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The value of oestrogen receptor, progesterone receptor and keratins 5 and 14 immunohistochemistry in the evaluation of epithelial proliferations at cauterised margins in breast-conserving surgery specimens

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ABSTRACT

In breast conservative surgery, it is sometimes difficult to decide whether the cauterised tissue at the inked margin represents normal / hyperplastic or neoplastic tissue. We retrospectively assessed the value of ER, PR, CK5 and CK14 IHC in clarifying the nature of cauterised tissues at the margins concerning 34 lesions of 23 patients. 27 cases belonged to lesions that could not be adequately classified on the basis of the HE stains. Two thirds of them could be classified as non-neoplastic or neoplastic and two thirds of the remaining could be favourised as neoplastic or non-neoplastic, with 3/27 cases remaining uncertain. All 4 IHC reactions were helpful in classifying the lesions in almost half of the cases. However, 3 or 4 immunostains were supportive of the classification in 19/27. The most useful stains were the keratins, generally demonstrating a matching pattern of cell labelling with CK5 and CK14. ER and PR were somewhat less useful in classifying uncertain lesions. Considering all the 27 questionable lesions, IHC with ER, PR, CK5 and CK14 clarified the lesions at the cauterised margins in 23 cases. Taken all these considerations into account, CK5, CK14, PR and ER IHC may help in distinguishing between cautery damaged neoplastic and non-neoplastic tissues. All four IHC may yield the best support for decision making, but CK5 and/or CK14 may be sufficient in their own. The essential approach is that the results must be interpreted with caution, in the context of the given patient's disease, to avoid misinterpretations.

1. Introduction

In the treatment of breast cancer (BC), breast conserving surgery (BCS) and adjuvant radiotherapy have long proven to be equivalent with mastectomy in terms of local disease control and outcome [1,2], and there is even a suggestion that they are associated with better outcome [3]. The safety of breast conservation has been proven even in the case of oncoplastic techniques [4]. A factor that has been linked to local recurrences, is a tumour transecting (positive) surgical excision margin and the deduced residual cancer [5–8]. The practical approach and perceptions of what constitutes a negative (tumour free) surgical margin have changed over time, and currently "no ink on tumour" is widely considered the negative margin for invasive breast cancer (IBC) and a tumour free rim of at least 2 mm is considered sufficient for pure ductal carcinoma in situ (DCIS) [9–11] by some, whereas others are happy with a 1 mm wide margin for both IBC and DCIS [12].

While surgery with traditional scalpels and blades can give the best-preserved material for histological assessment, this has disadvantages because of more bleeding and intraoperative blood loss than electrocautery [13,14]. This is why "cold scalpels" have been widely replaced by electric cutting and sealing devices (electrocautery devices, electric or harmonic scalpels). Although these make surgery easier with less blood loss, they traumatize the tissues at a higher rate and grade, making margin assessment more troublesome. At times, it is difficult to decide whether the cauterised tissue at the inked margin represents normal / hyperplastic or neoplastic tissue.

Normal breast tissue and usual type hyperplasia is characterized by a mosaic-like staining pattern for oestrogen receptor (ER), progesterone

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receptor (PR), and some high molecular weight keratins, like the pair of keratins 5 and 14 (CK5, CK14) [15,16], whereas low grade neoplastic lesions, like atypical ductal hyperplasia and low grade DCIS are typically ER and PR diffusely positive and CK5, CK14 negative [15–17]. Higher grade carcinomas may have various patterns of ER and PR staining, but CK5 and CK14 are generally negative, though sometimes they can be diffusely positive.

In the present study, we retrospectively assessed the value of ER, PR, CK5 and CK14 immunohistochemistry (IHC) in clarifying the nature of cauterised tissues at the margins.

2. Materials and methods

We examined specimens from breast cancer patients treated by primary surgery at the Department of Surgery, Bács-Kiskun County Teaching Hospital between 2020 and 2023.

All specimens were received fresh at the Department of Pathology, larger resection specimens were inked (posterior margin stained blue, while the others stained black) and sliced parallelly before fixation, whereas smaller samples were submersed in the fixative in toto. All material was fixed in 10% neutral buffered formalin for at least one day. Margins were generally assessed through one to several blocks taken perpendicularly to the painted surface, unless they were deemed very distant from it.

