Original Research

The incidence, treatment and survival of patients with rare types of rectal malignancies in the Netherlands: A population-based study between 1989 and 2018

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Population-based study;
Incidence;
Rare cancer

Abstract  Aim: To describe the incidence, treatment and survival of patients with rare types of rectal malignancies in the Netherlands.
Methods: Data of patients with rectal malignancies diagnosed in the Netherlands between 1989 and 2018 were retrieved from the Netherlands Cancer Registry and grouped according to the RARECARE cancer list. Age-standardised incidence rates were calculated using the European Standard Rate. The Joinpoint Regression Program was used for analysing trends and joinpoints and for the estimation of annual percentage changes (APCs). Patient characteristics, treatment details and relative survival (RS) were reported for different histological types of rectal malignancies and compared between different time periods. RS was assessed using Kaplan-Meier analysis and log-rank test.
Results: A total of 88,299 cases of rectal malignancies were included of which 2125 (2.5%) were categorised as rare histological subtypes. The incidence of rectal neuro-endocrine tumours (NET) (APC: 6.2%, 95% confidence interval [CI]: 5.4%; 7.1%), rectal sarcoma (APC: 5.8%, 95% CI: 2.9%; 8.7%) and rectal adenocarcinoma (APC 1.0%, 95% CI: 0.26%; 1.8%) increased. Prognosis was best in patients with rectal NET (5-year RS: 72.4%, 95% CI: 62.9%; 81.8%).

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70.1%; 74.7%) and worst in patients with rectal melanoma (5-year RS: 8.9%, 95% CI: 5.1%; 15.7%). RS has improved in patients with rectal adenocarcinoma, rectal sarcoma and rectal lymphoma in 2008–2018 (p-values p < 0.001, p = 0.023 and p = 0.029).

**Conclusion:** Significant increases in incidence were observed for different types of rectal malignancies. Differences in incidence, treatment and survival found in this study could be useful to make clinicians aware of specific diseases.

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### 1. Introduction

Adenocarcinoma is the most common histological type of rectal cancer and accounts for more than 90% of all cases [1,2]. The remaining, less common types of rectal malignancies include neuro-endocrine tumours (NET), sarcoma, lymphoma, melanoma and squamous cell carcinomas (SCC).

So far, no studies describing the incidence of multiple histological subtypes of rectal malignancies have been conducted. Population-based data of rare types of rectal malignancies are scarce and are mainly limited to one specific entity [3–6]. An increase in the incidence of rectal adenocarcinoma in the Netherlands has been observed [7]. A nationwide bowel cancer screening programme was implemented in 2014, which likely has changed the incidence since then [8,9]. Whether there have been changes in the incidence of the rare types of rectal malignancies and the impact of the bowel screening program is yet unknown.

Multimodal therapeutic approaches for rectal malignancies are different between specific diseases [10–14]. Evidence for the treatment of rare types of rectal malignancies is often limited to small retrospective series and expert opinions. Management of rare types of rectal malignancies is therefore challenging and could lead to heterogeneity in treatment patterns.

Population-based data of patient outcomes could be useful in clinical practice. Comparing outcomes of different types of rectal malignancies in one specific population results in an unbiased estimation of patients’ probabilities of surviving. Both physicians and patients could use this information to estimate prognosis and to review suitable treatment options. Additionally, it is of interest whether treatment and survival of patients with rectal malignancies have changed over the study period.

In conclusion, a comprehensive overview evaluating the rare histological subtypes of rectal malignancies is missing. The aim of this population-based study is to describe the incidence, the treatment and the survival of rare histological subtypes of rectal malignancies in the Netherlands between 1989 and 2018, thereby providing data on adenocarcinoma as a reference.

