The impact of Ki-67 index, squamous differentiation, and several clinicopathologic parameters on the recurrence of low and intermediate-risk endometrial cancer

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ABSTRACT

Endometrial endometrioid carcinoma (EEC) represents approximately 75-80% of endometrial carcinoma cases. Three hundred and thirty-six patients with EEC followed-up in the authors’ medical center between 2010 and 2018 were included in our study. Two hundred and seventy-two low and intermediate EEC patients were identified using the European Society for Medical Oncology criteria and confirmed by histopathological examination. Recurrence was reported in 17 of these patients. The study group consisted of patients with relapse. A control group of 51 patients was formed at a ratio of 3:1 according to age, stage, and grade, similar to that in the study group. Of the 17 patients with recurrent disease, 13 patients (76.5%) were Stage IA, and 4 patients (23.5%) were Stage IB. No significant difference was found in age, stage, and grade between the case and control groups (p > 0.05). Body mass index, parity, tumor size, lower uterine segment involvement, squamous differentiation (SqD), and Ki-67 index with p=0.25 in the univariate logistic regression analysis were included in the multivariate analysis. Ki-67 was statistically significant in multivariate analysis (p = 0.018); however, there was no statistical significance in SqD and other parameters. Our data suggest that the Ki-67 index rather than SqD needs to be assessed for recurrence in patients with low- and intermediate-risk EEC.

KEYWORDS: Low-intermediate risk; endometrioid endometrial carcinoma; recurrence; squamous differentiation; Ki-67

INTRODUCTION

Endometrial cancer (EC) is the second most frequently encountered gynecological cancer worldwide, and endometrioid endometrial carcinoma (EEC) represents approximately 75-80% of patients with EC [1-3]. EC is categorized as low-, intermediate-, and high-risk according to the stage, tumor grade, and histological subtype [4]. According to the International Federation of Gynecology and Obstetrics (FIGO) staging for patients with EC, patients with Stage 1A-Grade 1/2 EEC are classified as the low-risk group, and patients with Stage 1A-Grade 3 and Stage 1B-Grade 1/2 EEC are included in the intermediate-risk group [4].

Although many factors such as histological subtype, Grade 3 tumor, ≥50% myometrium invasion, lymphovascular invasion, lymph node metastasis, and tumor size >2 cm are considered risk factors of recurrence, low- and intermediate-risk ECs have an excellent prognosis, with recurrence rates of about 5-6% without adjuvant therapy [5,6].

The relevance of Ki-67 as a biomarker for EC remains uncertain in the literature [7]. Ki-67 expression was reported to be positively correlated with tumor grade in patients with EEC [8]. However, there is a lack of consensus regarding its prognostic value in EC [9]. In the study of Jiang et al. [10], an increased risk of recurrence was found in Stage 1-2 EC patients with a high Ki-67 index.

Squamous differentiation (SqD), which describes tumors from cell layers with intercellular bridges and distinct cell membranes with or without keratinization, has been reported in approximately 13-25% of patients with EC [11-13]. The
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Dose of 18-24 gray (Gy) was planned with a fraction dose of 6-7 Gy [16].

Pathological assessment

Tumor size, histological type of tumor, grade, myometrial invasion, lymphovascular invasion, and lower uterine segment involvement were obtained from the patients’ pathology reports.

SqD was proven by detecting at least three of the four criteria listed below, and SqD was expected to account for at least 10% of the tumor [12,17]. The criteria sought for SqD are listed as follows: Sheet-like growth without glands or papillassading, sharp margins at a cell, thick and glassy eosinophilic cytoplasm, and nuclear/cytoplasmic ratio decreased more than foci elsewhere in the same tumor [12]. These criteria were used to detect SqD in reevaluations of each sample, and SqD was classified into two groups as either absent or present (Figure 2A).

Two independent pathologists reevaluated the Ki-67 proliferation index from immunohistochemically stained slides and SqD from hematoxylin-eosin stained slides. The slides of the cases were evaluated using a light microscope (model BX51TF, Olympus, Tokyo, Japan). The Ki-67 proliferation index was defined in the literature as the ratio of immunohistochemically stained nuclei to the total number of nuclei of tumor cells, independent of immunostaining intensity (weak,
moderate, and strong) (possible range: 0–100%) [18]. At least 1000 cells were counted at ×400 from the hotspot areas of each sample in our study. Only nuclear staining was considered positive immunostaining, and the staining was scored according to the percentage of nuclear staining (Figure 2B). The Ki-67 assay clone used was 30-9.

Ethical statement

Our study was conducted in accordance with the 1964 Helsinki Declaration. The clinical research ethics committee of the Bursa Uludag University Faculty of Medicine approved the study (Approval number: 2020-16/13).

Statistical analysis

The Shapiro–Wilk test was used to assess whether the variables followed a normal distribution. Variables were reported as median (minimum–maximum) values. According to the normality test results, Mann–Whitney’s U-test was used to compare the groups. Categorical variables were compared using the Chi-square test and Fisher’s exact test, and t3 propensity score matching was performed to determine the control group (in terms of age, FIGO stage, and grade). Univariate logistic regression analysis was performed to determine independent risk factors. Any variable with p<0.25, according to the univariate logistic regression analysis, was accepted as a candidate for the multivariate model. The outcomes were compared using SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp). A p < 0.05 was considered statistically significant.

RESULTS

The comparison of patients in the study group and the control group in terms of study variables is shown in Table 1. No significant difference was found in age, stage, and grade between both groups (p > 0.05). In addition, there was no statistically significant difference between the two groups in terms of body mass index (p = 0.079), the status of parity (p = 0.160), presence of myometrium invasion (p = 0.568), presence of lymphovascular space invasion (p = 0.355), median tumor diameter (p = 0.081), and lower uterine segment involvement (p = 0.095). There was also no statistically significant difference in lymph node dissection (p = 0.428) and adjuvant brachytherapy (p = 0.468).

SqD was observed in 7 patients (41.2%) in the study group and 11 (21.6%) patients in the control group. No significant difference was found in SqD between both groups (p = 0.126). The median ratio of Ki-67 was 40% (min–max range: 15–80) in the study group and 30% (min–max range: 10–50) in the control group, and it was statistically significant (p = 0.039).

Recurrences were reported 47.0% in vagina (8 patients), 23.5% in the lungs (4 patients), 5.9% in intra-abdominal lymph node (1 patient), 5.9% in peritoneum (1 patient), 5.9% in colon (1 patient), 5.9% in bone (1 patient), and 5.9% in bladder (1 patient).

After univariate logistic regression analysis, six parameters with p<0.25 were included in the multivariate logistic regression analysis: BMI, parity, tumor size, lower uterine segment involvement, SqD, and Ki-67 (Table 1). On multivariate analysis, only Ki-67 was significantly associated with recurrence (p = 0.018) (Table 2). The Ki-67 index had a 1.05-fold increased risk of recurrence in the low-intermediate-risk EEC study group than in the control group (Table 2).

DISCUSSION

In our retrospective case–control study, we found that SqD did not significantly affect recurrence in our patients with low and intermediate EEC. In contrast, the Ki-67 proliferation index had a significant effect on recurrence. No statistical significance was found for other parameters such as body mass index, parity, tumor size, and lower uterine segment involvement.

The importance of SqD on recurrence in EC patients has been investigated by a limited number of studies in the current period.

### TABLE 1. Univariate analysis of predictive recurrence for low- and intermediate-risk endometrioid endometrial cancer

| Variable                          | Study group (n=17) | Control group (n=51) | p   |
|-----------------------------------|--------------------|----------------------|-----|
| Age (y)                           |                    |                      |     |
| <65                               | 4 (23.5%)          | 39 (76.5%)           | <0.01|
| ≥65                               | 13 (76.5%)         | 22 (43.1%)           |     |
| Stage FIGO                        |                    |                      |     |
| Stage 1A                          | 13 (76.5%)         | 39 (76.5%)           | <0.01|
| Stage 1B                          | 4 (23.5%)          | 14 (27.5%)           |     |
| Grade                             |                    |                      |     |
| Grade 1                           | 8 (47%)            | 24 (47%)             |     |
| Grade 2-3                         | 9 (53%)            | 27 (53%)             | <0.05|
| BMI (Median, Range, kg/m²)        | 35.4 (25.0–48.5)   | 31.6 (21.5–63.7)     | 0.079|
| Parity                            |                    |                      |     |
| Nulliparite                       | 3 (17.6%)          | 5 (9.8%)             | <0.01|
| Present                           | 14 (82.4%)         | 48 (94.1%)           |     |
| Myometrium invasion               |                    |                      |     |
| Absent                            | 0                  | 3 (5.9%)             | 0.568|
| Present                           | 17 (100%)          | 48 (94.1%)           |     |
| Tumor size (Median, Range, cm)    | 3.8 (2.0–10.0)     | 3.0 (0.6–7.5)        | 0.081|
| LVSI (Absent/Present)             | 14 (82.4%)         | 47 (92.2%)           | 0.355|
| Present                           | 3 (17.6%)          | 4 (7.8%)             |     |
| Lower uterine segment involvement |                    |                      |     |
| Absent                            | 10 (58.8%)         | 42 (82.4%)           | 0.095|
| Present                           | 7 (41.2%)          | 9 (17.6%)            |     |
| Squamous cell differentiation      |                    |                      |     |
| Absent                            | 10 (58.8%)         | 40 (78.4%)           | 0.126|
| Present                           | 7 (41.2%)          | 11 (21.6%)           |     |
| Ki-67 (Median, Range, %)          | 40 (15–90)         | 30 (10–50)           | 0.039|
| Lymph node dissection             |                    |                      |     |
| Absent                            | 9 (52.9%)          | 22 (43.1%)           | 0.482|
| Present                           | 8 (47.1%)          | 29 (56.9%)           |     |
| Brachytherapy                     |                    |                      |     |
| Absent                            | 5 (29.4%)          | 20 (39.2%)           | 0.468|
| Present                           | 12 (70.6%)         | 31 (60.8%)           |     |

BMI: Body mass index; FIGO: International Federation of Gynecology and Obstetrics; LVSI: Lymphovascular space invasion. a – Fisher’s exact test; b – Mann–Whitney U-test; c – Chi-square test
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Table 3

Summary of squamous differentiation endometrioid endometrial cancer studies to predict recurrence

| References | Year | Country | Patient group | N | Study design | Analysis | Event | Risk of SqD | Other risk factors |
|------------|------|---------|---------------|---|--------------|----------|-------|-------------|-------------------|
| Present study | 2020 | Turkey | Low-intermediate EEC | 68 | Case–control | Multivariate | Recurrence | No | Ki-67            |
| Andrade et al. [22] | 2019 | Brazil | Low-intermediate EEC | 84 | Case–control | Multivariate | Recurrence | Yes | -                |
| Jiang et al. [21] | 2017 | China | Stage I EEC | 630 | Retrospective cohort | Univariate | Pulmonary Metastases | Yes | Tumor size, myometrial invasion |
| Misirlioğlu et al. [14] | 2012 | Turkey | Stage I EEC | 223 | Case–control | Univariate | Recurrence | Yes | Age, grade, lower uterine segment involvement and lymphovascular space invasion, tumor size, myometrial invasion |
| Sturgeon et al. [19] | 1998 | USA | Stage I–IV EC | 648 | Case–control | Univariate | Pathogenetic types of EC | No | -                |
| Lax et al. [20] | 1998 | USA | Stage I–IV EC | 77 | Case–control | Univariate | Overall survival | Variable | Mucinous, secretory, and ciliated cell component |
| Aebeler et al. [13] | 1992 | Norway | Stage I–IV EC | 255 | Retrospective cohort | Multivariate | Overall survival | Variable | Myometrial infiltration, vascular invasion, cervical involvement |
| Zaino et al. [15] | 1991 | USA | Stage I–II EC | 631 | Prospective cohort | Univariate | Node Metastasis | No | Histologic Grade |

EEC: Endometrioid endometrial cancer, EC: Endometrial cancer, SqD: Squamous differentiation

Although these studies contribute to the literature on the effect of SqD on recurrence, there is only one reported study to our knowledge, by De Andrade et al., investigating low-intermediate EEC patients [22].

In our study, we aimed to conduct a case–control study to investigate the effect of SqD on recurrence in low-intermediate-risk EEC patients. Unlike the study by De Andrade et al. [22], we formed the control group considering not only age and FIGO stage but also the grade. Additional risk factors such as myometrium invasion, lower uterine segment involvement, and Ki-67 index were included in the study.

| References | Year | Country | Patient group | N | Study design | Analysis | Event | Risk of SqD | Other risk factors |
|------------|------|---------|---------------|---|--------------|----------|-------|-------------|-------------------|
| Present study | 2020 | Turkey | Low-intermediate EEC | 68 | Case–control | Multivariate | Recurrence | No | Ki-67            |
| Andrade et al. [22] | 2019 | Brazil | Low-intermediate EEC | 84 | Case–control | Multivariate | Recurrence | Yes | -                |
| Jiang et al. [21] | 2017 | China | Stage I EEC | 630 | Retrospective cohort | Univariate | Pulmonary Metastases | Yes | Tumor size, myometrial invasion |
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| Sturgeon et al. [19] | 1998 | USA | Stage I–IV EC | 648 | Case–control | Univariate | Pathogenetic types of EC | No | -                |
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| Aebeler et al. [13] | 1992 | Norway | Stage I–IV EC | 255 | Retrospective cohort | Multivariate | Overall survival | Variable | Myometrial infiltration, vascular invasion, cervical involvement |
| Zaino et al. [15] | 1991 | USA | Stage I–II EC | 631 | Prospective cohort | Univariate | Node Metastasis | No | Histologic Grade |

EEC: Endometrioid endometrial cancer, EC: Endometrial cancer, SqD: Squamous differentiation

The effect of SqD on recurrence in patients with EC remains controversial. In the study of Misirlioğlu et al. [14], statistical significance was found in univariate analysis in patients with EEC with SqD in the subgroup analysis of patients with EC. However, multivariate analysis was not performed in their study [14]. Although SqD was statistically significant in patients with pulmonary metastasis in the study by Jiang et al. [21] of patients with Stage 1 EEC, disease recurrence was not discussed in the study. By supporting our findings, the effect of SqD on recurrence in EC patients was not shown in the studies of Zaino et al. [15] and Sturgeon et al. [19].

Ki-67 protein is present during all active stages of the cell cycle (G1, S, G2, and M), excluding the resting cells (Go) [23]. It is used as a marker of cellular proliferation; its prognostic and predictive value was shown in several cancer types, including EC [24,25]. The effect of the Ki-67
index on recurrence, especially in low-intermediate EEC, has not been sufficiently investigated in the current studies. The Ki-67 index was not included in the study of Andrade et al. [22] investigating low-intermediate EEC patients. In the study of Jiang et al. [21] in patients with Stage 1 EEC, the effect of the Ki-67 index was not statistically significant on the development of pulmonary metastasis; however, the effect on disease recurrence was not reported. Yu et al. [26] examined patients with Stages 1-4 EC and found that Ki-67 was associated with stage, differentiation, depth of myometrium invasion, and lymph node status. In the study of Lax et al. [20] investigating Stages 1-4 EEC, the Ki-67 proliferation index was significantly higher in endometrioid carcinomas with a high-grade squamous component than the other tumors with various types of cellular differentiation and pure low-grade EEC. Therefore, the effect of SqD should be evaluated concurrently with Ki-67 in multivariate analysis. Some previous studies reported that a high Ki-67 index correlated with a high percentage of p53 stained immunohistochemically [27,28]. However, as we emphasized before, the results regarding the prognostic value of the Ki-67 index in low- and intermediate-risk endometrial carcinoma are not precise. Besides, there is literature information that p53 mutation is associated with cell differentiation in many cancers [29-31]. These studies revealed that cells without p53 mutation or carrying p53 activation tended to be well differentiated. Since our study is retrospective and the p53 was not evaluated in all patients, it may be considered to conduct new molecular-based studies to elucidate the relationship of SqD with the increased Ki-67 index according to the p53 mutation or activation.

