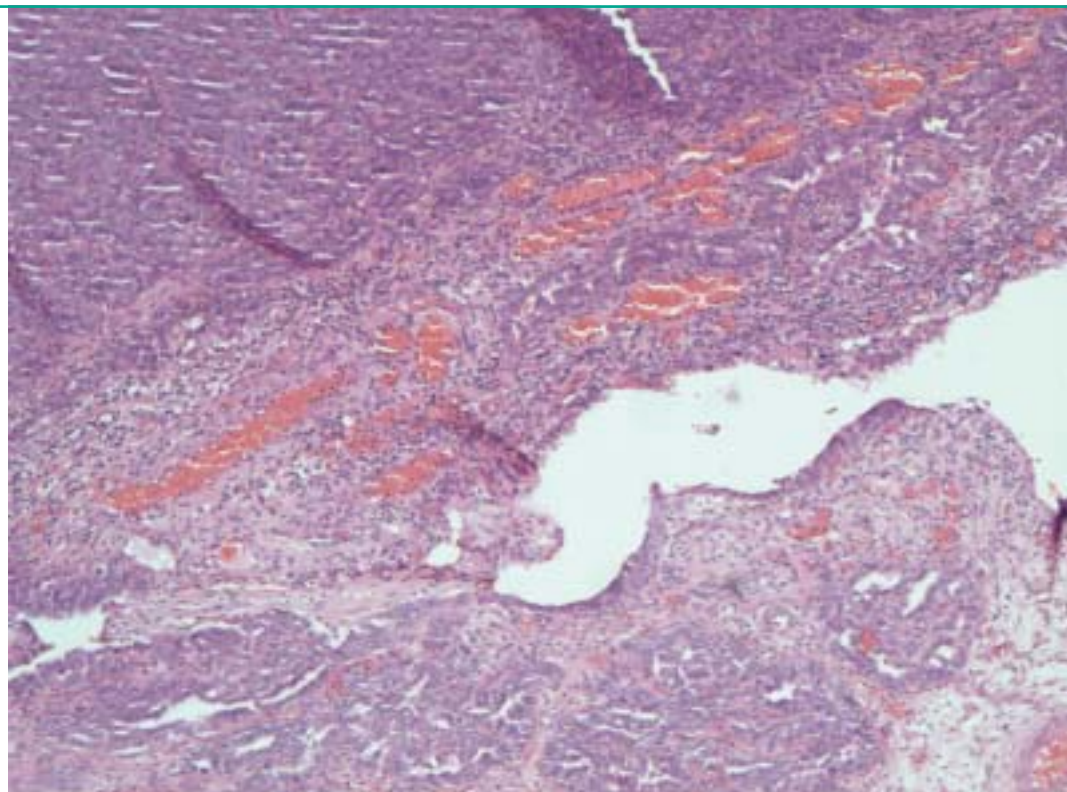Cheltenham General Hospital, Cheltenham, UK

Introduction

Primary cancer of the fallopian tube is a rare malignancy of the female genital tract. It accounts for between 0.1–1.8% of all gynaecological cancers diagnosed.[1,2] More than 60% of cases occur in postmenopausal women, with a mean age of 55 years.[3] Bilateral disease is uncommon and represents fewer than 25% of cases.[4]

Although the fallopian tubes are derived from the same embryonic structure as the uterus, malignant

lesions of the fallopian tubes behave like ovarian tumours both histologically and clinically.