### 2. Methods

#### 2.1. Data collection

Data of all patients diagnosed with rectal malignancies, registered in the Netherlands Cancer Registry (NCR) between 1989 and 2018, were collected. The NCR uses the Dutch Pathological-Anatomical National Automated Archive (PALGA) and the National Registry of Hospital Discharge Diagnoses as main data sources to identify patients with newly diagnosed malignancies. Data on patient and tumour characteristics and treatment were extracted by trained data managers from patients’ medical records. Follow-up of vital status was achieved by linking the NCR to the National Municipal Personal Records Database, which is updated annually. Topography and morphology was classified according to the International Classification of Disease for Oncology (ICD-O-3). Stage was determined according to the TNM classification, the Extent of Disease classification or the Ann Arbor staging system for lymphomas as appropriate [15]. Pathological TNM stage was supplemented with clinical TNM stage if pathological TNM stage was not available or in case of neoadjuvant treatment. TNM stage was based on the actual edition of the TNM classification at the time of diagnosis.

#### 2.2. Histological subtypes

Histological subtypes of rectal malignancies were classified according to the RARECARE Cancers list of March 2011 [16]. The RARECARE grouping method uses topography and morphology codes according to the ICD-O and correlates with the World Health Organisation’s (WHO) categorisation for malignancies. For analyses, histological subtypes were divided into six groups: rectal adenocarcinoma, rectal NET, rectal lymphoma, rectal sarcoma, rectal melanoma and rectal SCC. ICD-O-3 morphology codes of all histological subtypes per category were listed in appendix 1 and appendix 2. Malignancies with undefined or unspecific morphology codes according to the ICD-O-3 were analysed separately.
2.3. Statistics

Descriptive data were presented as count with percentages or median with interquartile ranges (IQR). Annual incidence rates were calculated per 100,000 person-years and standardised by age according to the European Standard Population. Trends in incidence for each morphological subtype were analysed using a jointpoint regression model fitted by Joinpoint Trend Analysis Software (version 4.8.0.1) (IMS, Inc. under contract for the National Cancer Institute, Bethesda, MD, USA) [17]. The software takes trend data (i.e. incidence rates) and fits the simplest jointpoint model that the data allow wherein the number of joinpoints is obtained using the Monte Carlo permutation test [18]. Annual percentage changes (APCs) with 95% confidence intervals (CIs) were also performed by the Joinpoint Trend Analysis Software and were calculated by fitting a regression model of the natural logarithm of incidence rates with the year of diagnosis as regressor. APCs were calculated either as an average over the whole period or over a segment between joinpoints when changes in trends occurred. Survival for different histological types of rectal malignancies was estimated by the method of Kaplan-Meier and was statistically tested by the log-rank test. Relative survival (RS) was assessed according to the Pohar Perme method using Dutch population life tables in R (‘relsurv’ package by Perme et al.) [19,20]. Median survival and 1-, 3- and 5-year survival rates with 95% CI were used to describe survival. Treatment and survival were presented in the periods of 1989–2007 and 2008–2018, and were compared by the chi-squared test and log-rank test, respectively. Missing values were not included in descriptive statistics. All analyses were performed using R version 3.6.1 (https://www.r-project.org/).

3. Results

A total of 88,299 cases of rectal malignancies were retrieved from the NCR in the period of 1989–2018. The majority of diagnosed neoplasms were adenocarcinoma (86,174 patients, 97.6%). Rare types of rectal malignancies included 1525 patients with rectal NET (1.7%), 225 patients with rectal sarcoma (0.3%), 147 patients with rectal lymphoma (0.2%), 134 rectal melanoma (0.2%) and 94 patients with rectal SCC (0.1%). A total of 1210 patients with undefined or unspecified morphology codes according to the ICD-O-3 were analysed separately. The incidence rates and baseline characteristics for each histological subtype are shown in Table 1 and Fig. 1.

