Review article

PTEN as a predictive marker of response to conservative treatment in endometrial hyperplasia and early endometrial cancer. A systematic review and meta-analysis

Antonio Travaglino[a], Antonio Raffone[b,*], Gabriele Saccone[b], Luigi Insabato[a], Antonio Mollo[b], Giuseppe De Placido[b], Fulvio Zullo[b]

[a] Anatomic Pathology Unit, Department of Advanced Biomedical Sciences, School of Medicine, University of Naples Federico II, Naples, Italy
[b] Gynecology and Obstetrics Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

ABSTRACT

Objective: Several markers have been studied to predict the responsiveness of endometrial hyperplasia (EH) and early endometrial cancer (EEC) to progestin therapy. PTEN has played a major role in this field, although its predictive significance is still undefined. We aimed to assess if loss of PTEN expression on pre-treatment endometrial specimen may be a predictive markers of response to progestins in EH and EEC.
Study Design: MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID and Cochrane Library were searched for relevant articles from the inception to May 2018. All studies assessing PTEN expression as predictive marker in EH and EEC treated with progestin were included. Relative risk (RR) for therapy failure was calculated with 95% confidence interval (CI) and a significant p-value<0.05, with a subgroup analysis based on the histologic category (EEC or EH) and the administration route of progestin (oral or intrauterine).
Results: Seven cohort studies assessing 376 patients were included. PTEN loss was not significantly associated with the outcome of therapy in the overall analysis (RR = 1.24, 95% CI, 0.88–1.76, p = 0.21), in + the subgroups of EEC (RR = 0.89, 0.32–2.49, p = 0.83), EH (RR = 1.30, 0.90–1.87 p = 0.16), oral progestin (RR = 1.25 0.88–1.79, p = 0.22) and intrauterine device (RR = 1.02, 0.36–2.87, p = 0.97).
Conclusion: PTEN seems not to be useful as predictive marker of response to the conservative treatment of EH and EC, regardless of the administration route (oral or intrauterine) of progestins. We advise future researcher not to further assess PTEN as a stand-alone predictive marker.

© 2018 Elsevier B.V. All rights reserved.

Contents

* Corresponding author at: Gynecology and Obstetrics Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Via Sergio Pansini, 5, Naples, 80131, Italy.
E-mail address: anton.raffone@gmail.com (A. Raffone).

Introduction

Endometrial cancer is the most common gynecologic malignancy in the Western world [1]. In over 80% of cases, it is preceded by endometrial hyperplasia (EH), an irregular proliferation of endometrial glands [2,3]. Incidence of EH is about 132/100.000 among women [4].

The revised 2014 WHO classification recognizes two types of EH based on the presence of cytologic atypia: EH without atypia (benign) and atypical EH (premalignant) [3]. The 20-year-risk of progression of EH without atypia to cancer is less than 5% [5], thus it may be managed with observation alone and follow-up biopsies. On the other hand, atypical EH requires a total hysterectomy, due to a risk of progression of 29% [5]. Progestins constitute the treatment of choice for symptomatic EH without atypia and for women with atypical EH who wish to preserve their fertility or who are not suitable for surgery [6]. Progestins may still be used for fertility-sparing treatment of endometrioid type, stage FIGO IA, well-differentiated early endometrial cancer (EEC) without tumor invasion of myometrium [7]. Progestins can be administered orally or through intrauterine device (levonorgestrel-releasing intrauterine device, LNG-IUD) [6,8].

However, despite progestins' effectiveness, a variable percentage of EH and EEC do not respond to therapy, or even progress to invasive disease [8].

This has led to a growing interest in searching for predictive markers of response to progestins on endometrial specimens, in order to avoid the risk of disease progression linked to an ineffective therapy. In particular, a major role has been played by immunohistochemistry, which is the most widely used tool in this field [9].

The tumor suppressor protein phosphatase and tensin homolog (PTEN) has been one of the most important markers studied in this field, due to its recognized role in endometrial carcinogenesis [2]. A prognostic significance of PTEN expression in EH has already been reported for the risk of concurrent cancer [10] and progression to cancer [11]. Some authors also suggested a role of PTEN in resistance to progestins [12,13], although this point has not yet been clarified.

Thus, the aim of this systematic review and meta-analysis was to assess if immunohistochemical loss of PTEN expression on pre-treatment endometrial specimen may be a predictive marker of response to progestins in EH and EEC.