Aetiology

Although no consistent predisposing factors have been identified, the aetiology may be similar to ovarian carcinoma. No statistically significant correlation has been found between tubal cancer and age, race, infertility, pelvic inflammatory disease, endometriosis or smoking. However, as with ovarian cancer, it has been reported that oral contraceptive use and pregnancy history may decrease tubal cancer risk significantly.[5] Indeed, some studies have demonstrated a similar frequency of structural chromosomal changes to those seen in ovarian cancer, including *BRCA1* and *BRCA2* gene mutations. Consequently, a common molecular pathogenesis has been suggested.[6]

In a study[7] of an Ashkenazi Jewish population, the lifetime risk of tubal cancer for patients with *BRCA* heterozygotes was greater than in the general

population, although the overall lifetime risk seems to be relatively low (0.6%). The study showed that mutation carriers had a younger mean age at diagnosis but, overall, better median survival. More recently, predictive *BRCA* testing in prophylactic salpingo-oophorectomy specimens has led to the recognition that clinically occult tubal carcinomas are frequently *in situ* or are small, early-stage invasive carcinomas.[8] There have also been reported cases of fallopian tube cancer and synchronous breast cancer.[9] On the basis of this evidence a case could be made for bilateral salpingectomy in all women who undergo prophylactic bilateral oophorectomy for increased risk of ovarian cancer.

Pathology

Like other cancers of the upper female genital tract, primary fallopian tube cancers show a histological dominance of serous type tumours **(Figure 1)**. More than 90% of fallopian tube carcinomas are papillary serous adenocarcinomas.[1] Other tumour types include endometroid, transitional cell, undifferentiated, clear cell and mixed. The fallopian tubes are relatively frequently involved secondarily from other primary sites: most often the ovaries, endometrium, gastrointestinal tract or breast. They may also be involved in primary peritoneal carcinomatosis.[10]

The close proximity of the fallopian tubes to the ovaries and the uterus sometimes makes it difficult to identify a true primary. The diagnostic pathological criteria for primary fallopian tube

malignancy shown in **Box 1** are widely accepted and commonly used.[11,12]

Diagnosis

Preoperative diagnosis of primary fallopian tube malignancy is very difficult, especially in the earlier stages, as it is not routinely suspected. Correct preoperative diagnosis is made in only around 0.3% of cases[13] and diagnosis is more frequently made perioperatively or postoperatively. Disease is often found incidentally at laparotomy.

If there are symptoms, abnormal vaginal bleeding or profuse watery vaginal discharge are the commonest. These may be associated with vague lower abdominal pain, abdominal distension and pressure. Fewer than 10% of women present with the classic description of hydrops tubae profluens: a palpable pelvic mass that resolves during examination and is associated with a watery vaginal discharge.[14] Rarely, it can manifest as an acute abdominal emergency with pelvic pain.[15] Clinical examination will sometimes reveal an adnexal mass.

Cytology

Tubal cancer has been diagnosed from incidental findings of abnormal glandular cells by routine cervical smear **(Figure 2)**. Clinicians, as well as pathologists, should consider the possibility of fallopian tube cancer if cervical or endometrial cytology shows atypical glandular cells but an endometrial or cervical primary cannot be proven. If a cytological specimen suggests adenocarcinoma, the most probable disease is endometrial adenocarcinoma, with the second most probable

• Tumour clearly arises from the endosalpinx
• Histology represents the epithelium of tubal mucosa
• Transition from benign to malignant epithelium is evident
• Ovary and endometrium are either normal or there is a tumour smaller than the one in the tube

Box 1
Pathological criteria for primary fallopian tube malignancy

disease being cervical adenocarcinoma or adenosquamous carcinoma. However, adnexal malignancies are responsible for up to 10% of cases.[16]

In a study[17] to determine the clinical usefulness of investigations to detect fallopian tube carcinoma, positive rates were found to be 25% for cervicovaginal smears and 50% for endometrial aspiration in the absence of endometrial invasion. Clinical staging or tumour differentiation did not influence the positive cytology. In another retrospective study,[18] preoperative cytological diagnosis was positive for malignant cells in up to 60% of women with fallopian tube carcinoma. The yield of positive cervical smear diagnoses in extrauterine malignancies is highest in women with a primary neoplasm.[19]

When atypical glandular cells are found by a routine smear, further diagnostic tools should include a repeat smear, colposcopy and hysteroscopy with endometrial biopsy. If cervical and endometrial assessment is negative, ultrasound, laparoscopy and even a laparotomy with pelvic clearance and pathological examination of the entire tubal specimen should be considered.

