ORIGINAL RESEARCH PAPER

Surgery

KEY WORDS: 2D-3D Ultrasound, Hysteroscopy, Hysterosonography, Tamoxifen.

WHICH IS THE MOST ACCURATE DIAGNOSTIC PROCEDURE IN TAMOXIFEN TREATED BREAST CANCER PATIENTS?

Izzo P	Department of General Surgery Pietro Valdoni, Policlinico Umberto I, La Sapienza University of Rome
Pugliese F	Department of General Surgery Pietro Valdoni, Policlinico Umberto I, La Sapienza University of Rome
Scarano Catanzaro V	Department of General Surgery Pietro Valdoni, Policlinico Umberto I, La Sapienza University of Rome
De Santis A.	Department of General Surgery Pietro Valdoni, Policlinico Umberto I, La Sapienza University of Rome
Razionale F	Department of General Surgery Pietro Valdoni, Policlinico Umberto I, La Sapienza University of Rome
Millarelli F	Department of General Surgery Pietro Valdoni, Policlinico Umberto I, La Sapienza University of Rome
Di Cello P	Department of General Surgery Pietro Valdoni, Policlinico Umberto I, La Sapienza University of Rome
Izzo S	Department of General Surgery Pietro Valdoni, Policlinico Umberto I, La Sapienza University of Rome
Izzo L*	Department of General Surgery Pietro Valdoni, Policlinico Umberto I, La Sapienza University of Rome, *Corresponding Author

ABSTRACT

Purpose: The aim of this study was to evaluate the diagnostic accuracy of bi-dimensional (2D) and three-dimensional (3D) transvaginal ultrasound (TVUS), hysterosonography (HSSG) and hysteroscopy in the detection of endometrial pathology in women treated with tamoxifen (TMX) for breast cancer.

Methods: Forty-two patients, affected by breast cancer under treatment with TMX, underwent 2D-3D TVUS, HSSG and hysteroscopy completed by biopsy, after abnormal findings following a routine 2D TVUS examination.

Results: 3D-TVUS was more accurate than 2D-TVUS in the detection of atrophic endometrium confirmed by biopsy and in the detection of endometrial polyps.

HSSG and hysteroscopy detected atrophic endometrium and endometrial polyps significantly better than ultrasound scan. Endometrial carcinoma was detected in two cases, and in both HSSG and hysteroscopy were 100% diagnostic.

Conclusion: In TMX treated breast cancer patients, HSSG and hysteroscopy provide more accurate diagnosis than 2D-3D ultrasound in the detection of treatment related endometrial lesions.

Introduction

We considered the evaluation of the diagnostic accuracy regarding different procedures for the detection of endometrial pathology in women treated with tamoxifen (TMX) for breast cancer. TMX is a non-steroidal triphenylene derivate with antiestrogenic properties on the breast, as competitive inhibitor of estradiol. The adverse effects of TMX could be: retinal changes, osteoporosis, atherosclerosis, thromboembolic disorders and endometrial stimulation. TMX also has estrogenic effects on endometrium, inducing a variety of disorders from cystic glandular atrophy to endometrial carcinoma [1,4,5]. The relative risk of developing endometrial cancer, during TMX treatment, increases from 1.5 to 7.5, and it seems to be correlated to both dose and length of treatment. There is no consensus regarding the best approach to follow up patients under TMX therapy for the screening of endometrial pathologies. Dilatation and curettage has been questioned because of morbidity, invasive nature and patients discomfort [1].

Transvaginal ultrasonography (TVUS, bi-dimensional [2D], three-dimensional [3D]) has been proposed as a method for monitoring the patients treated with TMX. Using a cut-off of 8-10 mm endometrial thickness, the false positive rate becomes 10-15%. Hysterosonography (HSSG) and hysteroscopy increase diagnostic accuracy of TVUS.

Materials and Methods

92 patients affected by breast cancer and in treatment with TMX, were followed up in our Institution from January 2010 to November 2017.

Exclusions criteria were: the not continuous and available follow-up by TVUS, the lack of HSSG or hysteroscopy and biopsy, the not regular use of TMX and death occurring during the study. After the former criteria were observed, 42 patients were eligible and recruited in this study. All patients received TMX 20 mg/day. After suspected endometrial lesion at first 2D TVUS examination, patients underwent 2D-3D TVUS scans and HSSG, and within 7-25 days, hysteroscopy and biopsy in day surgery. By means of HSSG, the regularity of the endometrial outline and the myometrial border were observed and the cavity was examined for any intrauterine structure delineated by the fluid.

All procedures followed were in agreement with the ethical standards of the committee on human experimentation of the institution.

No patient used other hormonal therapy.

Results

Mean patient age was 56.1 yrs, mean age at breast cancer diagnosis was 52.3 yrs and time lapse between diagnosis and menopause was 7.1 yrs.

Thirty-four women received TMX for a period longer > 24 months, 10 women received TMX for a period of 12-24 months and 4 for a

period < 12 months. The mean endometrial thickness was significantly higher when TMX intake was > 24 months ($p<0.01$). 3D-TVUS was more accurate than 2D-TVUS in the detection of 43% of atrophic endometrium confirmed by biopsy and in 45% of endometrial polyps. HSSG and hysteroscopy detected atrophic endometrium, endometrial polyps and endometrial carcinoma better than TVUS (Table 1).

Conclusion

Most postmenopausal patients receiving TMX show TVUS abnormalities of the endometrium: the most common finding on histology in asymptomatic subjects is an atrophic epithelium. Endometrial thickness is greater in TMX-treated patients than in controls but there is no evidence of an increase in preneoplastic changes [2].

The discrepancy is probably due to specific TMX-associated subepithelial changes. HSSG is not as invasive as hysteroscopy; it has more acceptable risks [3]. HSSG improves the sensitivity of TVUS, in particular, the cystic images that 2D-TVUS referred to endometrium, are cystic dilatations external to endometrium. HSSG screens patients who need hysteroscopy and hystological confirmation of TVUS detected endometrial abnormalities.

Endometrial thickness, measured and studied by TVUS, does not have an adequate correlation with endometrial pathologies in TMX treated women; HSSG guarantees the assessment almost as accurately as reached by hysteroscopy, particularly in cases of atrophic endometrium and endometrial polyps.

Table 1. Comparison between diagnosis accuracy of lesions by different procedures: TVUS, HSSG Hysteroscopy and Histology (n=42).

	2-D TV	3-D TV	HSSG	Hysteroscopy	Endometrial lesions°
Atrophic endometrium	4 (17%)	10 (43%)	20 (86%)	21 (91%)	23
Endometrial polyps	2 (18%)	5 (45%)	8 (72%)	10 (91%)	11
Endometrial Hyperplasia	-	2 (66.6%)	2 (66.6%)	2 (66.6%)	3
Endometrial carcinoma	-	1 (50.0%)	2 (100%)	2 (100%)	2
Normal findings	1 (33.3%)	2 (66.6%)	3 100.0%)	3 (100.0%)	3

° in all cases endometrial changes were confirmed by biopsy and histology.

References

1. Izzo L, Meggiorini ML, Nofroni I, Pala A, De Felice C, Meloni P, Simari T, Izzo S, Pugliese F, Impara L, Merlini G, Di Cello P, Cipolla V, Forcione AR, Paliotta A, Domenici L, Bolognese A. Insulin-like growth factor-I (IGF-1), IGF-binding protein-3 (IGFBP-3) and mammographic features. G Chir. 2012 May;33(5):153-62.
2. Abdaal A, Mushtaq Y, Khasati L, Moneim J, Khan F, Ahmed H, Bolton H. Post-menopausal bleeding - Is transvaginal ultrasound a useful first-line investigation in tamoxifen users? Post Reprod Health. 2018 Jan 1:2053369118755190.
3. Love CDB, Muir BB, Scrimgeour JB, et al. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. J Clin Oncol 1999;17:2050-5.
4. Rayter Z, Gazet JC, Shepherd J, et al. Gynecological cytology and pelvic ultrasonography in patients with breast cancer taking tamoxifen compared with controls. Eur J Surg Oncol 1994 ;20:134-40.
5. Soares SR, Barbosa dos Reis MMB, Camargos AF. Diagnostic accuracy of sonohysterography, transvaginal sonography and hysterosalpingography in patients with uterine cavity diseases. Fertil Steril 2000;73:406-11.
6. Swedish Breast Cancer Co-Operative Group. Randomized trial of 2 versus 5 years of adjuvant therapy in node positive breast cancer. J Natl Cancer Inst 1996;88:1553-58.
7. Vogel VG. Reducing the risk of breast cancer with tamoxifen in women at increased risk. J Clin Oncol 2001; 92:87-91.