Materials and methods

Study protocol

This study was performed according to a protocol recommended for systematic review and meta-analysis. The protocol defining methods for collecting, extracting and analyzing data was designed a priori. All review stages were conducted independently by two reviewers (AT and AR) and disagreements were resolved by discussion with a third author (GS).

Search strategy

Several researches were conducted using MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID and Cochrane Library as electronic databases. The studies were identified by using a combination of the following text words from the inception to May 2018: endometrial hyperplasia; endometrial cancer; endometrioid adenocarcinoma; endometrial intraepithelial neoplasia; EIN; therapy; treatment; fertility sparing; conservative; medroxyprogesterone; MPA; mirena; LNG; levonorgestrel; progestogen; progestin; response; resistance; persistence; outcome; PTEN; phosphatase and tensin homolog; marker; immunohistochemistry; immunohistochemical. Review of articles also included the abstracts of all references retrieved from the search.

Study selection

We included in our systematic review all randomized and non-randomized studies that satisfied the following inclusion criteria:

- study population constituted by women diagnosed with EH or EEC and conservatively treated with progestogens;
- assessment of the expression of PTEN on pre-treatment endometrial specimens by immunohistochemistry;
- assessment of the association between PTEN expression (presence *vs* loss) and the response to therapy (good *vs* poor, where 'good response' denoted a complete regression of EH or EEC);
- comparability of data.

Risk of bias assessment

According to the Methodological Index for Non-Randomized Studies (MINORS) [14], six domains related to risk of bias were assessed in each study: 1) Aim (i.e. clearly stated aim), 2) Rate (i.e. inclusion of consecutive patients), 3) Data (i.e. prospective collection of data), 4) Bias (i.e. unbiased assessment of study endpoints), 5) Time (i.e. follow-up time appropriate), 6) Loss (i.e. loss to follow-up). Review authors' judgments were categorized as "low risk," "high risk" or "unclear risk of bias."

Data extraction

Data were extracted from each study without modification. Two by twocontingency tables were prepared reporting two dichotomous qualitative variables: PTEN expression on pre-treatment biopsy ("presence" *vs* "loss") and response to conservative therapy ("good" *vs* "poor", where "good response" indicated a complete regression of disease). When discrepancies between text and tables were found, values from tables were used. In one study [15], 2 women treated with LNG-IUD showed no overt findings of EH on follow-up biopsy, although PTEN-null glands were still

present. These patients were considered as poor responders, since according to Mutter et al the presence of PTEN-null glands would indicate a latent precancer [16] and thus not a complete regression.

Data were also subdivided into subgroups based on the histologic diagnosis (EH or EEC) and administration route of progestins (oral or intrauterine).

Data analysis

The impact of PTEN status on the therapy outcome was assessed as relative risk (RR) for failure of therapy, with 95% confidence interval (CI). RR was calculated for each study and as pooled estimate and reported graphically on a forest plot. A p-value<0.05 was considered significant.

The inconsistency index (I^2) was used for the assessment of statistical heterogeneity among studies: heterogeneity was considered insignificant for $I^2<25\%$, low for $I^2<50\%$, moderate for $I^2<75\%$ and high for $I^2\geq75\%$. In case of $I^2\geq50\%$ a random effect model was used; in case of $I^2<50\%$ a fixed effect model was adopted.

A subgroup analysis was also performed (EH *vs* EEC; oral *vs* intrauterine progestins).

Data analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014).

Results

Selection and characteristics of the studies

The process of study selection is summarized in Fig. 1.

Seven studies assessing 376 patients were included [12,13,15,17–20]. Five studies were retrospective and 2 were prospective. The sample size ranged from 9 to 141.

Out of 376 EH, 217 had PTEN loss and 159 had PTEN presence at immunohistochemistry. Patients with good response were 275, while 101 had poor response. Patients age ranged from 19 to 79.
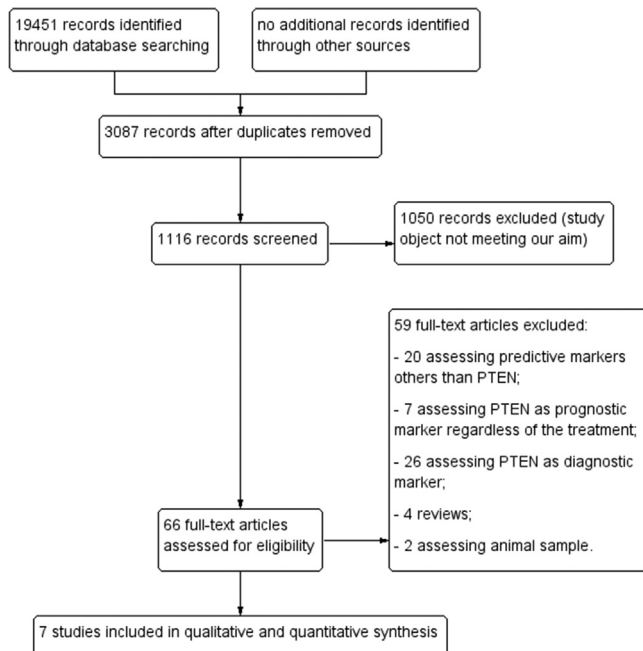