3.1. Incidence

Among the rare histological subtypes, the highest incidence rates were found for rectal NET (median annual incidence: 0.197 per 100,000, IQR 0.16−0.41) and the lowest for rectal SCC (median annual incidence: 0.015 per 100,000, IQR: 0.01−0.02). The median annual incidence of rectal adenocarcinoma was 14.2 per 100,000 (IQR: 12.2−16.7). Significant increases in incidence rates were found for rectal NET (APC: 6.2%, 95% CI: 5.4%; 7.1%), rectal sarcoma (APC: 5.8%, 95% CI: 2.9%; 8.7%) and rectal adenocarcinoma (APC 1.0%, 95% CI: 0.26%; 1.8%). For adenocarcinoma, a joinpoint was observed in the year of 2016, demonstrating a significant increase of 2.3% (95% CI: 2.0%; 2.5%) per year before 2016 followed by a significant decrease of 14.2% (95% CI: −23.4%; −3.8%) per year. The incidence rates of the five rare rectal cancers combined increased with 5.1% (95% CI: 4.4%; 5.8%) per year.

3.2. Patients and treatment

Median age at the time of diagnosis was highest in patients with rectal melanoma with 72.0 years (IQR: 63.0−78.0) and lowest in patients with rectal NET with 60.0 years (IQR: 49.0−69.0). Treatment details of each histological subtype are summarised in Table 2. For the rare subtypes of rectal malignancies, the rate of surgical resection ranged from 6% in patients with rectal lymphoma to 76% in patients with rectal NET. Local excision was performed in 62% of the patients with rectal NET. Radiation therapy combined with surgery was performed in 40,252 patients (47%) with rectal adenocarcinoma. Radiation therapy without surgery was performed in 31 patients with rectal SCC (33%). Chemotherapy was administered in 79 patients with rectal lymphoma (54%). Targeted therapy was performed in 92 patients with rectal sarcoma (41%) and in 44 patients with rectal lymphoma (33%), but was seldom used in patients with other rare types of rectal malignancies. No tumour-targeted treatment was reported in 37 patients with rectal lymphoma (25%). An overview of differences in treatment methods of patients diagnosed in 1989−2007 compared to patients diagnosed in 2008−2018 is shown in Supplementary Table 1. In the last decade of the study period (2008−2018), local excision was performed more in patients with rectal adenocarcinoma, rectal NET and rectal sarcoma compared to patients diagnosed before this period (1989−2007) (11% vs. 5%, 68% vs. 52% and 26% vs. 8%, all p-values: p < 0.001). In addition, surgery was performed less in these histological subtypes in the last decade of the study period (68% vs. 80%, 7% vs. 26% and 38% vs. 63%, all p-values: p < 0.001). Targeted or immunotherapy was administered more in 2007−2018 in patients with rectal adenocarcinoma, rectal sarcoma, rectal lymphoma and rectal melanoma (6% vs. 1%, 66% vs. 12%, 60% vs. 10% and 16% vs. 0%, all differences were statistically significant at α = 0.01).
3.3. Survival

Relative 5-year survival rates ranged from 8.9% (95% CI: 5.1%; 15.7%) for patients with rectal melanoma to 72.4% (95% CI: 70.1%; 74.7%) for patients with rectal NET (Table 3). Estimated survival for each histological subtype is depicted in Fig. 2. Compared to patients with adenocarcinoma, those with rectal NET and rectal sarcoma had better prognosis in terms of survival (5-year RS rates: resp. 72.4% [95% CI: 70.1%; 74.7%] and 64.6% [95% CI: 58.4%; 71.5%] vs. 53.1% [95% CI: 52.8%; 53.5%]). Prognosis of patients with rectal lymphoma was not statistically different from patients with rectal adenocarcinoma, with 5-year RS rates of 54.7% (95% CI: 46.9%; 63.8%) for patients with rectal adenocarcinoma, rectal sarcoma and rectal lymphoma diagnosed in 2008–2018 had significantly better survival compared to patients diagnosed in 1989–2007 (Fig. 3) (resp. p-values p < 0.001, p = 0.023 and p = 0.029).

Table 1
Incidence and baseline characteristics of different types of rectal malignancies in the Netherlands between 1989 and 2018.