During microscopic evaluation of routine diagnostic slides, IHC for ER, PR, CK5 and CK14 were ordered to clarify the neoplastic or non-neoplastic nature of artefactually distorted epithelium at the inked margin or very close to it. The results were evaluated in the context of the lesions and were interpreted as positive margins (ink on tumour), negative margins (ink on non-tumorous epithelium) or uncertain margins (when no firm statement could be reached even with the ancillary studies). Cases were collected in retrospect, and analysed as a group to see the value of these stains individually and in combination. Photomicrographs were taken with a Nikon digital camera mounted on a Nikon Eclipse Ci-L microscope to allow archiving of the lesions analysed.

The following antibodies were used for the IHC (ER: clone 6F11, Leica Biosystems Newcastle, UK, 1:200; PR: clone PgR312, Leica Biosystems Newcastle, UK, 1:400; CK5: clone XM26 Thermo-Fisher-Epredia-LabVision, Kalamazoo, MI, USA, 1:40 (or earlier Labvision, Fremont, CA, USA, 1:25, developed manually); CK14, clone LL002, Leica Biosystems Newcastle, UK, ready-to-use; (in earlier cases the same, but developed manually). The IHC stains were carried out on a Leica Bond Max autostainer, all but the CK5 reaction used ER1 (pH=6), whereas CK5 used ER2 (pH=9) as epitope retrieval solution. Incubation time was 20 minutes for all antibodies. All cases were evaluated in retrospect by the two authors, and consensus was reached on all lesions.

On occasions, one patient could have had several slides assessed and/or one slide could have had several questionable areas investigated. These latter areas formed the lesions referred to in the article. Some identified lesions could be classified without the use of the IHC stains, but as they were included on the slides and cauterised at some degree, they were used as controls of known nature (neoplastic vs non-neoplastic) whereas others were lesions of uncertain nature requiring clarification. These latter were classified into the five categories of neoplastic, favour neoplastic, uncertain, favour non-neoplastic and non-neoplastic on the basis of the immunostains and the histological context.

No ethical approval and informed consent were deemed necessary, as no intervention was done, no patient data were assessed, only the slides of cases with the relevant IHC stains ordered for cautery artefacts were reviewed in retrospect.

3. Results

Altogether we analysed 34 lesions of 23 patients. The neoplasms for which the operations were performed included 14 IBCs of no special type (NST) (6 cases with extensive intraductal component - EIC), 4 pure DCIS, 1 tubular carcinoma with EIC, 1 instance of microinvasive Paget's disease of the nipple and EIC, and a tumour bed following neoadjuvant systemic therapy for an IBC NST. Additionally, a case of atypical ductal hyperplasia and an intraductal papilloma were also included, as the identification of (further) neoplastic lesions in the cauterised area would have upgraded their diagnosis. All of the invasive carcinomas and 3/4 DCIS cases were ER and PR positive, whereas a single case of DCIS was ER and PR negative and human epidermal growth factor receptor 2 (HER2) positive with apocrine differentiation substantiated with the expression of androgen receptors and gross cystic disease fluid protein 15 (GCDFP-15). HER2 positivity was also a feature of the Paget's disease (ER and PR positive) investigated and the invasive carcinoma treated previously with systemic therapy; this latter had also been ER positive with unknown PR status.

Seven lesions served as controls, 3 obviously representing cauterised neoplastic tissues and 4 representing non-neoplastic tissues with cautery artefacts. The remaining 27 cases belonged to lesions that could not be adequately classified on the basis of the haematoxylin and eosin (HE) stains (Table 1).

Following the quadruple immunostaining, all but one control case showed the expected pattern of staining with the keratin antibodies; i.e. no staining in neoplastic and mosaic-like staining in non-neoplastic epithelium with myoepithelial labelling. The deviating case was one with no ER and CK14 staining but mosaic pattern of CK5 and PR staining (Case 12, Supplementary material). In contrast, steroid hormone receptor stainings were somewhat less often supportive, either due to negativity (e.g. Case 34, Supplementary material) or partial positivity in neoplastic lesions or complete lack of staining in the cauterised tissue (e.g. Case 12, Supplementary material).