Fig. 1. Flow diagram of studies identified in the systematic review (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).

Patients BMI ranged from 20 to 39. Histologic diagnosis included 239 non-atypical EH, 98 atypical EH and 39 EEC.

Progestins used included megestrol acetate (N = 65), norethindrone acetate (N = 14), medroxyprogesterone acetate (N = 207) administered orally, LNG-IUD (N = 84) or a mixture of more than one progestin (N = 9). Follow-up duration ranged from 1 to 26 months.

Characteristics of the included studies are shown in Table 1.

Risk of bias assessment

For the "aim" domain, all studies were categorized at low risk of bias, since they had a clearly stated aim.

For the "rate" domain, three studies were categorized at low risk, because they selected consecutive patients; the other 4 studies did not clearly specify this point, although it seems that they included all eligible patients in the period considered, thus they were considered at unclear risk.

For the "data" domain, 3 studies were categorized at low risk, since they collected data prospectively; the other 4 studies were considered at unclear risk because this information was not specified.

For the "bias" domain, only one study was categorized at unclear risk, because it considered non-atypical EH as a regression of atypical EH; the other 6 studies were considered at low risk, as a diagnosis complete response implied that no lesions had persisted at follow-up.

For the "time" domain, 4 studies were categorized at low risk, since they treated all patients at least for 6 months, as recommended by guidelines [6,7]; for the other studies the risk was unclear because the duration of therapy was 1–6 months.

For the "loss" domain, all studies were categorized at unclear risk, because the number of patients lost to follow-up was not specified.

Results of risk of bias assessment are shown in Fig. 2.

PTEN and therapy response

A loss of PTEN expression showed a relative risk for therapy failure of 1.24 (95% CI, 0.88–1.76); the impact on the risk was not significant (p = 0.21); there was no heterogeneity among studies ($I^2 = 0\%$) (Fig. 3).

In the subgroup of patients with EC (N = 39), RR was 0.89 (95% CI, 0.32–2.49), without significant impact on the therapy outcome (p = 0.83) and without heterogeneity ($I^2 = 0\%$). In the subgroup of patients with EH (N = 337), RR was 1.30 (95% CI, 0.90–1.87) without statistical significance (p = 0.16) and without significant heterogeneity ($I^2 = 16\%$). There was no significant difference between the two subgroup (Chi^2 = 0.45; p = 0.50) (Fig. 3).

On the basis of the treatment administered, the subgroup treated with oral progestin (N = 291) showed a non-significant RR of 1.25 (95% CI, 0.88–1.79, p = 0.22) with no heterogeneity ($I^2 = 0\%$). In the subgroup treated with LNG-IUD (N = 85), RR was 1.02 (95% CI, 0.36–2.87) without statistical significance (p = 0.97) and without heterogeneity ($I^2 = 0$). There was no significant difference between the two subgroup (Chi^2 = 0.14; p = 0.71) (Fig. 4).

Comment

Our results showed that the loss of PTEN expression, evaluated at immunohistochemistry, does not affect the outcome of progestin-based therapy of EH and EC.

PTEN gene is a tumor-suppressor gene, located at chromosome 10q23. It encodes a protein with a lipid phosphatase activity, which induces cell cycle arrest, and favors apoptosis upregulating AKT-dependent mechanisms and downregulating Bcl-2-dependent mechanisms, acting in opposition to PI3K. PTEN product has also a protein phosphatase activity, involved in the inhibition of cell

Table 1
Characteristics of the included studies.