CONCLUSION

In the literature, studies investigating the effect of SqD on recurrence in low-intermediate-risk EEC patients are limited to the best of knowledge. In low-intermediate-risk EEC patients, SqD and Ki-67 index should be evaluated concurrently for recurrence. This study enabled us to compare the effect of SqD on recurrence with the literature. Determining factors affecting recurrence in low-intermediate-risk EEC patients may lead to changes in follow-up and treatment algorithms.

REFERENCES

[1] Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global cancer statistics 2018. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2018:68-394. CA Cancer J Clin 2020;70(4):333. https://doi.org/10.3322/caac.21492.
[2] Gülekin M, Kucukkyzildiz I, Karaca MZ, Durand S, Bozgas T, Turan SH, et al. Trends of gynecological cancers in Turkey: Toward Europe or Asia? Int J Gynecol Cancer 2017;27(7):1524-33. https://doi.org/10.1097/IGC.0000000000001206.
[3] Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, et al. Current recommendations and recent progress in endometrial cancer. CA Cancer J Clin 2019;69(4):238-79. https://doi.org/10.3322/caac.21561.
[4] Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Mariani C, et al. Endometrial cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:v133-8. https://doi.org/10.1093/annonc/mdt333.
[5] Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirito NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A gynecologic oncology group study. Gynecol Oncol 2004;92(3):54-51.
[6] Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JL, Wärlam-Rodenbush CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. Lancet 2000;355(9213):1403-11. https://doi.org/10.1016/S0140-6736(00)02393-4.
[7] Kitson S, Sivilingam VN, Bolton J, McVey R, Nickhoo-Amiry M, Powell ME, et al. Ki-67 in endometrial cancer: Scoring optimization and prognostic relevance for window studies. Mod Pathol 2017;30(3):459-68. https://doi.org/10.1038/modpathol.2016.203.
[8] Stefanion I, Salvesen H, Immervoll H, Akslen L. Prognostic impact of histological grade and vascular invasion compared with tumour cell proliferation in endometrial carcinoma of endometrioid type. Histopathology 2004;44(5):472-9. https://doi.org/10.1111/j.1365-2559.2003.08182.x.
[9] Fanning J, Brown S, Phibbs G, Kramer T, Zaheer A. Immunohistochemical evaluation is not prognostic for recurrence in fully staged high-risk endometrial cancer. Int J Gynecol Cancer 2002;12(3):286-9. https://doi.org/10.1097/01525-1438.2002.01-01083.x.
[10] Jiang P, Jia M, Hu J, Huang Z, Deng Y, Lai L, et al. prognostic value of Ki67 in patients with stage 1-2 endometrial cancer: Validation of the cut-off value of Ki67 as a predictive factor. OncoTarg Ther 2020;13:10841. https://doi.org/10.2147/ott.s247140.
[11] Zaino R, Kurman RJ, editors. Squamous Differentiation in Carcinoma of the Endometrium: A Critical Appraisal of Adenoacanthoma and Adenosquamous Carcinoma. Seminars in Diagnostic Pathology; 1988.
[12] Kurman R, Carcangiu M, Herrington C, Youn R. WHO Classification of Tumours of Female Reproductive Organs Lyon: International Agency for Research on Cancer, Geneva: World Health Organization; 2014. p. 135-47.
[13] Abeler VM, Kjørstad KE. Endometrial adenocarcinoma with squamous cell differentiation. Cancer 1992;69:488-95. https://doi.org/10.1002/1097-0142(199205)69:5<488::AID-CNCR28 20690236>3.0.co;2-o.
[14] Misiriloğlu S, Guzel A, Gulec U, Gumurdulu D, Vardar M. Prognostic factors determining recurrence in early-stage endometrial cancer. Eur J Gynaecol Oncol 2012;33(6):610-4.
[15] Zaino R, Kurman R, Herbold D, Gliedman J, Bundy B, Voet R, et al. The significance of squamous differentiation in endometrial carcinoma. Data from a gynecologic oncology group study. Cancer 1999;86(10):2293-302. https://doi.org/10.1002/1097-0142(19991115)86:10<2293::AID-CNCR2 820681032>3.0.co;2-v.
[16] Uterine Neoplasms, Version 1.2021, NCCN Clinical Practice Guidelines in Oncology; 2021.
[17] Ellenson LH, Ronnett BM, Soslow RA, Zaino RJ, Kurman RJ. Endometrial carcinoma. In: Blaustein’s Pathology of the Female Genital Tract. Berlin, Germany: Springer; 2012. https://doi.org/10.1007/978-1-4471-0439-8_9.
[18] Aman NA, Doukoure B, Koffi KD, Kouyi BS, Traoré ZC, Koyoute M, et al. Immunohistochemical evaluation of Ki-67 and comparison
with clinicopathologic factors in breast carcinomas. Asian Pac J Cancer Prevent 2019;20(1):73.