Of the cases being uncertainly classifiable on HE stained slides, two thirds could be classified as non-neoplastic (Fig. 1, Case 9) or neoplastic (Fig. 2, Case 21), and two thirds of the remaining could be favourised as neoplastic or non-neoplastic, with 3/27 cases remaining uncertain (Fig. 3, Case 4) (Table 1).

All 4 IHC reactions were helpful in classifying the lesions as neoplastic or non-neoplastic in almost half of the cases, though this proportion was smaller when uncertain, i.e. problematic cases were considered. However, 3 or 4 immunostains were supportive of the classification in 19/27 (0,70; 95% confidence interval 0.50–0.86). The most useful stains were the keratins, generally demonstrating a matching pattern of cell labelling with CK5 and CK14; in a few instances (n=4), the two antibodies showed divergent results. ER and PR, especially the first were somewhat less useful in classifying uncertain lesions.

Considering all the 27 questionable lesions, IHC with ER, PR, CK5 and CK14 clarified the lesions at the cauterised margins in 23 cases (0,85; 95% confidence interval 0.66–0.96), and a further case (ER+PR+HER2+ DCIS with Paget's disease and microinvasion, Case 17, Supplementary material) with no staining with either of the 4 antibodies demonstrated an intensive HER2 staining and was classified as neoplastic on this contextual basis. Another lesion is worth mentioning (Case 13, Supplementary material), namely an apocrine DCIS, where CK5 and CK14 negativity was associated with ER and PR negativity, and this was interpreted as fully supportive of the lesion being classified as neoplastic.

4. Discussion

Mankind would probably be at ease in making decisions if most things could be categorised along a clear-cut dichotomic ("black or white") scale. However, this is not often the case. Biology is complex, and our methods of assessing its features are less than perfect. Therefore, easy decisions are not always possible. Decision making requires awareness of many circumstances and specific judgment for instances that are neither clearly yes nor clearly no (represent a shade of grey in the black and white world).

The perceptions and definitions of what constitutes a safe and

Table 1
Results of the four immunostains in different lesions.

		All	ER helpful	PR helpful	CK5 helpful	CK14 helpful	4 helpful	3 helpful	2 helpful
CTRL Non-neoplastic		4	2/4	4/4	4/4	3/4	2/4	1/4	1/4
CTRL Neoplastic		3	2/3	2/3	3/3	3/3	2/3	0/3	1/3
All certain cases		7	4/7	6/7	7/7	6/7	4/7	1/7	2/7
Uncertain	Non-neoplastic	15	14/15	13/15	14/15	14/15	10/16	6/16	0/16
	Favour non-neoplastic	2	0/2	0/2	2/2	2/2	0/2	0/2	2/2
	Uncertain	3	0/3	0/3	0/3	1/3	0/3	0/3	0/3
	Favour neoplastic	4	0/4	1/4	3/4	3/4	0/4	1/4	2/4
	Neoplastic*	3	1/3	2/3	2/3	2/3	1/3	1/3	0/3
All uncertain cases		27	15/27	16/27	21/27	22/27	11/27	8/27	4/27
All		34	19/34	22/34	28/34	28/34	15/34	9/34	6/34

CK5: keratin 5, CK14: keratin 14, CTRL: control, ER: oestrogen receptor, PR: progesterone receptor; * 1 case was not supported by any of the 4 IHC reactions, but was clarified by the HER2 immunostain being diffusely positive in the cauterised tissue (Case 17, Supplementary material).