<table>
<thead>
<tr>
<th></th>
<th>Adenocarcinoma</th>
<th>NET</th>
<th>Sarcoma</th>
<th>Lymphoma</th>
<th>Melanoma</th>
<th>SCC</th>
<th>Undefined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (per 100,000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14.20</td>
<td>0.197</td>
<td>0.036</td>
<td>0.024</td>
<td>0.023</td>
<td>0.015</td>
<td>0.171</td>
</tr>
<tr>
<td>IQR</td>
<td>[12.2; 16.7]</td>
<td>[0.16; 0.41]</td>
<td>[0.02; 0.05]</td>
<td>[0.02; 0.03]</td>
<td>[0.01; 0.03]</td>
<td>[0.01; 0.02]</td>
<td>[0.16; 0.21]</td>
</tr>
<tr>
<td>APC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>1.0%</td>
<td>6.2%</td>
<td>5.8%</td>
<td>1.3%</td>
<td>5.1%</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.26%; 1.8%</td>
<td>5.4%; 7.1%</td>
<td>2.9%; 8.7%</td>
<td>-1.0%; 3.6%</td>
<td>-1.3%; 11.8%</td>
<td>-1.7%; 0.2%</td>
<td>1.4% 3.0%</td>
</tr>
</tbody>
</table>

| Age Median | 68.0         | 60.0| 64.0    | 67.0     | 72.0     | 63.5| 79.0      |
| IQR        | [60.0; 76.0] | [49.0; 69.0] | [55.0; 75.0] | [55.0; 75.0] | [63.0; 78.0] | [56.2; 75.0] | [69.0; 85.0] |

| Gender | Male          | 51,831 (60%) | 825 (54%) | 145 (64%) | 92 (63%) | 59 (44%) | 47 (50%) | 617 (51%) |
|        | Female        | 34,343 (40%) | 700 (46%) | 80 (36%)  | 55 (37%) | 75 (56%) | 47 (50%) | 593 (49%) |

| cT-stage | 1 | 3381 (7%) | 271 (51%) | 5 (6%)   | -        | -       | 1 (2%)  | 11 (4%)  |
|          | 2 | 9827 (20%)| 49 (9%)   | 19 (24%) | -        | -       | 5 (9%)  | 56 (19%) |
|          | 3 | 25,864 (53%) | 114 (22%) | 35 (44%) | -        | -       | 19 (35%)| 135 (46%)|
|          | 4 | 9838 (20%) | 95 (18%)  | 21 (26%) | -        | -       | 30 (55%)| 93 (32%) |

| cN-stage | 0 | 31,844 (57%) | 338 (59%) | 70 (86%) | -        | -       | 25 (44%)| 125 (38%)|
|          | 1 | 14,970 (27%)| 127 (22%) | 11 (14%) | -        | -       | 16 (28%)| 124 (38%)|
|          | 2 | 9121 (16%) | 109 (19%) | -        | -        | -       | 16 (28%)| 76 (23%) |

| cM-stage | 0 | 65,396 (82%) | 807 (77%) | 85 (89%) | -        | -       | 58 (74%)| 241 (49%)|
|          | 1 | 14,578 (18%) | 242 (23%) | 11 (11%) | -        | -       | 20 (26%)| 249 (51%)|

| Stage (TNM, Ann Arbor) | 1 | 20,911 (25%) | 548 (60%) | 32 (34%) | 62 (45%) | -       | 14 (18%)| -        |
|                        | 2 | 19,339 (23%) | 39 (4%)   | 22 (24%) | 19 (14%) | -       | 14 (18%)| -        |
|                        | 3 | 27,191 (33%) | 92 (10%)  | 22 (24%) | 8 (6%)   | -       | 29 (37%)| -        |
|                        | 4 | 14,885 (18%) | 233 (26%) | 17 (18%) | 48 (35%) | -       | 22 (28%)| -        |

| Stage (EoD) | 1 | -          | 0 (0%)    | -        | 1 (0%)   | -       | 1 (0%)  | -        |
|            | 2 | -          | 187 (88%) | -        | 32 (29%) | -       | 86 (17%)| -        |
|            | 3 | -          | 1 (0%)    | -        | 5 (5%)   | -       | 98 (19%)| -        |
|            | 4 | -          | 1 (0%)    | -        | 16 (15%) | -       | 25 (5%) | -        |
|            | 5 | -          | 1 (0%)    | -        | 11 (10%) | -       | 17 (3%) | -        |
|            | 6 | -          | 22 (10%)  | -        | 45 (41%) | -       | 279 (55%)| -        |