https://doi.org/10.31557/apcj.2019.20.1.73.

[19] Sturgeon SR, Sherman ME, Kurman RJ, Berman ML, Mortel R, Twigg LB, et al. Analysis of histopathological features of endometrioid uterine carcinomas and epidemiologic risk factors. Cancer Epidemiol Prevent Biomark 1998;7(3):231-5.

[20] Lax SF, Pizer ES, Ronnett BM, Kurman RJ. Comparison of estrogen and progesterone receptor, Ki-67, and p53 immunoreactivity in uterine endometrioid carcinoma and endometrioid carcinoma with squamous, mucinous, secretory, and ciliated cell differentiation. Hum Pathol 1998;29(9):924-31.

https://doi.org/10.1016/s0046-8177(98)90197-6.

[21] Jiang W, Chen J, Tao X, Huang F, Zhu M, Wang C, et al. Possible risk factors of pulmonary metastases in patients with international federation of gynecology and obstetrics stage I endometrioid-type endometrial cancer. Int J Gynecol Cancer. 2017;27(6):1206-15.

https://doi.org/10.1097/igc.0000000000001002.

[22] Andrade DA, Da Silva VD, Matsushita GM, De Lima MA, Vieira MA, Andrade CE, et al. Squamous differentiation portends poor prognosis in low and intermediate-risk endometrioid endometrial cancer. PLoS One 2019;14(10):e0220086.

https://doi.org/10.1371/journal.pone.0220086.

[23] Scholzen T, Gerdes J. The Ki-67 protein: From the known and the unknown. J Cell Physiol 2000;182(3):311-22.

[24] Breast Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. 2020.

[25] Neuroendocrine and Adrenal Tumors, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. 2018.

[26] Yu CG, Jiang XY, Li B, Gan L, Huang JF. Expression of ER, PR, C-erbB-2 and Ki-67 in endometrial carcinoma and their relationships with the clinicopathological features. Asian Pac J Cancer Prevent 2015;18(1):6789-94.

https://doi.org/10.7314/apjc.2015.16.15.6789.

[27] Stănescu AD, Nistor I, Poteca AG, Dîtescu D, Comănescu M. Prognostic biomarkers in endometrial adenocarcinoma. Rom J Morphol Embryol 2014;55(4):1339-44.

[28] Budak E, Kahraman DS, Budak A, Yanareş A, Inan AH, Kanmaz AG, et al. The prognostic significance of serum CA125 levels with ER, PR, P53 and Ki-67 expression in endometrial carcinomas. Ginekol Pol. 2019;90(12):675-83.

https://doi.org/10.5603/gp.2019.0116.

[29] Radinsky R, Fidler IJ, Price JE, Esumi N, Tsani R, Petty CM, et al. Terminal differentiation and apoptosis in experimental lung metastases of human ovarian carcinoma cells. Oncogene 1994;9(7):1877-83.

[30] Lang D, Miknyoczki SJ, Huang L, Ruggeri BA. Stable reintroduction of wild-type P53 (MTmp53ts) causes the induction of apoptosis and neuroendocrine-like differentiation in human ductal pancreatic carcinoma cells. Oncogene 1998;16(12):1593-602.

https://doi.org/10.1038/sj.onc.1201665.

[31] Spike BT, Wahl GM. P53, stem cells, and reprogramming: Tumor suppression beyond guarding the genome. Genes Cancer 2012;3(4):404-19.

https://doi.org/10.1177/1947601911402224.

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