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Synchronous carcinomas of endometrium and ovary: A pragmatic approach

In a recent issue of Gynecologic Oncology Turashvili and colleagues from Memorial Sloan Kettering Cancer Center reported on a series of 74 women with concurrent carcinoma involving endometrium and ovary, 19 of which were considered independent primary 'synchronous' tumors by the reporting pathologists (Turashvili et al., 2018). This might naively seem to be a curious phenomenon; synchronous tumors involving two different sites, arising independently, would surely be an uncommon occurrence, apart from examples of metastasis within the genital tract i.e. endometrium to ovary or ovary to endometrium, given that the risk factors for endometrial and ovarian carcinoma are different. This is not a vanishingly rare occurrence, however, and in practice such cases come up for discussion with some regularity at our tumor boards.

Just how commonly one encounters synchronous carcinomas involving endometrium and ovary depends on how you perform your literature search. A cursory look at the literature will tell you that 5% of "endometrial carcinomas" and 10% of "ovarian carcinomas" are associated with synchronous tumors in the ovary or endometrium, respectively (Zaino et al., 2001; Soliman et al., 2004). In 2018, though, we would want a more penetrating look at this question. Ovarian carcinoma is not a single disease and considering it as such masks important differences between the histotypes. For example, synchronous endometrial involvement is rare with high-grade serous, low-grade serous or mucinous carcinomas of ovary, but synchronous endometrial carcinoma or atypical hyperplasia can be present in up to half of patients with the endometriosis-associated forms of ovarian carcinoma (endometrioid, clear cell or mixed endometrioid/clear cell) (Chui et al., 2014; Heitz et al., 2014a). Endometrial carcinoma histotypes, unlike ovarian carcinoma histotypes, do not define diseases with consistent molecular abnormalities, and the 4 Cancer Genome Atlas-based molecular subtypes of endometrial carcinoma can be considered to be analogous to the 5 histotypes of ovarian carcinoma, in that they define diseases with different risk factors, precursor lesions, response to therapy and outcome (The Cancer Genome Atlas Network, 2013; Kommoss et al., 2018). Synchronous ovarian carcinoma is seen in hypermutated endometrial carcinomas with mismatch repair deficiency (MMRd), ultramutated endometrial carcinomas with mutations in the exonuclease domain of polymerase-epsilon (POLE), and endometrial carcinomas with low mutation burden/few somatic copy number abnormalities (characterized by wildtype p53 expression and absence of molecular features of the other three molecular subtypes, variously referred to a no specific molecular profile (NSMP) or p53wt)[unpublished data].

The challenge presented by synchronous carcinomas of endometrium and ovary is not related to the high-grade tumors with disseminated disease; these are clearly metastases, and most arise in the endometrium. The problematic aspect of synchronous carcinomas of ovary and endometrium is the observation that most such tumors are low-grade (grade 1 or 2) endometrioid carcinomas involving both ovary and endometrium, that typically do not involve other anatomic sites, and are associated with a favorable outcome, at least relative to what would be expected were these advanced stage endometrial carcinomas with extrauterine spread (Ulbright and Roth, 1985; Heitz et al., 2014b). This led to the reasonable conclusion that such tumors must be independent primary tumors, and histopathological criteria were proposed to allow separation of synchronous endometrial and ovarian carcinomas into those that are independent primary tumors and those that are metastatic (typically from endometrium to ovary), with the former staged as two independent primary tumors (Scully et al., 1998). As noted by Turashvili et al., these criteria can be difficult to apply in practice as some cases are indeterminate, with features supportive of both independent primary tumors and a single tumor with metastasis.

This approach to primary site assignment has remained in use for decades and has largely withstood the test of time in clinical practice. In 2016, however, two independent studies established that synchronous endometrial and ovarian carcinoma, even though classified as independent primary tumors based on the existing criteria, were clonally related, by demonstrating identical mutations present in both endometrial and ovarian tumors (Anglesio et al., 2016; Schultheis et al., 2016). Even tumors of different histotype in ovary and endometrium e.g. clear cell and endometrioid, were demonstrably clonally related. We have existed since then in a state of cognitive dissonance, in that we continue to classify tumors as "independent primary carcinomas of ovary and endometrium" in practice, while knowing them to be clonally related i.e. metastasis. The situation is very similar to what occurred a few years ago when we designated most extra-uterine high-grade serous carcinomas as ovarian primaries, using criteria of long-standing, even though the accumulating data clearly demonstrated that the fallopian tube was the primary site (Singh et al., 2015). Just as this led to new criteria for primary site assignment being developed for tubal/ovarian carcinomas, we now need an approach to synchronous endometrial and ovarian carcinomas that can reconcile the new genomic information with clinical practice.