| Differentiation | Well | 4065 (7%) | 475 (67%) | 50 (43%) | -       | -       | 6 (12%) | 2 (3%)   |
|                | Moderately | 48,681 (80%) | 69 (10%) | 21 (18%) | -       | -       | 25 (48%)| 3 (4%)   |
|                | Poor | 8001 (13%) | 120 (17%) | 41 (30%) | -       | -       | 21 (40%)| 43 (62%) |
|                | Undifferentiated | 78 (0%) | 46 (6%)  | 3 (3%)   | -       | -       | 0 (0%)  | 21 (30%) |

Abbreviations: APC, annual percentage changes, NET, neuro-endocrine tumour, SCC, squamous cell carcinoma, TNM, tumour node metastasis, EoD, Extend of Disease.
Percentages might not add up due to rounding.
* Ann Arbor staging system for lymphomas.
4. Discussion

In this population-based study including patients diagnosed with different histological subtypes of rectal malignancies between 1989 and 2018 in the Netherlands, rare types of rectal tumours accounted for about 2.5% of all cases, which is comparable with studies reporting the incidence of rare colorectal cancers [21,22]. In the rare subtypes of rectal malignancies, a significant increase in incidence was observed in rectal NET and rectal sarcoma. The incidence of rectal adenocarcinoma also increased. Surgery was performed in the majority of patients with adenocarcinoma (81%) and was used in a small proportion of patients with rectal lymphoma (6%). Major differences were found in prognosis of patients with rare rectal malignancies with 5-year survival rates ranging from 72% for rectal NET and 9% for rectal melanoma. Survival of patients with rectal NET and rectal sarcoma was better compared to patients with rectal malignancies.

![Fig. 1. Incidence of different types of rectal malignancies in the Netherlands between 1989 and 2018. Annual incidence rates are visualised by single data points with Joinpoint regression model as plot. • Indicates that the annual percentage change (APC) is significantly different from zero at α = 0.05.](image)
adenocarcinoma. Significant improvement in terms of relative survival was found in the last decade of the study period for patients with rectal adenocarcinoma, rectal sarcoma and rectal lymphoma.

In 2014, the national screening program for colorectal cancer was implemented in the Netherlands, which did not seem to affect the incidence of the rare histological subtypes (Fig. 1). However, high incidence rates of rectal adenocarcinoma were observed in the years 2014, 2015 and 2016. In those years, almost 20 new diagnoses per 100,000 persons were observed annually, which was followed by a decrease in incidence the years after. This is congruent with the hypothesis that screening will eventually reduce the incidence of cancer due to the detection and resection of premalignant lesions before invasive cancer can occur [23–25]. Currently, the decreasing trend in incidence in rectal adenocarcinoma is still ongoing in the Netherlands as is shown by premature NCR data from 2019 to 2020 (available at https://iknl.nl/en/ncr) [26].

Over the whole study period, a statistically significant increase in incidence of 1.0% per year was found for rectal adenocarcinoma, which is in line with previous studies reporting incidence of rectal cancer in the Netherlands [7,9]. Also, the incidence rates of the five rare rectal cancers combined increased with 5.1% per year.
One possible cause that might have played a role in this increase is the introduction of new diagnostic modalities, such as the magnetic resonance imaging (MRI) in 2001 [27]. It is plausible that more accurate imaging and advanced endoscopy methods have led to the detection of more indolent tumours (e.g. rectal NET) that would have otherwise gone undetected [28]. The MRI might have also contributed to a shift of staging more rectosigmoid tumours as rectal cancer [29]. Although screening and diagnostic modalities might explain the fluctuations in incidence which were found in this study, it is most likely that changes in diet, smoking, physical behaviour and obesity have also played an important role in the more graduate increase of the incidence of rectal cancer in the past decades, which is seen globally [23,30,31]. Finally, other factors that might influence in the worldwide increasing incidence of rectal cancer are not fully understood [32]. No decreases in incidence were found in any of the analysed subtypes. Therefore, it is unlikely that the increasing incidence observed in adenocarcinoma was caused by the accumulation of wrongly diagnosed tumours from other subtypes.