YEAR	FIRST AUTHOR	COUNTRY	STUDY DESIGN	PERIOD OF ENROLLMENT	SAMPLE SIZE	AGE	BMI	SAMPLING METHOD	NAH	AH	EC	MGA	NETA	MPA	LNG	MIX	TREATMENT DURATION	GOOD	POOR
2007	Minaguchi	Japan	retrospective	1989–2003	31	19–60	n.r.	curettage	–	12	19	–	–	31	–	–	2–18 months	26	5
2007	Yamazawa	Japan	prospective	1999–2005	9	28–40	n.r.	curettage	–	–	9	–	–	9	–	–	6–9 months	7	2
2008	Milam	USA	retrospective	n.r.	38	20–79	n.r.	biopsy	13	25	–	18	5	16	–	–	1–12 months	16	22
2010	Akesson	UK	prospective	1999–2004	34	36–77	21–49	n.r.	29	5	–	–	–	–	34	–	26 months	28	6
2012	Upson	USA	retrospective	1985–2005	112	<39 to >70	<25 to >30	n.r.	72	40	–	46	9	50	–	9	ns	80	32
2015	Orbo	Norway	retrospective	2005–2011	141	<44 to >52	<20 to >30	Pipelle	125	16	–	–	–	93	48	–	6 months	112	29
2016	Van Gent	Netherlands	retrospective	2002–2012	11	27–38	20–39	biopsy, curettage	–	–	11	1	–	8	2	–	6–19 months	6	5
TOTAL			2 prospective 5 retrospective	1985–2012	376	19–79	20–39	–	239	98	39	65	14	207	84	9	1–26 months	275	101

NAH: non-atypical hyperplasia; AH: atypical hyperplasia; EC: endometrial cancer; MGA: megestrol acetate; NETA: norethindrone acetate; MPA: medroxyprogesterone acetate; LNG: levonorgestrel-releasing intrauterine device; MIX: mixture of more than one progestin; n.r.: not reported.
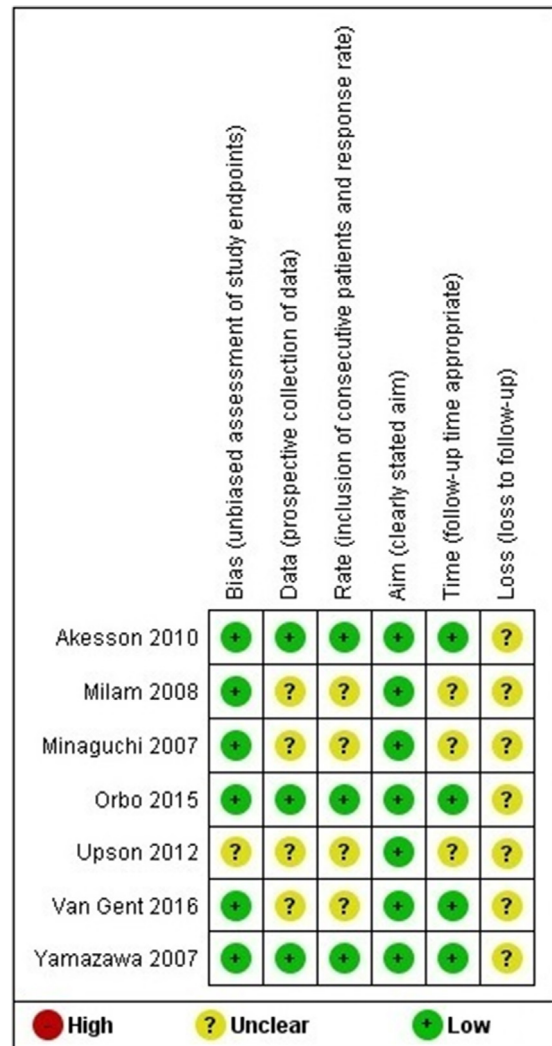

Fig. 2. Assessment of risk of bias. Summary of risk of bias for each study; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias.

spread, focal adhesion formation and growth-factor-stimulated MAPK signaling [21].

PTEN has played a major role in the study of endometrial carcinogenesis, since PTEN gene is the most commonly mutated in endometrioid carcinoma [22].

In particular, PTEN has been studied as the main marker of endometrial precancerous lesion; Mutter et al. indeed reported that PTEN loss at immunohistochemistry might differentiate premalignant EH from benign functional EH [16,23].

In 2013, the Cancer Genome Atlas Research Network identified four distinct molecular categories of EC. In the categories 'ultra-mutated', 'hypermutated' and 'copy number low', which are typically endometrioid, PTEN mutations were found in 94%, 88% and 77% respectively. In the last category ('copy number high'), mainly constituted by serous EC, PTEN mutations were found only in 15% of specimens [22].

A loss of PTEN expression was found to be prognostic for progression of EH to EC [11], and for the presence of a coexistent EC after a diagnosis of EH [10]. Given the widespread use of conservative therapy of EH and EC, great importance has been given to the search for predictive markers of response [24–27]. PTEN has still played a major role in this field, although results about its predictive ability appear contrasting [12,13,15,17–20].
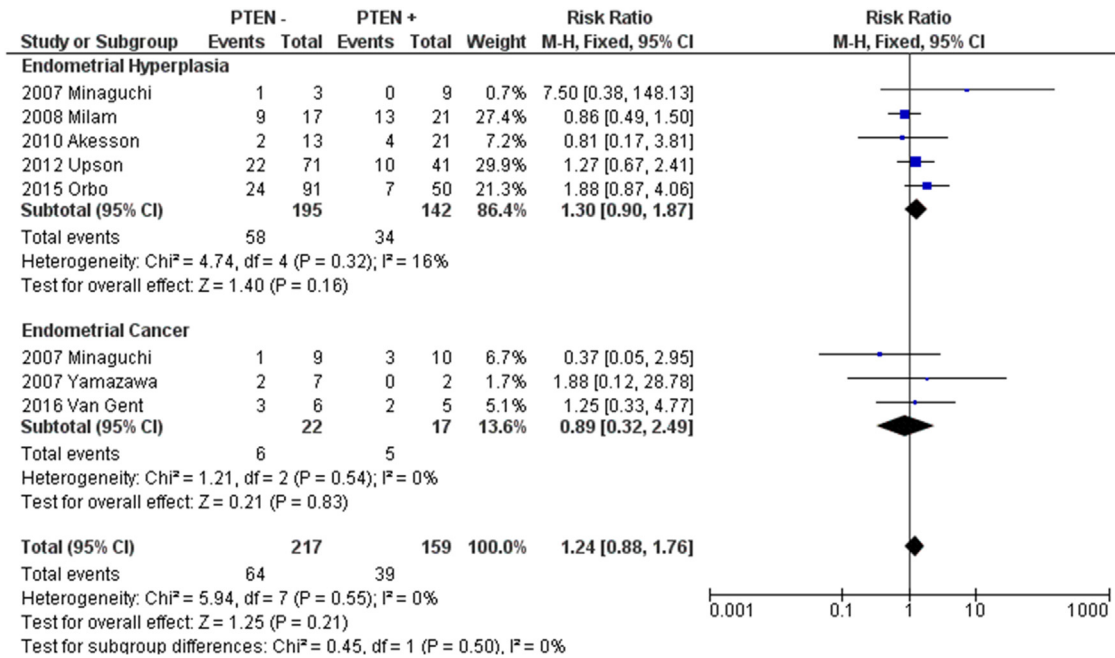
Fig. 3. PTEN loss in predicting the response to therapy in endometrial hyperplasia and early endometrial cancer. Forest plots report graphically the relative risk for therapy failure according to the histologic diagnosis (endometrial hyperplasia *vs* endometrial cancer).
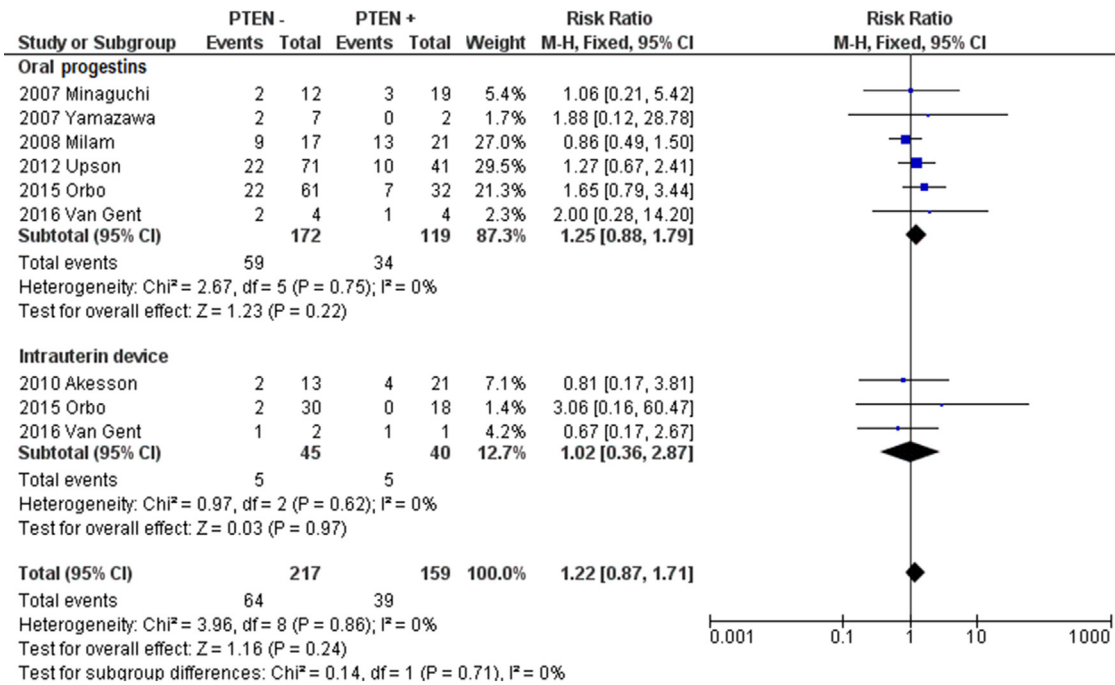

Fig. 4. PTEN loss in predicting the response to therapy in endometrial hyperplasia and early endometrial cancer. Forest plots report graphically the relative risk for therapy failure according to the type of progestin administered (oral *vs* intrauterine).

In patients with EC, we found that PTEN loss was associated with good response to progestins (RR = 0.89), although not significantly (p = 0.83). In this regard, a recent study showed that PTEN loss at immunohistochemistry did not influence the prognosis in EC [29].

In the subgroup of EH, PTEN loss showed a RR of 1.30, which indicates a negative impact on the response to therapy, although still without statistical significance (p = 0.16). Since PTEN loss in EH was shown to be predictive for the risk of cancer [10,11], it is possible that a minor influence on the response may exist.

Even when assessed separately in women treated with oral progestins and LNG-IUD, the predictive value of PTEN loss was never significant.

Anyway, while the statistical significance might be achieved by assessing a larger sample, the impact on the response to therapy would still appear insufficient to have a bearing on the patient management, due to the low values of RR observed. Conservative management of atypical EH and EEC is not indeed the standard treatment, and the risk of progression to invasive disease is already taken into account, so patients undergo a close follow-up. Being

the regression rates reported for LNG-IUD over 90% [8], a predictive marker should increase the risk of failure at least 3–4 folds to have a clinical significance.

All these results indicate that PTEN immunohistochemical status does not significantly impact on the response to progestins in EH and EC. Thus, further studies in this field should no more assess PTEN as a stand-alone predictive marker.

In this regard, two studies among those included in our review suggested a possible predictive role for PTEN if assessed together with other molecules. In particular, Minaguchi et al. reported that the presence of at least one between PTEN loss and low expression of phospho-AKT was associated with higher therapy failure, compared to the absence of both [12]. Milam et al. showed that a decreased PTEN expression accompanied by a phospho-mTOR overexpression on the follow-up biopsy is associated with a poor response [13]. Remarkably, both phospho-AKT and phospho-mTOR are molecules involved in the same pathway as PTEN [12,13]. Nonetheless, evidence in this field it is weak and it is unclear which significance these findings may have in the patient management. Several other predictive markers have been assessed by immuno-histochemistry in EH and EC. Among these, estrogen and progesterone receptors have shown association with good response to progestins in some studies [17–19]. By contrast, other studies showed opposite results [12,24], and European guidelines discourage their use [7]. One study showed that deficient expression of mismatch repair proteins was predictive of poor response, with perfect specificity [27]; however, given some limitations inherent to the study population, this result need to be further confirmed [28].

With the recent progresses about the molecular definition of endometrial neoplastic specimens [22,29,30], in the near future the role of such molecules might be clarified.

Strengths and limitation

To the best of our knowledge, this is the first review assessing the role of PTEN in the conservative management of EH and EEC. Our study clarified that immunohistochemical expression of PTEN does not affect the outcome of progestin-therapy in EH and EC, independently from histologic category or type of progestin administered.

A limitation of our study might be the relatively small size of the sample assessed (N = 376), although the absence of heterogeneity among studies (I^2 = 0%) and the constancy of RR values in the several groups give solidity to our results. Furthermore, we considered PTEN expression assessed by only immunohistochem-istry. Several concerns with PTEN immunohistochemistry have been reported, such as subjectivity in the interpretation of immunostaining and lack of a standard protocol [31]. On the other hand, immunohistochemistry allows evaluating both inten-sity and distribution of the marker expression. There is evidence that PTEN immunohistochemistry may outperform PTEN gene sequencing [32]. For our analysis, we took into account only a complete loss of immunostaining, which should be easily readable even without expertise in immunohistochemistry. Anyway, to the best of our knowledge, there are no studies evaluating the predictive value of PTEN by techniques other than immunohis-tochemistry in patients with EH and/or EC treated with progestins progestin. Two studies assessed the association between PTEN mRNA and progesterone receptor expression, showing conflicting results [33,34]. However, studies demonstrating associations between PTEN and progesterone receptor expression may have limited value, as the expression of progesterone receptor seems to not reliably reflect the responsiveness to progestins [7].

Another limitation may be the absence of studies treating patients by hysteroscopic resection plus progestin, which has

recently been described as the most effective conservative treatment for EH and EC [35,36].

Finally, we were unable to extract data separately for atypical and non-atypical EH.

Conclusion

Loss of PTEN expression seems not to be useful as predictive marker of response to progestins in EH and EEC, regardless of the administration route (oral or intrauterine). We advise future researcher not to further assess PTEN as a stand-alone predictive marker. However, the combined assessment of PTEN with other markers might have a predictive utility, but further evidence is required in this regard.

Disclosure

The authors report no conflict of interest.

Financial support

No financial support was received for this study.

References

[1] Ferlay J., Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN. Int J Cancer 2012;2015(136):E359–86.
[2] Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. Mod Pathol 2000;13:295–308.
[3] Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. WHO classifica-tion of tumours of female reproductive organs. 4th ed. Lyon: IARC; 2014.
[4] Reed SD, Newton KM, Clinton WL, Epplein M, Garcia R, Allison K, et al. Incidence of endometrial hyperplasia. Am J Obstet Gynecol 2009;200(678): e1–6.
[5] Jr Lacey JV, Sherman ME, Rush BB, et al. Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. J Clin Oncol 2010;28:788–92.
[6] Management of endometrial hyperplasia Green-top guideline No. 67 RCOG/ BSGE joint guideline | February. 2016.
[7] Colombo, et al. ESMO-ESGO-ESTRO consensus Conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol 2016;27:16–41.
[8] Zhang Q, Qi G, Kanis MJ, et al. Comparison among fertility-sparing therapies for well differentiated early-stage endometrial carcinoma and complex atypical hyperplasia. Oncotarget 2017;8(34):57642–53.
[9] Sanderson PA, Critchley HOD, Williams ARW, Arends MJ, Saunders PTK. New concepts for an old problem: the diagnosis of endometrial hyperplasia. Hum Reprod Update 2017;23(2):232–54.
[10] Pavlakis K, Messini I, Vrekoussis T, et al. PTEN-loss and nuclear atypia of EIN in endometrial biopsies can predict the existence of a concurrent endometrial carcinoma. Gynecol Oncol 2010;119(3):516–9.
[11] Baak JP, Van Diermen B, Steinbakk A, et al. Lack of PTEN expression in endometrial intraepithelial neoplasia is correlated with cancer progression. Hum Pathol 2005;36(5):555–61.
[12] Minaguchi T, Nakagawa S, Takazawa Y, et al. Combined phospho-akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. Cancer Lett 2007;248(1):112–22.
[13] Milam MR, Soliman PT, Chung LH, et al. Loss of phosphatase and tensin homologue deleted on chromosome 10 and phosphorylation of mammalian target of rapamycin are associated with progesterone refractory endometrial hyperplasia. Int J Gynecol Cancer 2008;18(1):146–51.
[14] Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73(9):712–6.
[15] Orbo A, Arnes M, Lysa LM, Straume B. Expression of PAX2 and PTEN associates to therapy response in endometrial hyperplasia. Anticancer Res 2015;35:6401–9.
[16] Mutter GL, Ince TA, Baak JPA, Kust GA, Zhou XP, Eng C. Molecular identification of latent precancers in histologically Normal endometrium. Cancer Res 2001;61:4311–4.
[17] Yamazawa K, Hirai M, Fujito A, et al. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. Hum Reprod 2007;22(7):1953–8.
[18] Akesson E, Gallos ID, Ganesan R, Varma R, Gupta JK. Prognostic significance of estrogen and progesterone receptor expression in LNG-IUS (mirena) treatment of endometrial hyperplasia: an immunohistochemical study. Acta Obstet Gynecol Scand 2010;89(3):393–8.

