Response to neoadjuvant therapy (Recommended)

Reason/Evidentiary Support

There is no recommended or agreed system for tumour regression grading (TRG) of ovarian/tubal/peritoneal carcinomas that have been treated with neoadjuvant chemotherapy (this largely applies to pelvic high-grade serous carcinomas) despite the fact that oncologists often request this information because it is potentially a helpful morphological marker to assess the response to neoadjuvant treatment after surgery and identify patients who may be eligible for entry into trials. TRG has been shown to provide valuable prognostic information in patients with carcinomas of the breast, stomach, oesophagus and colorectum who have been treated with neoadjuvant chemotherapy and serves as a morphological marker to guide further treatment after surgery.\textsuperscript{1,3} The applicability of several well-known and widely used systems for TRG has been considered for pelvic gynaecological carcinomas. Some of the systems that are used for breast carcinoma are unduly complex and include the separate assessment of both the primary tumour and involved lymph nodes.\textsuperscript{5-8} Most of the different TRG systems for gastrointestinal tumours are relatively simple to use,\textsuperscript{2,9,10} although the reported reproducibility of these systems is variable.\textsuperscript{11-14} TRG is usually applied to the primary site of unifocal tumours in the breast and gastrointestinal tract. In contrast, pelvic high-grade serous carcinomas tend to affect multiple intra-abdominal sites in addition to the primary site of origin. They also typically evoke a desmoplastic host reaction and the inclusions of fibrosis as a criterion for tumour regression has the potential to provide misleading data.

Four studies have assessed tumour regression after neoadjuvant chemotherapy in advanced-stage ovarian cancer and all showed a correlation between response and survival; however, all used different scoring criteria, did not validate their criteria in an independent series of cases, and did not assess reproducibility of their criteria.\textsuperscript{15-18} A more recent study has tested and validated the prognostic significance of response criteria, and assessed reproducibility in two independent series of high-grade pelvic serous carcinoma.\textsuperscript{15,19} The latter study suggests that a 3-tier scoring system (the Chemotherapy Response Score (CRS)) is most reproducible and that the system is simple and easy for all pathologists to apply, irrespective of their level of experience in gynaecological pathology. In this study the prognostic significance of the CRS as applied to omental tumour deposits was superior to the CRS of the primary tumour. The study (which included 60 patients in the test cohort and 71 in the validation cohort) used a modification of the Dworak system\textsuperscript{10} and demonstrated good inter-observer reproducibility and significant association with clinical outcome. Although further studies are needed to confirm the findings, this is the grading system currently recommended by the ICCR. The method is as follows:

1. Scoring should be carried out on a single H&E-stained section (refer to discussion of omental sampling in Note 7 MACROSCOPIC DESCRIPTION OF OMENTUM).
2. A single block of involved omental tissue that shows the least response to chemotherapy should be selected (if there is no residual omental tumour a Chemotherapy Response Score/CRS score of 3 is given - see table below)
3. The amount of viable tumour should be assessed; this may or may not show degenerative changes in the form of nuclear atypia, smudging of the nuclear chromatins and cytoplasmic clearing.
4. A 3-tier system for CRS should be used:

<table>
<thead>
<tr>
<th>Chemotherapy Response Score (CRS)\textsuperscript{19}</th>
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<tbody>
<tr>
<td><strong>Score</strong></td>
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<tr>
<td>1</td>
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* Regression associated fibro-inflammatory changes: fibrosis associated with macrophages, including foam cells, mixed inflammatory cells and psammoma bodies; to be distinguished from tumour-related inflammation or desmoplasia.
5. The presence of fibrosis may be helpful in marking the site of previous tumour infiltration.
   a. When found in the absence of tumour, fibrosis is likely to indicate regression.
   b. If fibrosis occurs in association with tumour, this may simply reflect tumour-associated desmoplasia rather than regression.
   c. However, when fibrosis in association with tumour is accompanied by an inflammatory response (so-called ‘fibro-inflammatory’ response – fibrosis with associated macrophages and a mixed population of inflammatory cells), this indicates regression.
   d. Psammoma bodies may mark the site of previous tumour and can sometimes appear more numerous because their density increases in areas where tumour has disappeared.
6. As a guide, >95% of tumour should be viable for a score of 1, and <5% for a score of 3.
7. In studies to date using this system or a closely related system, a difference in prognosis was shown only when tumours with a CRS score of 1 or 2 were compared with those having a CRS score of 3.1519 However, the ICCR recommends use of the 3-tier system to gather more data for future studies.
8. Note that this system has only been applied to high-grade serous carcinomas to date.

References:

