The immunohistochemical expression of D-type cyclins in Endometrial Stromal Sarcomas.

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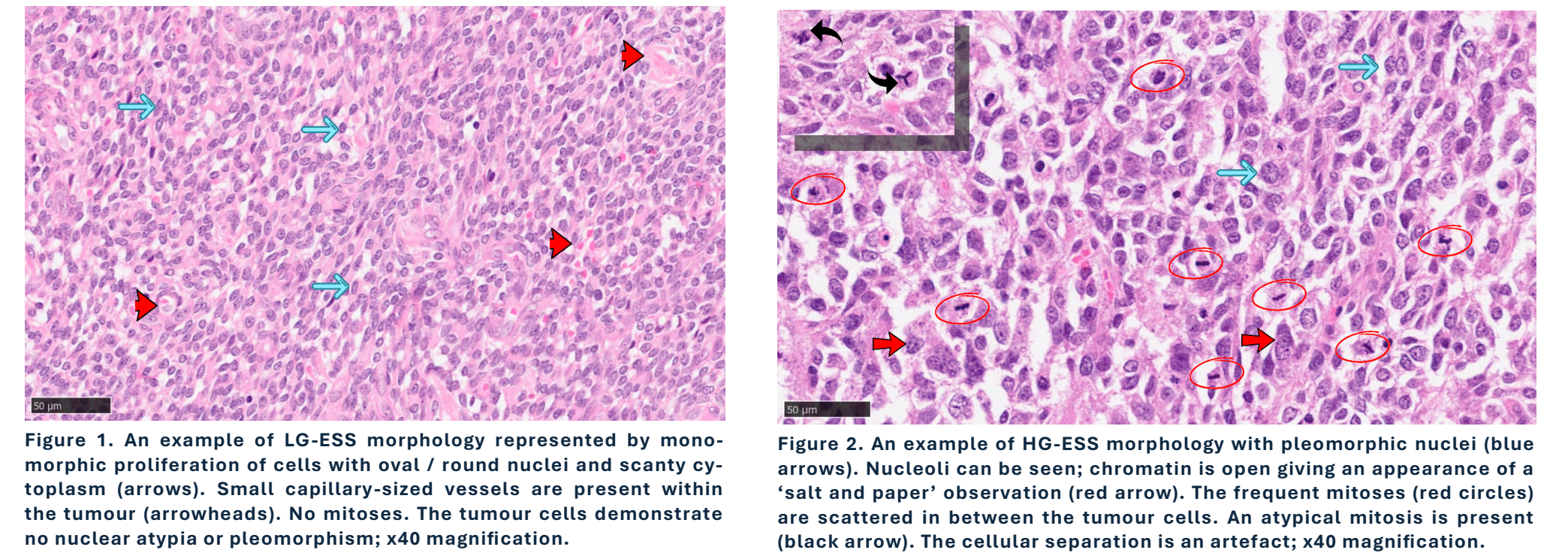
Introduction

Histological differentiation of endometrial stromal sarcomas (ESS) into low-grade (LG) and high-grade (HG) entities utilises cyclin D1 [1]. The cyclin D family also includes D2 and D3; however, diagnostic practice has not yet exploited them. Cyclin D1 can be a prognostic factor for predicting worse survival in patients with carcinomas [2]. Limited research has searched for the relationship between cyclin D family markers and survival in ESS patients. This study evaluated the prevalence of ESS in England, UK, clinicopathological and prognostic characteristics, including the immunohistochemical (IHC) expression of cyclin D1, D2, D3.

Materials & Methods

The Get Data Out reported in England between 2013 and 2020 was reviewed [3]. The pathology database of a general hospital was searched for primary uterine ESS cases. Using the morphological features, cases were categorised into LG (Fig.1) and HG (Fig.2) and tested with IHC (Fig. 3-4).

Results

The cumulative prevalence of ESS cases ranged between 66-98 per year (IR 0.119–0.174) (Tab.1). Thirteen cases (morphologically, 7 LG and 6 HG) showed cyclin D1 and D2 correlation (p-value < .001). Cyclin D3 correlated with the LVSI (p-value 0.049) in LG cases. The overall survival (OS) between LG and HG was significant (p-value 0.022), but not the disease-free survival (DFS) (Fig. 5-7).

Figure 1. An example of LG-ESS morphology represented by monomorphic proliferation of cells with oval / round nuclei and scanty cytoplasm (arrows). Small capillary-sized vessels are present within the tumour (arrowheads). No mitoses. The tumour cells demonstrate no nuclear atypia or pleomorphism; x40 magnification.