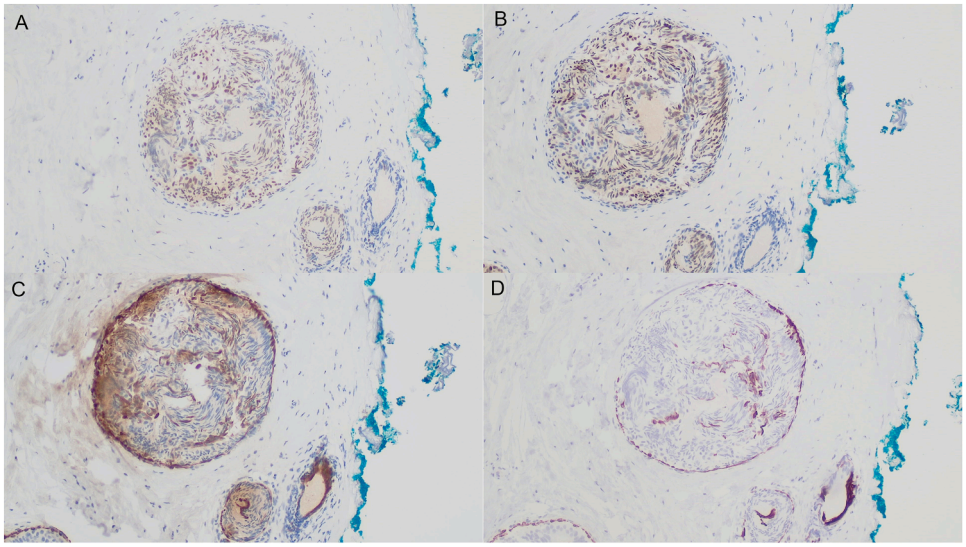

Fig. 1. Cauterised non-neoplastic tissue close to the inked margin demonstrating various degrees of mosaic like staining with all four antibodies; (A) ER x10, (B) PR x10, (C) CK5 x10, (D) CK14 x10. ER: oestrogen receptor, PR: progesterone receptor, CK5: keratin 5, CK14: keratin 14.

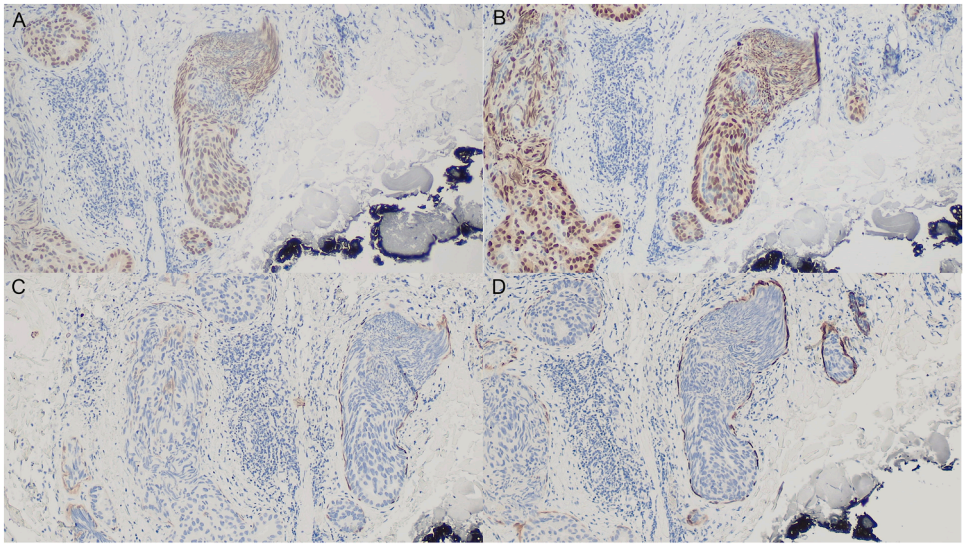

Fig. 2. Cauterised neoplastic tissue close to the inked margin demonstrating various intensities of rather diffuse ER (A) and PR (B) positivity, and various intensity of myoepithelial labelling along with tumour cell negativity with CK5 (C) and CK14 (D) (All at medium power, x10 objective.). ER: oestrogen receptor, PR: progesterone receptor, CK5: keratin 5, CK14: keratin 14.

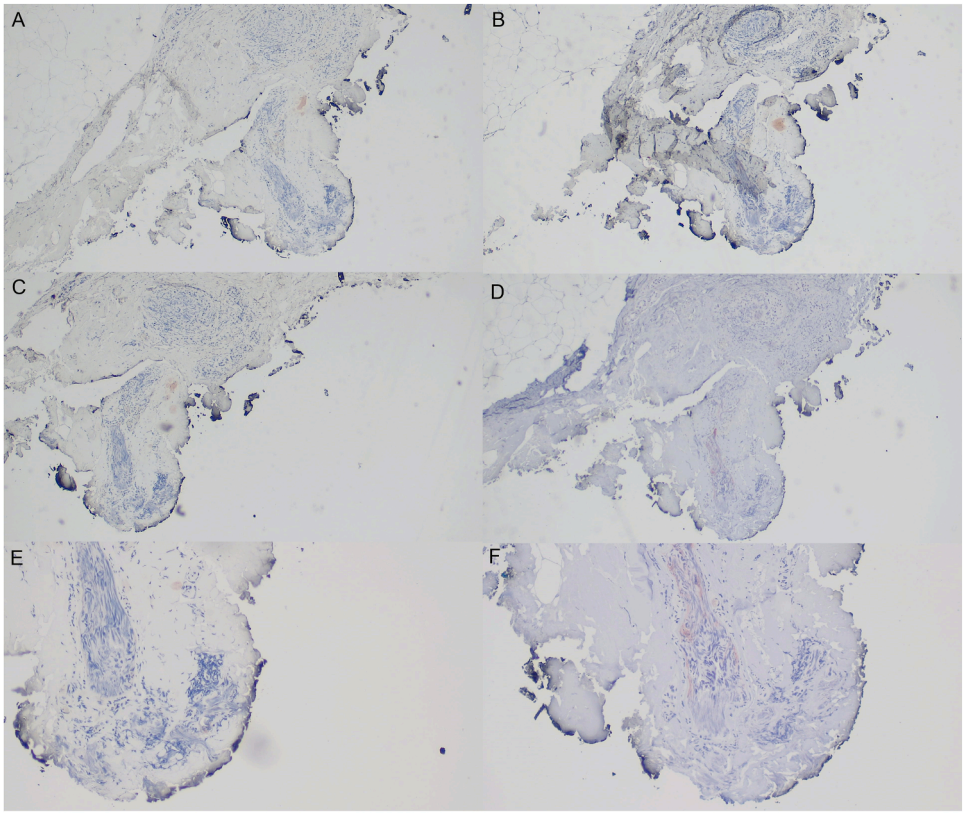

Fig. 3. A case remaining unclassifiable on the basis of the quadruple immunostain with all antibodies being negative; (A): ER x4, (B) PR x4, (C) CK5 x4 (D) CK14 x4, (E) CK5 x10 (F) CK14 x10. ER: oestrogen receptor, PR: progesterone receptor, CK5: keratin 5, CK14: keratin 14.

tumour-free margin at breast conserving surgery have changed over time. Early recommendations suggested a free margin of at least 5 mm for invasive carcinoma and 10 mm for DCIS [18,19], but with accumulating evidence, this has changed to a more conservative approach, and at present no ink on tumour [9,10] and 1- or 2-mm tumour-free band of non-tumorous tissue [10,11] are considered sufficient for IBC and DCIS, respectively, in order to reduce local recurrences. Cautery artefacts interfere with the pathology reporting of margins, as it is not easy to decide whether the "burnt", traumatized tissue represents part of a neoplasm, or is an innocuous bystander.

In our daily practice, when challenged by this issue, we used the common knowledge that normal to hyperplastic (non-neoplastic) breast tissue share a mosaic-like staining pattern with ER, PR and the CK5/CK14 pair of keratins, whereas low grade neoplasia has a typical strong and diffuse ER and PR staining and lack CK5 and CK14 staining in neoplastic cells [15–17]. In this retrospective analysis, we tried to evaluate the value of this knowledge in practice. Some other contexts have also been part of the series: e.g. an ER- and PR-negative apocrine tumour, where lack of staining for these steroid hormone receptors could also favour the neoplastic nature of the cauterised tissue.

Cauterised and/or necrotic tissues maintain some epitopes useful in their identification with IHC [20–25]. Based on results by Judkins et al., the cytokeratins are well preserved in necrotic tissues, more precisely damaged tissues seem to retain immunoreactivity with CK AE1 and AE1/AE3 antibodies in epithelial tumours; they stained 10/14 necrotic carcinomas [20]. In contrast, leukocyte common antigen (LCA) and S100 showed false-positive labelling in some necrotic carcinomas along with specific or partial specific staining in the examined lymphomas and melanomas, respectively [20]. Although the tissue is undergoing necrosis, CK expression remains specific; no false positivity was detected in non-epithelial tumours [20]. In a separate study, the same authors specifically looked at 20 thyroid neoplasms, including 12 cases with post fine-needle aspiration necrosis, and 11 tumours originating from different organs with necrosis serving as controls [21]. CK AE1/AE3 was at least focally positive in nearly half of the examined necrotic areas (9/20), but PanCK was less useful in necrotic tissues; it was positive in viable epithelial tumour cells, but it proved to be negative in the necrotic areas [21]. Thyroglobulin, retained positivity in 13/20 necrotic thyroid tumour areas, including areas with AE1/AE3 negativity, and was negative in non-thyroid neoplasms [21]. Of note, some necrotic cases demonstrated complete loss of immunoreactivity with all antibodies examined [20,21]. Similar conclusions can be reached in non-epithelial neoplasms, e.g. the IHC expression of melanocytic markers can be maintained in necrotic neoplasms, but aspecific staining may interfere with specific staining; and the most severe the tissue damage, the more unlikely is an IHC marker to be retained [22]. It is believed that coagulative tissue damage caused by electric surgical devices, i.e. cautery artefacts closely resemble tissue necrosis, and IHC can be of help in identifying tissue origin and neoplastic versus non-neoplastic nature.

Antibody panels can be helpful in damaged tissues surrounding the resection margins in different organs. In prostate samples, 34β-E12 (HMWCK), p63 and Alfa-Methylacyl Coenzyme A Racemase (AMACR) is used in daily practice to identify carcinomas and distinguish them from non-neoplastic glandular tissues. These antibodies can also be used in the evaluation of areas with artificial damage. Pierconti F et al. examined 30 crushed radical prostatectomy samples and 25 crushed transurethral prostatic resection samples with equal number of control cases with this antibody panel [23]. While the controls showed the expected results with the complete panel (though with lack of AMACR in 7/25 cases of adenocarcinoma), only HMWCK and AMACR gave the same expected results in the thermally damaged areas, and p63 expression was missing not only in the 5 neoplastic areas, but also in 37/50 instances of benign prostatic glands demonstrating the presence of basal cells by HMWCK and being negative for AMACR [23]. Groisman et al. could distinguish between thermally coagulated adenomatous and non-adenomatous colorectal polyps on the basis of the maintained Ki67

(MIB1) staining pattern [24]. Smoothelin expression (highlighting the muscularis propria of urinary bladders but being only weakly positive in the muscularis mucosae) was maintained in all 46 cauterised transurethral tumour resection specimens and helped in identifying muscle invasive tumours [25].

These results point to the fact that IHC markers differ in retaining their expression in damaged tissues. While p63 is more susceptible to cautery artefacts, keratin, like HMWCK (which also contains the CKs 5 and 14 studied in our series) expression better reflects vital tissue reactivity in both cauterised [23] and necrotic tissues [20].

As one could expect, the use of the quadruple IHC stain did not make all the decisions black and white, although in the majority (two thirds) of the cases, it helped to make a firm categorization, and in two thirds of the remaining cases it helped to reach a conclusion that could be taken into account in treatment planning. In a limited number of cases (about one tenth), the IHC did not help at all. The antibodies were not equivalent, and all four were supportive of the classification in only about 40% of the cases. In general, keratins were found more helpful. In a previous study, Nayak et al., found that CK5/6 and high-molecular-weight cytokeratin (HMWCK; 34β-E12) were useful in classifying 11 and 11 mildly to moderately cauterised breast tissues at the margin into hyperplastic versus neoplastic, and the IHC also helped them to segregate 11 severely cauterised margins into those involved by neoplasia vs hyperplasia [26]. In fact, there was no case, where neither of the two keratins were of help and the steroid receptors assisted in the clarification, but there were a few cases, where one of the keratins failed to give (strong) evidence in favour of either a neoplastic or a non-neoplastic nature (Case 10, Supplementary material-CK14, Case 22, Supplementary material-CK5), and here the ER and PR stains had some additional value. There were also a few cases where all four IHCs failed (e.g. Fig. 3). The keratins may also be helpful in distinguishing between cauterised invasive and in situ carcinoma at the margin owing to the presence or absence of the peripheral (myoepithelial) staining (See control to Case 30, Supplementary material).

