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Adjuvant treatment of endometrial cancer in molecular era: Are we ready to move on?

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ABSTRACT

For many decades, the Bokhman dualist vision was used to stratify endometrial cancer (EC) in good or bad tumors. Nowadays, a more robust and reliable molecular stratification is taking place with the The Cancer Genome Atlas Research Network (TCGA) classification bringing new and important information in the field. Collaborative groups are replicating TCGA using accessible tools with immunohistochemistry. It's time to move on and include this information along with pathology features to better delineate adjuvant treatment in EC.

1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries. About 57,004 new cases are expected this year (2020) in United States and 131,216 cases in European Union (Cancer today, Feb). In low middle-income countries, it is only surpassed by cervical cancer, but data predicts a higher incidence in the near future owing to aging of the population and increasing rate of obesity (Paulino et al., 2018).

The majority of women are postmenopausal and have early stage disease: three quarters of EC are diagnosed as FIGO 2018 stage I–II (Siegel et al., 2020). Abnormal vaginal bleeding triggers the diagnosis in these women. Since Gynecologic Oncology Group (GOG) study 33 demonstrated that surgical stage is more accurate than clinical stage, EC has been staged with surgical resection of the uterus and adnexal along with pelvic/paraaortic lymph nodes (Creasman et al., 1987). Until now, there are no data showing gains in terms of overall survival for adjuvant treatment of early stage disease and the decision about offering patients adjuvant therapy is guided by adverse prognostic factors on the final pathology report, such as: deep myometrium invasion, grade 3, histology type (serous, clear cell and carcinosarcoma) and the presence of lymph vascular space invasion (LVSI). International guidelines, like the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), have a wide range of possibilities, from observation to adjuvant chemoradiation what reflects the lack of high-quality level of evidence for offering adjuvant chemotherapy (CT) or radiotherapy (RXT) (Colombo et al., 2016; NCCN - Evidence-Based Cancer, 2020 Feb). For locally advanced disease (FIGO 2018 III-IV), adjuvant CT is the standard of care.

The Cancer Genome Atlas Research Network (TCGA) of tumors is bringing new insights in many tumors and it is not different in EC (The Cancer Genome Atlas Research Network and Levine, 2013). Here we discuss how this classification could contribute and influence the decision to offer adjuvant treatment in this tumor.

2. Historical perspective of adjuvant treatment in early stage EC

The indication of adjuvant therapy for EC has been for decades mostly based upon poor pathologic factors seen in the final report (Table 1 summarizes risk classification according to trial and society guidelines). Three randomized trials evaluated pelvic RXT) in patients FIGO 1988 stage I-II (Creutzberg et al., 2000; Keys et al., 2004; NCIC, 2020). Although they clearly showed a better local control, all of then failed to demonstrate gains in overall survival. Multivariable analysis revealed that patients who derived most of benefit from RXT were those who presented with a combination of adverse factors (older age, deep myometrium invasion, presence of LVSI and grades 2–3). In the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) 1 study, patients were deemed to have intermediate risk if they were more than 60 years of age associated with more than 50 % of myometrium invasion or grade 3 tumors. In GOG99, high-intermediate risk patients were defined as follows: 70 years or more with one risk factor, 50–70 years with two risk factors and less than 50 years with 3 risk factors. In these patients, RXT diminished local recurrence from 24 to

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Table 1
Risk classification according to trials or society guidelines.

	Low risk	Intermediate risk	High intermediate risk	High risk / Advanced disease
PORTEC1	Grade 1 endometrial adenocarcinoma Stage IA	Endometrial adenocarcinoma Stage I based on uterine factors: Grade 1 histology and myometrial invasion of ≥ 50 % Grade 2 histology with any myometrial invasion Grade 3 histology with myometrial invasion < 50 %	Age > 60 years with grade 1 or 2 histology and myometrial invasion > 50 % Age > 60 years with grade 3 histology and myometrial invasion < 50 %	Stage III–IV disease Uterine serous carcinoma or clear-cell carcinoma of any stage
GOG 99	Grade 1 or 2 endometrioid cancers confined to the endometrium Stage IA	Age ≤ 50 years and ≤ 2 pathological risk factors* Age 50–69 years and ≤ 1 pathological risk factors* Age ≥ 70 years and no pathological risk factors*	Any age and 3 pathological risk factors* Age 50–69 years and ≥ 2 pathological risk factors* Age ≥ 70 years and ≥ 1 pathological risk factors*	Stage III–IV disease, irrespective of histology or grade Uterine serous carcinoma or clear-cell carcinoma of any stage
ESMO 2011	Stage IA grade 1 and grade 2 endometrioid type	Stage IA grade 3 endometrioid type Stage IB grade 1 and grade 2 endometrioid type	..	Stage IB grade 3 endometrioid type Non-endometrioid disease of all stages
ESMO 2015	Stage IA grade 1 and grade 2 endometrioid type with no LVSI	Stage IB grade 1 and grade 2 endometrioid type with no LVSI	Stage IA grade 3 endometrioid type regardless of LVSI Stage I grade 1 and grade 2 endometrioid type with LVSI, regardless of depth of invasion	Stage IB grade 3 endometrioid type regardless of LVSI Stage II Stage III –IVA Non-endometrioid disease of all stages†