Figure 2. An example of HG-ESS morphology with pleomorphic nuclei (blue arrows). Nucleoli can be seen; chromatin is open giving an appearance of a 'salt and paper' observation (red arrow). The frequent mitoses (red circles) are scattered in between the tumour cells. An atypical mitosis is present (black arrow). The cellular separation is an artefact; x40 magnification.
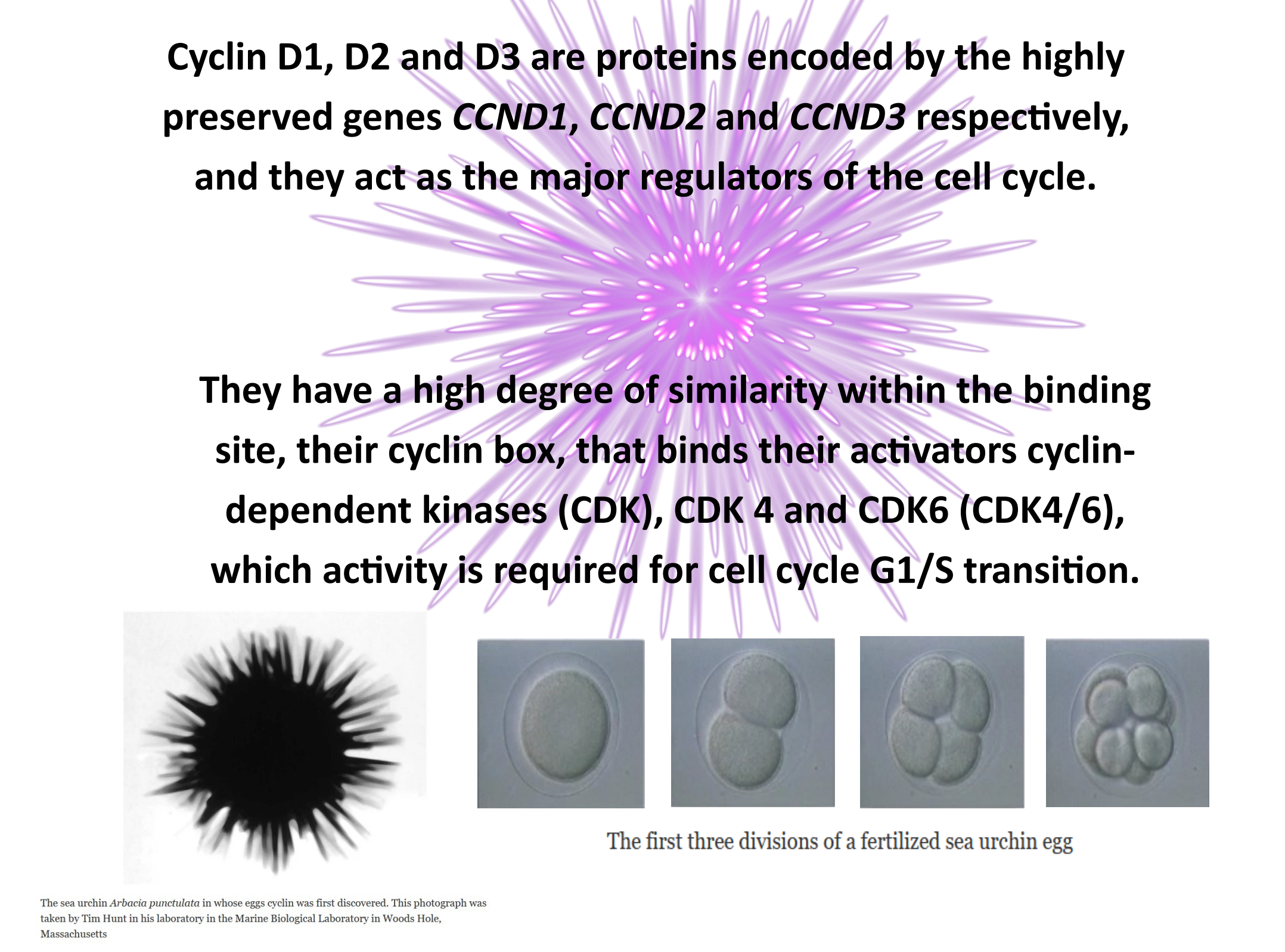
Discussion / Conclusion

ESS are ultra-rare tumours with a low incidence rate. Both cyclin D1 and D2 negative cases had a longer DFS and OS, compared to positive cases, regardless of morphological findings. Hence, Cyclin D markers might be explored as prognostic in ESS. Positive cyclin D1 indicated a positive cyclin D2 case; therefore, either marker could aid in histopathologic examination to distinguish LG from HG ESS, given the right clinical context.

References

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Key words: ESS, HG ESS, LG ESS, cyclin D, immunohistochemistry, survival

Cyclin D1, D2 and D3 are proteins encoded by the highly preserved genes *CCND1*, *CCND2* and *CCND3* respectively, and they act as the major regulators of the cell cycle.

They have a high degree of similarity within the binding site, their cyclin box, that binds their activators cyclin-dependent kinases (CDK), CDK 4 and CDK6 (CDK4/6), which activity is required for cell cycle G1/S transition.