CA125 is raised in a significant percentage of cases (up to 70%). There has been a reported
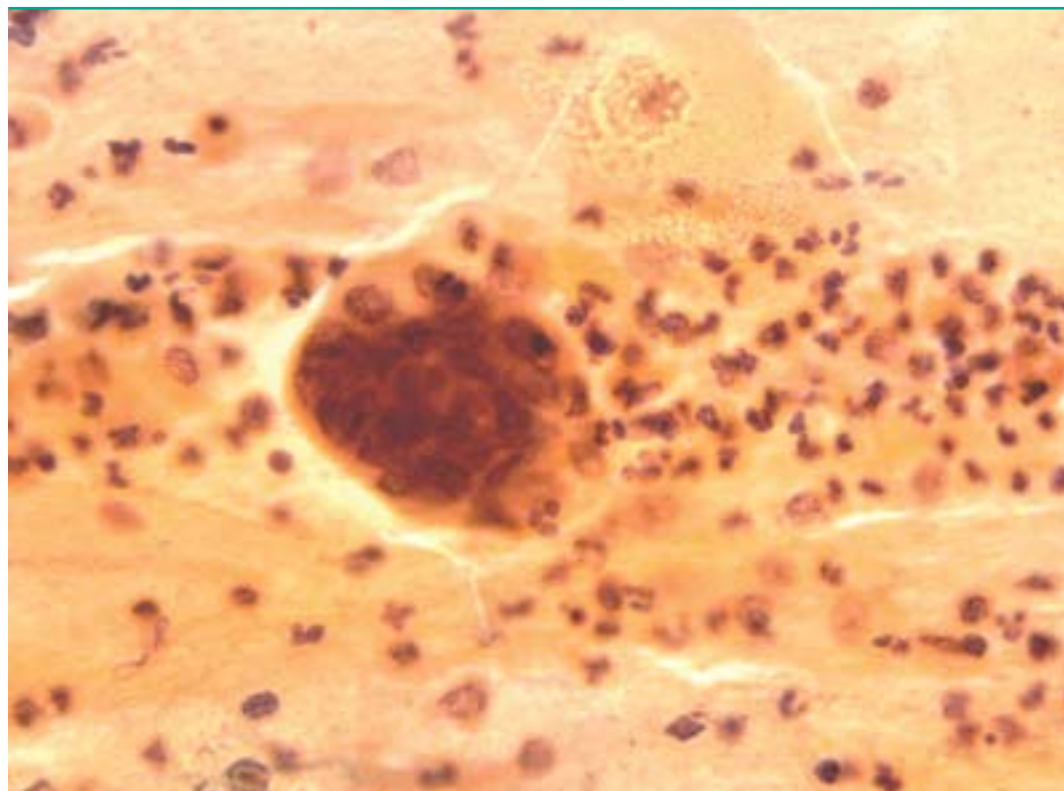

Figure 2
Cytological appearance of fallopian tube cancer

increase of serum CA125 levels with higher clinical stages.[17]

Imaging

Ultrasound is the simplest and usually the initial imaging investigation. It helps to detect adnexal masses, although it is often non-specific in its findings. Fallopian tube malignancies should be considered where unexplained solid masses, corresponding with the expected location of the tubes, are seen in association with normal ovaries.

tissue masses and less enhancement than myometrium. CT is more useful for detecting nodal involvement.[22,23]

Surgical pathological staging

The most commonly used staging method is the International Federation of Gynecology and Obstetrics (FIGO) surgical pathological staging system **(Table 1)**.[1] Operative findings may be modified by clinical, imaging or histological evaluation.