PORTEC 1 = Post-Operative Radiation Therapy in Endometrial Carcinoma. GOG = Gynaecologic Oncology Group adjuvant radiation for intermediate-risk endometrial cancers. LVSI = lymphovascular space invasion. ESMO = European Society for Medical Oncology. *Risk factors: grade 2 or 3 histology, positive LVSI, myometrial invasion to outer third. †Serous adenocarcinoma, clear cell adenocarcinoma, or other type of carcinoma.

12 % in GOG 99 and 20 % to 5% in PORTEC1. These trials showed that the majority of recurrence occurred in the vaginal vault (75 % in PORTEC-1), thus researchers launched the second randomized trial (PORTEC2) in patients with intermediate risk and demonstrated that brachytherapy (BT) is non inferior compared to RXT, giving the same vaginal control and better quality of life (Nout et al., 2010). Unfortunately, most of the patients in these trials discussed above were considered low risk patients which probably diluted the benefit of RXT.

Adverse prognostic factors are continuum variables and patients having more factors at disease presentation have poorer outcomes, with high rate of distant relapse and lower rates of survival. Based on this knowledge, adjuvant CT had been evaluated and initial trials tried to show an advantage compared to RXT. These studies included patients raging from stage I to III and adjuvant CT did not demonstrate better outcomes compare to RXT, although these trials showed a better local control with RXT and better distant control with CT (Maggi et al., 2006; Susumu et al., 2008). The recently published GOG 249 focused in patients with high intermediate risk early stage EC and compared CT plus BT (3 cycles of carboplatin and paclitaxel) to RXT. Again, CT/BT did not prolong overall (5-year OS, HR 1.04; 90 % CI 0.71–1.52) and recurrence free survival (5- year RFS, HR 0.92; 90 %CI 0.69–1.23), but added more acute grade 3/4 toxicity (Randall et al., 2019). Also, RXT showed a better pelvic and paraaortic control than CT (9% vs 4%).

The next steps were to combine CT and RXT (CRT) to improve both local and distant control and this accounted for the most recent trials in adjuvant setting of EC (Hogberg et al., 2010). Except for one trial, PORTEC3, they were not able to show better overall survival for the combined modality. PORTEC3 was a randomized phase 3 trial in patients deemed to have high risk early stage (FIGO IB grade 3, IB with LVSI, stage II to III or any stage with invasive serous or clear cell histology). Standard treatment for these population (RXT) was compared to CRT. In the last publication, with a longer follow-up, CRT showed a significant gain in failure free survival (5-year FFS, HR 0.70; 95 % CI 0.52 − 0.94) as well as OS (5-year OS, HR 0.70; 95 % CI 0.51 − 0.97) for the whole population. In a post hoc analysis, the benefit seemed to be restricted to patents with stage III and serous histology, without a benefit for the combined modality in patients with stage II disease (de Boer et al., 2019).

In regard to locally advanced disease, the second positive randomized trial (GOG 122) demonstrated that 8 cycles of doxorubicin plus cisplatin improved overall survival in patients with stage III and IV EC and became the standard treatment for these population (Randall et al., 2006). A more recent study, GOG 258, tried to add RXT to CT in the same population. Unfortunately, it did not achieve its primary endpoint showing no gain in relapse free survival (5-year RFS, HR 0.90; 95 % CI 0.74–1.10). CRT was associated with a lower incidence of vaginal recurrence (2% vs. 7%; HR, 0.36; 95 % CI, 0.16 to 0.82) and pelvic and paraaortic lymph node recurrence (11 % vs. 20 %; HR, 0.43; 95 % CI, 0.28 to 0.66) than CT alone. OS, secondary end-point, is still immature but it does not seem that it will be different between both arms (Matei et al., 2019).

