Tumour site/Histological sites of tumour involvement (Core)

Sites of tumour involvement should be recorded as this is necessary for tumour staging. Although site assignment (tube versus ovary versus peritoneum) for clear cell, endometrioid, low grade serous and mucinous carcinomas is generally not problematic since almost all arise in the ovary, except for occasional cases arising in extraovarian endometriosis, the same is not true for high grade serous carcinomas (HGSCs).

It was first recognised in 2001, that a high percentage of so-called ovarian HGSC in women with germline *BRCA1* mutations arise in the fimbrial end of the fallopian tube.[1,2] This was initially reported in risk reducing salpingo-oophorectomy specimens where early pre-invasive HGSCs were much more likely to be present in the fallopian tube than ovary. These serous tubal intraepithelial carcinomas (STIC) harbour identical *p53* mutations to the extratubal tumour, establishing that they are clonal.[3] Comparison of telomere length and centrosome amplification in matched STIC and ovarian HGSC suggests that the STICs develop before the ovarian tumours and are in fact a precursor and not a metastatic focus.[4,5] Finally, although numbers are small, early, incidental non-*BRCA1/2* associated (sporadic) HGSCs are predominantly detected in the fallopian tube mucosa, especially the fimbria, rather than the ovary.[6] In summary, there is compelling evidence that the precursors of HGSC originate in the fallopian tube in patients with germline *BRCA1* mutations, and there is accumulating and convincing evidence that this is also true for sporadic HGSC. Assignment of primary site should therefore reflect our current understanding of where HGSCs originate, based on data from the study of early incidental or pre-invasive HGSC. However, some cases of ovarian and primary peritoneal HGSCs do not show STIC lesions or tubal mucosal HGSC despite entire submission of the grossly normal fallopian tubes for histological evaluation. In a consecutive series of non-uterine HGSCs classified as ovarian or peritoneal based on pre-International Federation of Gynaecology and Obstetrics (FIGO) 2014 criteria in which the fallopian tubes were examined in their entirety, STICs were identified in 59% of cases, and invasive HGSC of the mucosa of the fallopian tube in an additional 15% of cases.[7,8] In other cases, the fimbrial end of the fallopian tube was obliterated by a tubo-ovarian mass.

According to the 2014 FIGO Staging System, the primary site of non-uterine HGSC is designated as ovarian, tubal or primary peritoneal.[8] In some cases it may not be possible to ascertain the primary site of origin, and these should be categorised as 'undesignated' in the new staging system.[8] The descriptor 'tubo-ovarian HGSC' can also be used in practice for those cases of advanced stage HGSC where there is uncertainty about primary site, e.g., pre-treatment biopsy from the omentum. The problems in ascertaining the primary site and the variation in practice amongst pathologists have significant implications for epidemiological studies, determination of tumour incidence and mortality, data collection by cancer registries and entry into clinical trials. Based on the 2020 World Health Organization Classification,[9] recommendations for assigning the site of origin of extra-uterine HGSC are provided in the following section. Using these criteria, assignment of primary site is no longer based on the site of greatest volume/size of tumour but the presence of STIC or tubal mucosa involvement by HGSC indicates a fallopian tube origin, as does partial or total obliteration of one or both fallopian tubes by a tumour mass. Application of these criteria will be important in ensuring consistency between different pathologists in assigning the site of origin of HGSC with obvious important implications for cancer registration and other parameters.[10]

Suggestions for assigning site of origin

The following suggestions are not intended to be an exhaustive list nor are they intended to be binding, and assignment of origin in an individual case (Figure 1) is left to the discretion of the pathologist and the clinical team, ideally in the setting of a multidisciplinary team meeting. Undoubtedly, there will be evolution over time in our ability to accurately assign the primary tumour site, but the following are intended as practical guidelines for handling cases at the present time:[10]

1. The fallopian tubes, or at least their fimbrial ends, should be well sampled – whenever possible - in all cases of HGSC by a sectioning and extensively examining the fimbriated end (SEE-FIM)-like protocol[3] to avoid missing this important site of disease, which probably represents the tumour origin in the large majority of cases.
2. The presence of STIC, in the absence of invasive HGSC involving the fallopian tube, should be considered as tubal primary for staging purposes, e.g., points 4 and 7.
3. The presence of STIC without invasion or extratubal spread should be staged as FIGO Stage IA tubal carcinoma (although these have a favourable prognosis, based on limited experience to date[11]) but with an annotation that there is no 'invasive' carcinoma.
4. Cases with only STIC in the fallopian tube, ovarian surface involvement or parenchymal involvement not exceeding 5 millimetres (mm) and widespread peritoneal involvement, which would traditionally be categorised as primary peritoneal carcinoma,[12] should be classified as tubal primaries.
5. Cases with HGSC located within the mucosa of the fallopian tube, including its fimbrial end, with or without STIC in any portion of the fallopian tube and with no, minimal or even substantial ovarian involvement should be categorised as tubal primaries. Note that the distinction between STIC and intramucosal HGSC of the fallopian tube is subjective, with the latter showing a greater degree of stratification and architectural complexity.
6. Cases in which the fallopian tube is not identifiable, having presumably been overgrown by the ipsilateral adnexal mass, or the distal end of the fallopian tube is incorporated into a large tubo-ovarian mass should also, based on current understanding, be diagnosed as tubal primaries. It is emphasised that a careful effort must be made to identify the tube in all cases.
7. Cases with a dominant ovarian mass(es) and identifiable fallopian tubes with STIC should be classified as tubal primaries.
8. Cases with a dominant ovarian mass(es) and identifiable fallopian tubes without STIC or mucosal involvement by HGSC, after SEE-FIM, should be classified as ovarian primaries.
9. Cases should be categorised as primary peritoneal carcinoma by the conventional criteria below[9] *and* only after complete histological examination of the fallopian tubes (including the non-fimbrial portions) has excluded the presence of STIC or a small tubal HGSC or ovarian involvement by HGSC.
10. All cases classified as 'undesignated' for FIGO staging purposes should be further described as 'tubo-ovarian' or 'tubal/ovarian' to distinguish them from serous carcinoma originating in the uterus. Using the suggestions presented here, these should represent a small proportion of HGSC.
11. Cases with unilateral or bilateral HGSC in the ovary and/or STIC or HGSC in the tube but with an endometrial serous intraepithelial or invasive carcinoma should be carefully evaluated for an endometrial versus a tubo-ovarian primary (WT1 may be of value in such cases - see **ANCILLARY STUDIES**, to distinguish between ovarian and uterine carcinoma). The majority of such cases will represent adnexal metastases from an endometrial serous carcinoma.[13]