[19] Upson K, Allison KH, Reed SD, et al. Biomarkers of progestin therapy resistance and endometrial hyperplasia progression. Am J Obstet Gynecol 2012;207(1) e1–8 36.

[20] van Gent MD, Nicolae-Cristea AR, de Kroon CD, et al. Exploring morphologic and molecular aspects of endometrial cancer under progesterone treatment in the context of fertility preservation. Int J Gynecol Cancer 2016;26(3):483–90.

[21] Okuda Tsuyoshi, Sekizawa Akihiko, Purwosunu Yuditiya, et al. Genetics of endometrial cancers. Obstet Gynecol Int 2010;2010:984013.

[22] Cancer Genome Atlas Research Network, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497(7447):67–73.

[23] Mutter GL, Lin MC, Fitzgerald JT, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst 2000;92 (11):924–30.

[24] Gunderson CC, Dutta S, Fader AN, et al. Pathologic features associated with resolution of complex atypical hyperplasia and grade 1 endometrial adenocarcinoma after progestin therapy. Gynecol Oncol 2014;132(1):33–7.

[25] Ørbo A, Arnes M, Lyså LM, Borgfeldt C, Straume B. HE4 is a novel tissue marker for therapy response and progestin resistance in medium- and low-risk endometrial hyperplasia. Br J Cancer 2016;115(6):725–30.

[26] Tierney KE, Ji L, Dralla SS, et al. Endoplasmic reticulum stress in complex atypical hyperplasia as a possible predictor of occult carcinoma and progestin response. Gynecol Oncol 2016;143(3):650–4.

[27] Zakhour M, Cohen JG, Gibson A, et al. Abnormal mismatch repair and other clinicopathologic predictors of poor response to progestin treatment in young women with endometrial complex atypical hyperplasia and well-differentiated endometrial adenocarcinoma: a consecutive case series. BJOG 2017;124 (10):1576–83.

[28] Derbyshire AE, Ryan N, Crosbie EJ. Biomarkers needed to predict progestin response in endometrial cancer. BJOG 2017;124(September 10):1584.

[29] Karnezis AN, Leung S, Magrill J, et al. Evaluation of endometrial carcinoma prognostic immunohistochemistry markers in the context of molecular classification. J Pathol Clin Res 2017;3(4):279–93.

[30] Travaglino A, Raffone A, Saccone G, et al. Loss of bcl-2 immunohistochemical expression in endometrial hyperplasia: a specific marker of precancer and novel indication for treatment. A systematic review and meta-analysis. Acta Obstet Gynecol Scand 2018(Aug 31).

[31] Bingham V, Ong CW, James J, et al. PTEN mRNA detection by chromogenic, RNA in situ technologies: a reliable alternative to PTEN immunohistochemistry. Hum Pathol 2016;47(January1):95–103.

[32] Djordjevic B, Hennessy BT, Li J, et al. Clinical assessment of PTEN loss in endometrial carcinoma: immunohistochemistry Out-performs Gene sequencing. Mod Pathol 2012;25(May 5):699–708.

[33] Samulak D, Grosman-Dziewiszek P, Michalska MM, et al. Evaluation of expression of the PTEN gene, oestrogen and progesterone receptors as diagnostic and predictive factors in endometrial cancer. Pathol Oncol Res 2014;20(January1):191–6.

[34] Skrzypczak M, Merx I, Schüler-Toprak S, et al. Molecular profiling of estrogen receptor α and progesterone receptor transcript variants in endometrial cancer. Steroids 2015;104:122–8 Dec.

[35] Zhang Q, Qi G, Kanis MJ, et al. Comparison among fertility-sparing therapies for well differentiated early-stage endometrial carcinoma and complex atypical hyperplasia. Oncotarget 2017;3;8(May 34):57642–53.

[36] Giampaolino P, Di Spiezio Sardo A, Mollo A, et al. Hysteroscopic endometrial focal resection followed by levonorgestrel intrauterine device insertion as a fertility-sparing treatment of atypical endometrial hyperplasia and early endometrial cancer: a retrospective study. J Minim Invasive Gynecol 2018;11 (July18)30347–9 pii: S1553-S4650.