3. The TCGA and its reproducibility in clinics

More recently, the TCGA brought important knowledge regarding the molecular profile of EC. In this project, a comprehensive analysis was performed in endometrioid, serous and mixed histology EC (The Cancer Genome Atlas Research Network and Levine, 2013). Using next generation sequencing, researchers were able to stratified these tumors in four distinct groups based on transcriptomic, genomic and proteomic characterization of 373 endometrial carcinomas: POLE ultra-mutated, MSI hypermutated, copy number low and copy number high (serous-like). POLE subgroup (POLE, 7% of the cohort) was characterized by an usually high mutations rates in *POLE* gene (*POLE* mut) and despite of having association with poor pathologic features (high grade and deep myometrium invasion) they had the best prognosis with improved PFS.

MSI group (28 %) showed mutations in *MLH1, MSH2 MSH6* or *PMS2* gene and had an intermediate prognosis. Copy number high (CNH, 26 %), or serous-like group, was characterized by mutations in *TP53* (*TP53* mut) and comprised all the serous histology as well as 5% of grade 1–2 and 25 % of grade 3 endometrioid histology. They have the worse prognosis. Copy number low (CNL, 39 %) was associated with intermediate prognosis and showed no specific mutations as seen in the former groups, but a high frequency of *CTNNB1* mutations rate (52 %). The assay utilized to define groups in TCGA is expensive, not pragmatic and not easily applicable in daily clinics. Simply, cheaper and reliable manner to replicate mutations in MSI and TP53 genes have already been shown with immunohistochemistry for MLH1, MSH2, MSH6 and PMS2 and p53 [Sari et al., 2019; Singh et al., 2020; McConechy et al., 2015). Unfortunately, *POLE* mutations don't have an immunohistochemistry surrogate and it is still needed to sequence the gene. Based on this fact, two international groups developed and validated different and more accessible methods to define the same molecular groups as TCGA.

The first group, from Vancouver, utilized immunohistochemistry for p53 and MMR proteins, sequencing solely *POLE* gene (Talhouk et al., 2015). They created a molecular classifier called PROMISE (Proactive Molecular Risk Classifier for Endometrial Cancer). In the discovery cohort they were able to reproduce the same classification as TCGA (Talhouk et al., 2015). They showed in multivariable analysis that molecular classification and clinical pathologic risk group was associated with outcomes. Compared to the traditional clinical pathologic risk classification, they demonstrated high proportion (50 %) of patients in the POLE subgroup (excellent prognosis) being classified as ESMO high-risk, and at least 25 % of those in the high copy number subgroup would be classified as ESMO low/intermediate risk, raising the question of over and undertreatment respectively. Later, researchers were able to confirm this approach in a broader cohort and validate in an external one (Talhouk et al., 2017; Kommoss et al., 2018). In a systematic review and metanalysis of 1171 patients that evaluated histopathological characterization of PROMISE molecular subtypes the authors showed that the POLE group was associated with grade 3 in 39.6 %, deep myometrial invasion present in 27.3 %, and ESMO high risk in 33.4 %; p53 group was associated with grade 3 in 90 %, deep myometrial invasion present in 48.9 %, ESMO high risk in 84.7 %; MMRd was associated with grade 3 in 47.4 %, deep myometrial invasion present in 44.5 % and ESMO high risk in 50 % [Raffone et al., 2020].

At the same time of the Canadian group, overseas, researchers from Leiden, Holland, developed a similar manner to reproduce the TCGA groups. They performed an analysis of MSI and hotspot mutations in 14 genes, including *POLE* and *TP53*, in 947 patients with early stage endometrioid endometrial carcinomas from PORTEC1 and 2 trials: 9% had TP53 mut, 26 % MSI, POLE 6% and no specific molecular profile (NSMP) 59 % ((Stelloo et al., 2016)). They found that integration of established clinicopathologic factors resulted in a stronger model with improved risk prognostication. Also, approximately 15 % of high intermediate risk patients had unfavorable features (such as *TP53* mut and L1CAM positivity) and 50 % favorable features (such as *POLE* mutations *CTNNB1* wild type). Although the Vancouver collaboration group utilized mainly patients in ESMO low/intermediate risk classification and Leiden mainly patients with high-intermediate features, subsequent reports have also shown that this molecular classifier can be replicated in high-risk patients, young women and have high concordance between pre-operative endometrial biopsy and the final pathology (Stelloo et al., 2015; Britton et al., 2019; Abdulfatah et al., 2019; Talhouk et al., 2016). Interestingly, one study performed on high-risk grade 3 endometrioid carcinomas has shown that the prognosis of NSMP subgroup, usually considered as the best one after the POLE subgroup, tended to become worse than that of the MSI subgroup, although not significantly (Bosse et al., 2018). In one of this study that tried to refine prognosis and identify targetable pathways in high risk endometrial cancer, when excluding non-endometrioid tumors, the analysis was still able to discriminate poor versus good prognosis groups (Stelloo et al., 2015). Of note, the prognosis of the NSMP subgroup becomes similar to that of the p53 subgroup, while the prognosis of the POLE subgroup becomes similar to that of the MSI subgroup.

