

EXPRESSION OF BCL-2 IN IMPRINT SMEARS OF ENDOMETRIAL CARCINOMA

KOSMAS KONSTANTINOS^{1*}, MITROPOULOU
GEORGIA², STAMOULAS MARIOS³, KLAPSINO
EIRINI⁴, MAROUGA ANNA⁵

¹ Department of Cytopathology, General Chest Diseases Hospita
of Athens «SOTIRIA», Greece

² Pathology Department, «Agia Sofia» Children's Hospital of Athens,
Greece

³ Department of Obstetrics & Gynaecology, Chesterfield Royal Hospital,
Derbyshire, UK

⁴ Department of Cytology, Diagnostic and Therapeutic Center of Athens
«Hygeia», Athens, Greece

⁵ Department of Cytopathology, Athens University, Medical School,
«Attikon» University Hospital, Athens, Greece

E-mail: kosmas_konstantinos@yahoo.gr^{*1},
mitropoulougeorgia@yahoo.gr², mdstamoulas@yahoo.gr³,
eirini_kl@yahoo.com⁴, marougaanna@yahoo.gr⁵

The aims of this study were to determine the expression of Bcl-2 in endometrial adenocarcinomas in imprint smears as an alternative technique rather than the frozen section and to correlate the results with clinicopathologic parameters of primary untreated endometrial cancer patients. One hundred twenty-six patients with endometrial carcinoma were evaluated with samples freshly resected after a total abdominal hysterectomy during a 29-month period. One hundred two cases were type I and 24 type II endometrial adenocarcinomas. Positive expression of Bcl-2 was observed only in type I and in low grade carcinomas. Immunocytochemical findings from Bcl-2 stain, appeared to be a valuable predictor of endometrial cancer diagnosis and postoperative prognosis in most cases in endometrial cytology with imprint smears. Furthermore, positive expression of Bcl-2 was related to morphologic features of less aggressiveness (pathogenetic type I, low-grade, early advanced stage, deep myometrial involvement <1/2 or not) tumors.

Key words: Endometrial carcinoma, Bcl-2, imprint cytology, immunocytochemistry, endometrial cancer diagnosis

ЕКСПРЕСІЯ BCL-2 В МАЗКАХ-ВІДБИТКАХ ЕНДОМЕТРІАЛЬНОЇ КАРЦИНОМИ

Мета дослідження полягала у визначенні експресії Bcl-2 в ендометріальних аденокарциномах за допомогою мазків-відбитків, як альтернативної техно-

логії, на відміну від використання заморожених зрізів та у кореляції результатів з клініко-патологічними параметрами пацієнтів з раком ендометрію до проведення первинного лікування. Було досліджено зразки ста двадцяти шести пацієток з ендометріальною карциномою за використання нещодавно резекованих зразків, отриманих після повної абдомінальної гістеректомії протягом 29-місячного періоду. Сто два зразки показали ендометріальну аденокарциному типу I і 24 – типу II. Позитивну експресію Bcl-2 спостерігали лише у карциномах типу I і низькодиференційованих карциномах. Виявилось, що імуноцитохімічні результати відбитку Bcl-2 є цінним прогностичним фактором для діагностики раку ендометрію і пост-оперативного прогнозу у більшості випадків ендометріальної цитології за використання мазків-відбитків. Крім того, позитивна експресія Bcl-2 була пов'язана з морфологічними ознаками меншої агресивності (патогенетичний тип I, низькодиференційований, рання прогресуюча стадія, глибоке враження міометрію <1/2 або ні) пухлин.

Ключові слова: ендометріальна карцинома, Bcl-2, цитологія відбитків, імуноцитохімія, діагностика раку ендометрію.

REFERENCES

1. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. Global Burden of Disease Cancer Collaboration. *JAMA Oncol.*, 2017, vol. 3, no. 4, pp. 524–48. PMID:27918777. <https://doi.org/10.1001/jamaoncol.2016.5688>.
2. Bokhman, J.V., Two pathogenetic types of endometrial carcinoma. *Gynec. Oncol.*, 1983, vol. 15, no. 1, pp. 10–7. PMID:6822361.
3. Lax, S.F., Kurman, R.J., A dualistic model for endometrial carcinogenesis based on immunohistochemical and molecular genetic analyses. *Verh. Dtsch. Ges. Pathol.*, 1997, vol. 81, pp. 228–32. PMID:9474874.
4. Kurman, R.J., (ed). *Blaustein's pathology of the female genital tract*. 6th ed. New York: Springer, 2011, pp. 384–95.
5. Liu, F.S., Molecular carcinogenesis of endometrial cancer. *Taiwan. J. Obstet. Gynecol.*, 2007, vol. 46, no. 1, pp. 26–32. PMID:17389185. [https://doi.org/10.1016/S1028-4559\(08\)60102-3](https://doi.org/10.1016/S1028-4559(08)60102-3).
6. Lax, S.F., Pizer, E.S., Ronnett, B.M., and Kurman, R.J., Comparison of estrogen and progesterone receptor, Ki-67, and p53 immunoreactivity in uterine endometrioid carcinoma and endometrioid carcinoma with squamous, mucinous, secretory, and cili-

© KOSMAS KONSTANTINOS,
MITROPOULOU GEORGIA, STAMOULAS MARIOS,
KLAPSINO EIRINI, MAROUGA ANNA, 2020

- ated cell differentiation. *Hum. Pathol.*, 1998, vol. 29, no. 9, pp. 924–31. PMID:9744308.
7. Lax, S.F., Pizer, E.S., Ronnett, B.M., and Kurman, R.J., Clear cell carcinoma of the endometrium is characterized by a distinctive profile of p53, Ki-67, estrogen, and progesterone receptor expression. *Hum. Pathol.*, 1998, vol. 29, no. 6, pp. 551–8. PMID:9635673.
 8. Hecht, J.L., Ince, T.A., Baak, J.P., Baker, H.E., Ogden, M.W., and Mutter, G.L., Prediction of endometrial carcinoma by subjective endometrial intraepithelial neoplasia diagnosis. *Mod Pathol.*, 2005, vol. 18, no. 3, pp. 324–30. PMID:15529181. <https://doi.org/10.1038/modpathol.3800328>.
 9. Mutter, G.L., Baak, J.P., Crum, C.P., Richart, R.M., Ferenczy, A., and Faquin, W.C., Endometrial precancer diagnosis by histopathology, clonal analysis, and computerized morphometry. *J. Pathol.*, 2000, vol. 190, no. 4, pp. 462–9. [https://doi.org/10.1002/\(SICI\)1096-9896\(200003\)190:4<462::AID-PATH590>3.0.CO;2-D](https://doi.org/10.1002/(SICI)1096-9896(200003)190:4<462::AID-PATH590>3.0.CO;2-D).
 10. Oehler, M.K., Brand, A., and Wain, G.V., Molecular genetics and endometrial cancer. *J. Br. Menopause Soc.*, 2003, vol. 9, no. 1, pp. 27–31. PMID:12804310.
 11. Osford, S.M., Dallman, C.L., Johnson, P.W., Ganesan, A., and Packham, G., Current strategies to target the anti-apoptotic Bcl-2 protein in cancer cells. *Curr. Med. Chem.*, 2004, vol. 11, no. 8, pp. 1031–9. PMID:15083809.
 12. Maia, H.Jr., Maltez, A., Studart, E., Athayde, C., and Coutinho, E.M., Ki-67, Bcl-2 and p53 expression in endometrial polyps and in the normal endometrium during the menstrual cycle. *BJOG.*, 2004, vol. 111, no. 11, pp. 1242–7. PMID:15521869. <https://doi.org/10.1111/j.1471-0528.2004.00406.x>.
 13. Porichi, O., Nikolaidou, M.E., Apostolaki, A., Tserkezoglou, A., Arnoyiannaki, N., Kassanos, D., Margaritis, L., and Panotopoulou, E., BCL-2, BAX and P53 expression profiles in endometrial carcinoma as studied by real-time PCR and immunohistochemistry. *Anticancer Res.*, 2009, vol. 29, no. 10, pp. 3977–82. PMID:19846939.
 14. Appel, M.L., Edelweiss, M.I., Fleck, J., Rivero, L.F., Rivoire, W.A., Mõnego, H.I., and Dos Reis, R., P53 and BCL-2 as prognostic markers in endometrial carcinoma. *Pathol. Oncol. Res.*, 2008, vol. 14, no. 1, pp. 23–30. PMID:18398703. <https://doi.org/10.1007/s12253-008-9000-9>.
 15. Peiry, G., Diebold, J., Baretton, G.B., Kimmig, R., and Löhns, U., Cellular apoptosis susceptibility gene expression in endometrial carcinoma: correlation with Bcl-2, Bax, and caspase-3 expression and outcome. *Int. J. Gynecol. Pathol.*, 2001, vol. 20, no. 4, pp. 359–67. PMID:11603220.
 16. Kurman, R.J., (ed). *Blaustein's pathology of the female genital tract*. 6th ed. New York: Springer, 2011, pp. 394–5.
 17. Kurman, R.J., (ed). *Blaustein's pathology of the female genital tract*. 6th ed. New York: Springer, 2011, pp. 401–3.
 18. Stewart, C.J., Brennan, B.A., Koay, E., Naran, A., and Ruba, S., Value of cytology in the intraoperative assessment of ovarian tumors: a review of 402 cases and comparison with frozen section diagnosis. *Cancer Cytopathol.*, 2010, vol. 118, no. 3, pp. 127–36. PMID:20544702. <https://doi.org/10.1002/cncy.20073>.
 19. Ahmareen, Khalid, Anwar Ul Haque. Touch Impression Cytology Versus Frozen Section as Intraoperative Consultation Diagnosis. *Inter. J. Pathol.*, 2004; vol. 2, no. 2, pp. 63–70.
 20. Liu, Y., Silverman, J.F., Sturgis, C.D., Brown, H.G., Dabbs, D.J., Raab, S.S., Utility of intraoperative consultation touch preparations. *Diagn. Cytopathol.*, 2002, vol. 26, no. 5, pp. 329–33. PMID:11992378. <https://doi.org/10.1002/dc.10102>.
 21. Kolte, S.S., Satarkar, R.N., Role of scrape cytology in the intraoperative diagnosis of tumor. *J. Cytol.*, 2010, vol. 27, no. 3, pp. 86–90. PMID:21187882. <https://doi.org/10.4103/0970-9371.71871>.
 22. Rider, V., Progesterone and the control of uterine cell proliferation and differentiation. *Front Biosci.*, 2002, vol. 7, pp. 1545–55. PMID:12045023.
 23. Elmore, S., Apoptosis: a review of programmed cell death. *Toxicol. Pathol.*, 2007, vol. 35, no. 4, pp. 495–516. <https://doi.org/10.1080/01926230701320337>.
 24. Bukholm, I.K., Nesland, J.M., Protein expression of p53, p21 (WAF1/CIP1), bcl-2, Bax, cyclin D1 and pRb in human colon carcinomas. *Virchows Arch.*, 2000, vol. 436, no. 3, pp. 224–8. PMID:10782880.
 25. Linjawi, A., Kontogiannea, M., Halwani, F., Edwardes, M., and Meterissian, S., Prognostic significance of p53, bcl-2, and Bax expression in early breast cancer. *J. Am. Coll Surg.*, 2004, vol. 198, no. 1, pp. 83–90. PMID:14698315. <https://doi.org/10.1016/j.jamcollsurg.2003.08.008>.
 26. Vaskivuo, T.E., Stenbäck, F., and Tapanainen, J.S., Apoptosis and apoptosis-related factors Bcl-2, Bax, tumor necrosis factor-alpha, and NF-kappaB in human endometrial perlasia and carcinoma. *Cancer.*, 2002, vol. 95, no. 7, pp. 1463–71. PMID:12237915. <https://doi.org/10.1002/cncr.10876>.
 27. Erkanli, S., Eren, F., Pekin, S., and Bagis, T., BCL-2 and P53 expression in endometrial carcinoma. *J. Exp. Clin. Cancer Res.*, 2004, vol. 23, no. 1, pp. 97–103. PMID:15149157.
 28. Dobrzycka, B., Terlikowski, S.J., Garbowicz, M., Niklinski, J., Chyczewski, L., and Kulikowski, M., The prognostic significance of the immunohistochemical

- expression of P53 and BCL-2 in endometrial cancer. *Folia Histochem. Cytobiol.*, 2011, vol. 49, no. 4, pp. 631–5. PMID:22252757.
29. Kokawa, K., Shikone, T., Otani, T., Nishiyama, R., Ishii, Y., Yagi, S., and Yamoto, M., Apoptosis and the expression of Bax and Bcl-2 in hyperplasia and adenocarcinoma of the uterine endometrium. *Hum. Reprod.*, 2001, vol. 16, no. 10, pp. 2211–8. PMID: 11574518.
30. Sari, I., Gocmen, A., Bitiren, M., Cakmak, E.A., The relationship between expression of p53/bcl-2 and clinicopathological criteria in endometrioid adenocarcinomas of the endometrium. *Eur. J. Gynaecol. Oncol.*, 2004, vol. 25, no. 1, pp. 79–80. PMID: 15053067.
31. Kalogiannidis, I., Bobos, M., Papanikolaou, A., Makedos, A., Amlianitis, I., Vergote, I., Nenopoulou, E., and Makedos, G., Immunohistochemical bcl-2 expression, p53 overexpression, PR and ER status in endometrial carcinoma and survival outcomes. *Eur. J. Gynaecol. Oncol.*, 2008, vol. 29, no. 1, pp. 19–25. PMID:18386458.

Received March 27, 2019

Received May 20, 2019

Accepted May 18, 2020