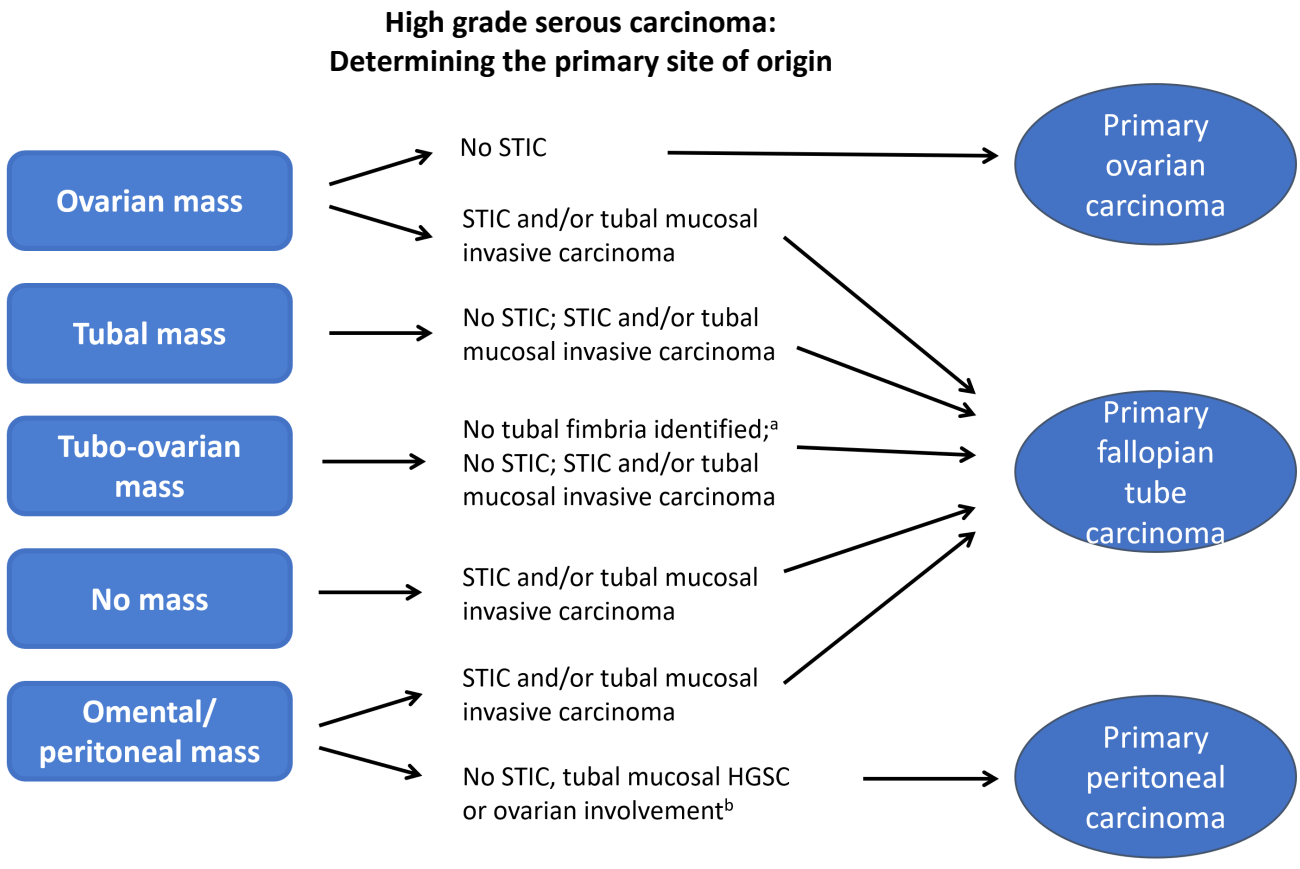

Figure 1: High grade serous carcinoma: determining the primary site of origin. Serous tubal intraepithelial carcinoma (STIC).

[a] Failure to detect the tubal fimbria implies overgrowth by tumour.

[b] Apply criteria as specified in the commentary.

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