CNL is the biggest group in the molecular classifier and efforts to find another molecular factor that can further stratify this population become an important goal. The TransPortec consortium found that DNA damage response biomarkers can refine high risk EC. Among the NSMP, H2AX positivity (protein involved in DNA damage) was associated with poor disease-free survival (Auguste et al., 2018).

It is noteworthy that these molecular subgroups are almost exclusive and tumors that harbor two or more mutations are extremely rare. Talhouk et al. found 3.4 % of more than 1 molecular classifier in the confirmation cohort of PROMISE (Talhouk et al., 2017). Leon del Castillo et al. reported that 4.5 % of their cohort presented with multiple classifier, most of them with MMRd/p53 (48.1 %) and POLE/p53 (22.9 %) (León-Castillo et al., 2020). Interestingly, in both scenarios, outcomes are most similar to MMRd and POLE instead of p53. Also, they demonstrated that theses tumors showed sub clonal p53 overexpression, suggesting that *TP53* mutation was a secondary event acquired during tumor progression.

4. Is there any evidence of molecular classifier to guide adjuvant treatment?

Although there is no randomized controlled trial that can definitively guide physicians to use adjuvant therapy based on molecular profile in EC, some retrospectively analysis has been consistently showing the potential of this approach. In patients with MSI tumors, CT does not seem add any benefit. In an exploratory analysis of NRG/GOG study (GOG 210) evaluating patients with MMRd EC, the differences in efficacy of adjuvant treatment with respect to PFS was not statically significant, with a trend for improved PFS (HR 0.24; 95 %CI 0.05–1.16, $p = 0.07$) only for probably MMRd cases (defined as MSI-positive and/or IHC defect with absence of MLH1 methylation) (McMeekin et al., 2016). In another publication, 535 patients received adjuvant treatment (RXT and/or CT), 30.3 and 69.7 % had MMRd and MMR proficient tumors respectively. In multivariable analysis, MMR status does not remain associated with significant differences in PFS (HR 0.74; 95 %CI 0.46–1.17) (Kim et al., 2018).

In the 10 years follow up of the PORTEC 2 trial, BT continued to offer equal vaginal control as RXT (3.4 vs 2.4 %, $p = 0.55$) and pelvic control favoring RXT (pelvic recurrence of 6.3 % vs 0.9 %, $p = 0.004$) (for the PORTEC Study Group et al., 2018). Isolated pelvic recurrence was not significantly different between both arms (2.5 vs 0.5 %, $p = 0.10$). Patients were analyzed with the presence of prognostic biomarkers such as p53, L1CAM and substantial LVSI, and total pelvic control was better with RXT when they were present. In PORTEC3, as discussed before, chemoradiation improved recurrence free as well as overall survival compared to RXT in ESMO high risk patients. The authors performed an extrapolatory analysis classifying patients into the molecular classifier and the distribution was as follows: POLE 12.7 %, p53 22.4 %, MSI 33.4 % and NSMP 31.5 %. They replicate the findings in TCGA regarding outcomes with p53 mutant having the worst prognosis, POLE the best, and intermediate prognosis among those in MSI and NSMP (5-year RFS of 50 %, 98 %, 74 % and 76 % respectively, $p < 0.0001$). Only patients with p53 mutations derived benefit in RFS from the added CT (HR 0.50; 95 %CI 0.28 − 0.88), while not in others group. Another interesting finding was those patients with POLE mutations had an excellent outcome regardless of the treatment arm (RFS 100 % vs 97 % in CRT and RT respectively, $p = 0.37$) and we must keep in mind that these patients have poor prognostic pathological features.