It seems that ER staining, at least with the 6F11 clone antibody used in this context may be more compromised by the thermocoagulative alterations caused by cautery; the reactions were often weaker, or completely vanishing. It might happen that alternative antibodies may yield different results. The trouble with this phenomenon may arise from the fact that some of our cauterised tissues became pseudo-negative, and in some contexts, an ER-negative tumour and an ER-pseudo-negative cauterised tissue may lead to a wrong interpretation. Therefore, these immunostains always need to be interpreted in the proper context.

Recognizing the value of the quadruple IHC being at least partially helpful in many cases, we have also identified some practical and potential limitations. Although mosaic like CK5 and CK14 staining supports a non-neoplastic nature of the cauterised tissue, residual luminal epithelial cells (e.g. in case of pagetoid spread or partial involvement of the duct) as well as myoepithelial cells in papillomas involved by a neoplastic process may yield a similar pattern (e.g. Case 26 and its control, Supplementary material). A rarity, the tall cell carcinoma with reverse polarity may also display a focal, mosaic-like staining with CK5 (or CK14) [27]. A previous study referred to above [26], investigated HMWCK (34β-E12) in the same context, but CK5 and/or 14 seem better, as HMWCK also stains the majority of cells in lobular neoplasia and little positivity has also been found in ductal neoplasia [28]. Some tumours, invasive or their in situ precursors, may also exhibit a staining with these basal keratins either as a morphological evidence of basal-like differentiation in triple negative carcinomas [27,29] or along with ER positivity and HER2 negativity as reported in up to 8% of this group of tumours in a large cumulative series [30]. The mosaic-like ER an PR staining pattern of usual type hyperplasia and normal breast tissue is a helpful feature in classifying cauterised breast tissues, especially when it can be contrasted with the full-blown diffuse and strong positivity of low-grade DCIS, atypical hyperplasia, some invasive carcinomas and higher grade DCIS or the absolute negativity of apocrine carcinomas or triple-negative cancers. On the other hand, apocrine lesions of any type are ER and PR negative [31] whereas columnar cell lesions share the immunophenotype of low-grade DCIS, and recently a papillary variant has also been described [32], raising the possibility of potential misinterpretation. Many cancers have a heterogeneous labelling for ER and PR, and this should also be considered when interpreting the staining pattern of cauterised areas. At times, other supplementary IHCs may also be of help, like HER2 or apocrine markers (Cases 13 and 17, Supplementary material). Ross et al. have used a triple stain (CK7 to identify the epithelial nature, p63 for myoepithelial cells and E-cadherin to distinguish between lobular and ductal (in situ) carcinomas) to identify and classify minimal foci of breast cancer in core needle biopsies and excision specimens, and found this to be useful in at least one case where cautery artefact resulted in the distortion of the architecture at the inked margin [33], however, their study was not specifically devised to assess IHC results in cauterised breast tissues, and literature data cited above suggest that p63 may not be ideal in this context [23].

5. Conclusions

Taken all these considerations into account, CK5, CK14, PR and ER IHC may help in distinguishing between cautery damaged neoplastic and non-neoplastic tissues. All four IHC may yield the best support for decision making, but CK5 and/or CK14 may be sufficient in their own. The essential approach is that the results must be interpreted with caution, in the context of the given patient's disease, to avoid misinterpretations.

CRediT authorship contribution statement

Gábor Cserni: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. **Szintia Almási:** Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prp.2024.155280.

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