The first three divisions of a fertilized sea urchin egg

The sea urchin *Arbacia punctulata* in whose eggs cyclin was first discovered. This photograph was taken by Tim Hunt in his laboratory in the Marine Biological Laboratory in Woods Hole, Massachusetts

ESS show diverse morphological appearances and a variety of cellular differentiation and histological patterns. This makes the histopathological diagnosis of these tumours difficult. IHC is frequently used to classify entities within the ESS spectrum, and it also holds potential for exploring prognostic features.
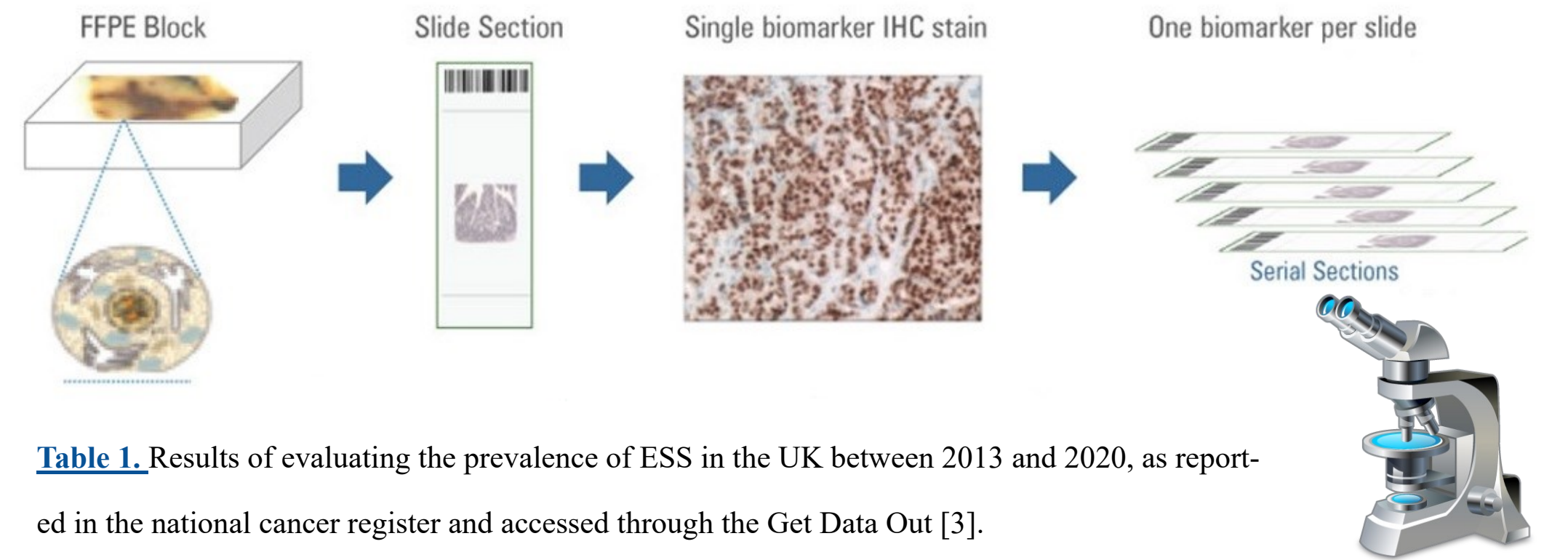

Table 1. Results of evaluating the prevalence of ESS in the UK between 2013 and 2020, as reported in the national cancer register and accessed through the Get Data Out [3].

Year	Tumour Type	Incidence	Population	Incidence rate
2013	ESS	86	53,865,817	0.16
2014	ESS	82	54,316,618	0.151
2015	ESS	86	54,786,327	0.157
2016	ESS	66	55,268,067	0.119
2017	ESS	85	55,619,430	0.153
2018	ESS	94	55,977,178	0.168
2019	ESS	98	56,286,961	0.174
2020	ESS	91	56,550,138	0.161

Figure 3. A positive nuclear staining with anti-cyclin D3. The WSI view demonstrates homogeneous distribution throughout the tumour area (dark brown). The intensity is strong within the entire tumour. All neoplastic cells as shown in the higher magnification demonstrate strong nuclear expression; x20 magnification.

Figure 5. Cyclin D1 grouping by positive and negative staining in OS (A) and in DFS (B) curves for all cases.

Figure 6. Cyclin D2 grouping by positive and negative staining in OS (A) and in DFS (B) curves for all cases.

Figure 4. A negative staining with anti-cyclin D1 within the neoplastic cells (highlighted by a circle), whereas ectocervical epithelium is positive at the basal layer, which can be considered as a positive internal control. At higher magnification (the background image) the blood vessels are also positive as a positive internal control (arrows); x10 magnification.

Figure 7. Cyclin D3 grouping by positive and negative staining in OS (A) and in DFS (B) curves for all cases.