5. Other relevant targets in molecular subgroups

Others targets can be found in all four molecular groups defined by the TCGA. In CNH, HER2 is amplified in 25 % of the tumors. In a randomized phase II study, the addition of trastuzumab to carboplatin and paclitaxel was evaluated in 61 patients with stage III and IV or recurrent HER2 positive serous EC (Fader et al., 2018). Trastuzumab increased median progression free survival in the whole population (12.6 vs 8.0 months, p = 0.005) and the benefit was even higher for those with stage III and IV who underwent primary surgery. This combination received indication in the NCCN guidelines. Also, another way to target CNH tumors could be thru homologous recombination deficient (HRD). In a report, HRD was observed in 24 % of cases and was restricted to non-endometrioid endometrial cancers (NEEC), with 46 % of NEECs being HRD compared with none of the endometrioid endometrial cancers (EEC, P 1/4 0.014) (de Jonge et al., 2019). Although there is no clinical trial in adjuvant setting, in one case report olaparib was offered to a patient with metastatic endometrioid endometrial cancer who had received several lines of chemotherapy for multiple relapses over 9 years and displayed a profound sensitivity to platinum-containing regimens. She showed a significant reduction in the size of the brain metastases and subjective improvement in tumor-related symptoms that lasted for 8 months (Forster et al., 2011).

POLE and MSI tumors are considered immunologically hot tumors because of the high mutational burden and formation of neoantigens. Some articles reported a high rate of PD1 and PDL1 expression as well as a high density of tumor infiltrate lymphocytes (Howitt et al., 2015). Others reports have shown that high levels TIL's and a high relation between TIL's and lymphocyte T regulator are associated with better prognosis (de Jong et al., 2009). Indeed, anti-PD1/PDL1 agents (such as pembrolizumab, avelumab, atezolizumab and dorstalimab) showed good response rates and disease control in metastatic or recurrent EC with MSI and POLE mutations (Le DT et al., 2017; Azad et al., 2020; Santin et al., 2016; Liu et al., 2019).

6. Future perspective

Although POLE tumors have consistently demonstrating good outcomes, it is difficult to draw any firm conclusion if they have a good prognosis *per si* or if they are predictive of response to adjuvant therapy. Due to poor pathologic features, POLE tumors have been treated most of the time with some type of adjuvant treatment, either CT or RXT. In a report by Van Gool et al., they examined the recurrence free survival of patients with *POLE mut* and *POLE wild type* in the PORTEC 1 cohort (Van Gool et al., 2018). Patients with *POLE mut* in the observation arm showed an outstanding recurrence free survival compared to RXT arm (RFS 100 % vs 80 %, p = 0.049). They also performed a sensitivity analysis of *POLE mut* embryonic mouse stem cells to RXT and selected chemotherapeutics but failed to show an increase sensitivity to RXT and chemotherapeutic agents, with exception of fludarabine and cytarabine. They concluded that the good prognosis cannot be explained by increased sensitivity to adjuvant treatment. Future trials must address the question of whether adjuvant treatment is of any benefit for POLE tumors. Indeed, PORTEC4a is the only trial addressing the question of the benefit of adjuvant treatment based on molecular and pathologic features. In this study, patients will be classified as low, intermediate and high-risk categories based on the presence of p53 mutation, L1CAM positivity and LVSI presence. After this stratification, patients will be offered observation, BT or RXT (Wortman et al., 2018).

Immunotherapy has been changing the landscape treatment of EC in the recurrent and metastatic setting. Pembrolizumab has shown activity in MSI and POLE tumors and received an agnostic indication for MSI tumors (Research C, 2020). Also, the combination of pembrolizumab and lenvatinib, an antiangiogenic tyrosine kinase inhibitor, has also shown activity in MSS tumors, and granted indication for MSS endometrial tumors by the FDA (Makker et al., 2019; Canada, 2020). Although, there is no phase III trial opened in the adjuvant setting of EC, there are some phase 1/2 trials focusing on the role of adjuvant anti-PD1/PDL2 (NCT02630823, NCT03694834, NCT03932409, NCT04214067, NCT02728830).

For patients with CNH tumors, trastuzumab showed activity in serous tumors with HER2 positivity and studies should focused in this biomarker like breast cancer. Unfortunately, no randomized trials are underway to confirm these findings, neither for the use of newer anti-HER2 agents such as pertuzumab and TDM1.

7. Conclusion

The dualist vision of EC is giving place to a more robust and reliable molecular stratification. EC research evolved with the TCGA classification bringing new and important information in the field. Collaborative groups were able to replicate TCGA using accessible tools with immunohistochemistry. EC guidelines incorporate prognostic features to guide adjuvant treatment and allow physicians a wide range of possibilities. Although there is no randomized controlled trial yet to corroborate solely the molecular classifier as a tool for decision making, it's time to move on and include this information along with pathology features to better delineate adjuvant treatment in EC.

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Declaration of Competing Interest

None

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