Table 1	FIGO stage		TNM stage[a]
FIGO staging for fallopian tube carcinoma		Primary tumour cannot be assessed	TX
	0	No evidence of primary tumour	T0
		Carcinoma in situ	Tis
	I	**Tumour confined to fallopian tubes**	**T1**
	IA	Tumour limited to one tube, without penetrating the serosal surface; no ascites	T1a
	IB	Tumour limited to both tubes, without penetrating the serosal surface; no ascites	T1b
	IC	Tumour limited to one or both tubes, with extension onto/through the tubal serosa; or with positive malignant cells in the ascites or positive peritoneal washings	T1c
	II	**Tumour involves one or both fallopian tubes with pelvic extension**	**T2**
	IIA	Extension and/or metastasis to uterus and/or ovaries	T2a
	IIB	Extension to other pelvic organ	T2b
	IIC	IIB/C with positive malignant cells in the ascites or positive peritoneal washings	T2c
	III	**Tumour involves one or both fallopian tubes with peritoneal implants outside the pelvis and/or positive regional lymph nodes**	**T3 & /N1**
	IIIA	Microscopic peritoneal metastasis outside the pelvis	T3a
	IIIB	Macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension	T3b
	IIIC	Peritoneal metastasis more than 2 cm in greatest dimension and/or positive regional lymph nodes	T3c &/N1
	IV	**Distant metastasis beyond the peritoneal cavity**	**M1**

[a]TNM = tumour-nodes-metastasis

Reported features of fallopian tube cancer on ultrasound include a sausage-shaped mass, cystic spaces with mural nodules and a multilocular mass with a cogwheel appearance. Three-dimensional ultrasound can help to detect papillary protrusions, pseudoseptae, tumoural lakes, microaneurysms, arteriovenous shunting, blind ends and dichotomous branching, all of which are typical for malignant tumour vessels. Furthermore, multiple sections of the tubal 'sausages' can enable detection of local tumour spread and capsule infiltration. In addition, colour Doppler can help to detect neovascularisation and low resistance indices within solid components.[4,20,21]

Computed tomography (CT) or magnetic resonance imaging (MRI) can help to delineate the mucosal tumour and characteristic tubular shaped adnexal mass, which are distinguishable from ovarian cystic masses. With both CT and MRI the lesion may appear relatively small, solid and lobulated when not associated with a hydrosalpinx. MRI is probably more useful than CT in further evaluating the adnexal mass after the initial ultrasound. MRI has become an important tool in the evaluation of the mass because of its multiplanar capability and unsurpassed soft tissue contrast. It can also show up associated peri-tumoural ascites, intrauterine fluid collections and hydrosalpinges. On CT scan the lesion has attenuation equal to that of other non-specific soft

More than 50% of women present with stage I or stage II disease, 40% with stage III disease and 5–10% with stage IV disease.[1,24] A somewhat lower incidence of advanced disease is seen in these women than in those with epithelial ovarian carcinomas, presumably because of earlier occurrence of symptoms, particularly vaginal bleeding or discharge.

Treatment

The management of fallopian tube cancer is principally the same as that for ovarian cancer. In established cancer there is no role for conservative surgery. In a young woman who wishes to retain fertility, limited surgery may be considered for well-differentiated stage I disease confined to one side after detailed evaluation and careful discussion. However, limited surgery is not encouraged in view of the significant rate of lymph node metastases. Metastases to the para-aortic lymph nodes have been documented in at least 33% of women with all stages of disease.

Women diagnosed incidentally at surgery for a benign condition should be considered for repeat surgical staging.

FIGO stage I and stage II disease

Laparotomy with a midline incision for careful evaluation of the abdominal and pelvic cavity to delineate the extent of disease is recommended. Washings of the peritoneal cavity followed by total

abdominal hysterectomy with bilateral salpingo-oophorectomy should be carried out, along with sampling of the pelvic and para-aortic lymph nodes, infracolic omentectomy and appendicectomy.