In their study, Turashvili et al. take the important step of setting aside assignment of primary site, instead refocusing the discussion on the risk of recurrence. This is important because of the possibility of overtreatment if there is overemphasis on primary site assignment which, if guided by the molecular results, would lead to synchronous endometrial and ovarian carcinomas being considered advanced stage. In looking past primary site assignment and stage, and looking instead at what matters most to the patients, i.e. outcome, they point the way past our current impasse, where clinical practice and our knowledge of tumor biology are at odds. In their study they attempt to identify risk groups that can guide treatment decisions, based on regression analysis. The first stratification point is between endometrioid (low risk) and non-endometrioid (high-risk). So far so good, but the issue of 'synchronous' primaries only ever related to low grade endometrioid carcinomas at both sites. Furthermore the clinically relevant goal is

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separation of patients into those who should and should not receive adjuvant therapy, so attention should be focused particularly on this decision point. Arguably the only patients who should not be offered adjuvant therapy are those with a predicted disease specific survival in the range of 95% or better, equivalent to stage IA grade 1 or 2 endometrioid endometrial carcinomas, or stage IA grade 1 or 2 endometrioid ovarian carcinomas. None of the groups identified by their regression analysis meets this threshold. Very importantly, the group of patients who come closest to this very stringent cut-off is those with tumors considered independent primary tumors by the pathologist (their Fig. 3D). This observation, confirming the clinical utility of the criteria we have long used for risk assessment, effectively brings us full circle. Given that recent studies have established the clonal identity of these tumors, the traditional criteria for primary site assignment (Scully et al., 1998) can now be "re-purposed" for risk assessment, in an abbreviated form. Low risk synchronous endometrial and ovarian carcinomas are grade 1 or 2 'endometrioid' carcinoma at both sites, with risk of recurrence equivalent to a combination of stage IA endometrial and stage IA (and possibly IC1) ovarian carcinomas, i.e. ***absence*** of all of the following: deep myometrial invasion, cervical involvement, significant lymphovascular space invasion, bilateral ovarian involvement, ovarian surface involvement, positive washings, or extra-uterine/extra-ovarian involvement, including nodal spread.

A question not yet addressed is how to handle the staging of synchronous endometrial and ovarian carcinomas. The concern, as noted previously, is that if they are considered advanced stage endometrial carcinomas there is the risk of overtreatment. There is a precedent for clonally related tumors being staged as independent primary tumors. For example, HPV-associated vulvar squamous cell carcinomas arising in patients with a past history of cervical dysplasia or carcinoma share viral integration sites, and thus clonality, with the cervical squamous cell lesion (Vinokurova et al., 2005). Similarly patients with multiple transitional cell carcinomas of bladder and ureter will have each tumor staged independently, despite their being clonally related. Biologically these examples appear to be similar to the phenomenon of synchronous tumors of endometrium and ovary, in that neoplastic cells detach and spread through a continuous physical space, beyond the organ of origin, but lack full metastatic potential, in that they typically cannot invade vessels and metastasize via lymphatics or blood vessels. We propose that the staging guidelines for endometrial and ovarian carcinomas be modified to accommodate the situation of synchronous carcinomas that are confined to uterus and ovary, as defined above, so that such tumors are either staged independently or assigned a specific subcategory of stage III (endometrium) or II (ovary), acknowledging the evidence that they are clonally related. In such patients, both tumors will have to be low risk, based on current treatment guidelines, to qualify for surgery only, without adjuvant therapy. While at the present time this approach appears reasonable based on retrospective evidence, further studies are needed to determine whether treatment decisions based on studies of patients with either endometrial or ovarian carcinoma, are applicable to patients with synchronous endometrial and ovarian carcinoma, using consistent and reproducible diagnostic criteria. Such a goal cannot be achieved with single-centre studies and requires multi-centre and international collaboration.

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