Women with a final histology of adenocarcinoma *in situ* or a stage I grade I tumour do not require postoperative adjuvant chemotherapy. All other women should be considered for adjuvant platinum-based chemotherapy with or without paclitaxel. It has been reported to provide a clinical remission rate of up to 85%.[1,25–27]

FIGO stage III and stage IV disease
Optimal debulking surgery and postoperative chemotherapy with paclitaxel and platinum combined is the standard management for advanced disease. Women who have not undergone optimal debulking at initial diagnosis (i.e. because of medical contraindications and subsequent inoperability, or extensive upper abdominal disease) should receive platinum-based chemotherapy followed by re-evaluation after three cycles of chemotherapy. If there has been an improvement in the extent of the disease or the medical condition of the woman, interval debulking surgery may be considered. However, this practice has not been validated by any prospective trial in fallopian tube cancer. Women with distant metastases need to have the primary site of disease confirmed by histology. Women too ill to receive chemotherapy should be offered symptomatic treatment.[1,25,28,29]

Follow-up and recurrence
Data on the recurrence of this disease are insufficient. Local recurrence is observed in the pelvis or abdomen but distant organ metastases, most often to the lungs, brain and kidneys, can also occur.[30] There is no definite evidence to show that intensive follow-up in asymptomatic women has any positive impact on overall survival. However, early diagnosis of recurrence should, theoretically, offer better results.

The aims of follow-up are:

- evaluation of immediate response to treatment (including collection of data on the efficacy of treatment)
- recognition and management of treatment related complications
- detection of persistent or recurrent disease.

Follow-up is usually carried out between three to six months initially and then yearly up to five years. It is mainly clinical, with history taking and physical examination (including pelvic, breast and rectal examinations) to exclude any clinical signs of recurrence. The serum CA125 titre may also be checked, especially if it was raised at primary diagnosis, although the impact of such a practice on survival is unclear. Imaging investigations should only be performed if the clinical findings or the tumour markers suggest possible recurrence. CT is an effective means of identifying patients with recurrent ovarian/fallopian tube cancer.[31]

Treatment for persistent or recurrent disease should be based mainly on the length of the recurrence-free interval, whereas secondary cytoreduction can be considered for selected women with localised late relapses.[32]

Survival
The overall five-year survival rate for patients with epithelial tubal cancer is about 33–40%, with a reported symptom-free survival rate of up to 21% **(Table 2)**. This number is higher than that of women with ovarian cancer and reflects the somewhat higher proportion with early stage disease. However, when compared stage for stage, women with early fallopian tube cancer may have a poorer prognosis than those with ovarian cancer: presumably this is related to the significant rate of lymph node metastases. The influence of prognostic factors on the results of treatment, including clinical stage, histological grading and depth of infiltration, has been evaluated. Only depth of infiltration proved to be statistically significant.[12,29,33]

FIGO stage	Incidence (%)	5-year survival (%)
Stage 1	50[a]	65
Stage 2		50–60
Stage 3	40	10–20[b]
Stage 4	5–10	

[a]stage 1 and 2 combined; [b]stage 3 and 4 combined

Table 2
Incidence and five-year relative survival by FIGO stage

Screening
The rarity of fallopian tube cancer means that there is no recommendation for screening.

Other fallopian tube tumours
Rare tumours of the fallopian tube include sarcomas, choriocarcinomas, germ cell tumours and lymphomas. Management of these cases should be on an individual basis, although the principle of primary surgery followed by chemotherapy applies in most cases. Choriocarcinomas and germ cell tumours can occur at a younger age and fertility preserving surgery may be considered in these cases since many women have a good response to chemotherapy.[34–37]

Conclusion
With the wider acceptance of pathological definition and FIGO staging, management of primary fallopian tube cancer is becoming more standardised. Aetiology and management are similar to epithelial ovarian cancer, but stage at

diagnosis, lymphatic spread and overall survival appear to be different. Further multi-centre clinical research is required to confirm these findings, to improve diagnosis and compare different treatment regimens.

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