Multimodal treatment strategies such as surgery, radiation therapy, chemotherapy and targeted therapy...
were reviewed for each histological subtype. One interesting finding was the high proportion of patients with rectal NET that was treated with local excision (62%). This, plus the fact that these tumours were generally diagnosed at a relatively low stage, suggests that these tumours were probably encountered and resected during endoscopic procedures such as screening colonoscopies. Although small polyoid NET lesions are generally asymptomatic and indolent, international guidelines still recommend treating these lesions with surgical resection or with endoscopic excision due to the metastatic potential of larger NET [33].

Another interesting finding in this study was the proportion of rectal SCC patients (33%) receiving radiation therapy and no surgery. Chemoradiation as primary treatment is proven effective in patients with SCC in the anal canal but is not standard treatment in patients with rectal SCC [34–36]. In case of potentially curable disease, patients with rectal SCC are traditionally treated with chemoradiation therapy followed by surgery [14,37]. However, more recent retrospective studies reveal that definite chemoradiation therapy as primary treatment can also achieve local control in patients with rectal SCC [38,39]. In this present study, it is unclear whether these rectal SCC patients were deliberately treated with curative radiation therapy or that they were wrongly diagnosed as anal SCC. Although the advent of new modalities has changed treatment patterns during the long study period, the heterogeneity in treatment approaches found in this study demonstrates that management of rare rectal malignancies can be difficult.

In the last decade of the study period, significant changes in treatment modalities were observed in all histological subtypes (Supplementary Table 1). Less surgery, but more local excision was performed in almost every histological subtype of rectal cancer in the years 2008–2018. This is line with the trend of performing less extensive surgery and more organ preservation. Also, targeted and immunotherapy was administered more frequently in this period. Patients with rectal adenocarcinoma and rectal SCC diagnosed in the last decade of the study period have been treated with more radiation therapy and chemotherapeutic agents compared to patients diagnosed before 2008.

Prognosis in terms of relative survival was poorest in patients with rectal melanoma and rectal SCC and is comparable with other (population-based) studies [4,40]. Dismal survival is probably due to the aggressive biological behaviour of these malignancies and the late detection of the disease. Rectal melanoma is commonly diagnosed as a locoregional advanced tumour or as metastatic disease, leaving no curative therapeutic options [41,42]. In this present study, locally advanced and metastatic disease were relatively common in patients with rectal SCC (65%) and rectal melanoma (51%), confirming this hypothesis. Relative survival improved in the last decade of the study period for rectal adenocarcinoma, rectal sarcoma and rectal lymphoma and is probably the result of the combination of better diagnostic modalities, population screening and more effective treatment regimens. Patients with unspecified or undefined rectal tumours had very poor prognosis. This might be explained by the logical thought that there is little added value of assessing histological conformation in patients with low life expectancy (e.g. very old age or extensive metastasized disease).

Some limitations in this population-based study should be noted. Owing to retrospective analysis of data collected by the NCR, it is possible that bias occurred due to missing or incorrect data. Also, major fluctuations in annual incidences were observed for the rare rectal malignancies. APCs might therefore be less accurate, which could have affected findings in this study. Staging was based on the classification at the time of diagnosis, which could have led to inconsistency in the reported stage distribution. However, it should be noted that this present study is one of the first to reveal the age-standardised incidence rates with APCs of various uncommon types of rectal malignancies.

In conclusion, different histological subtypes, other than rectal adenocarcinoma, are uncommon and together only account for 2.5% of all rectal malignancies. Increasing incidences were seen for rectal NET, rectal sarcoma and rectal adenocarcinoma. Prognosis of patients with rare types of rectal malignancies ranged from excellent for rectal NET to extremely poor for rectal melanoma. As data of uncommon histological subtypes of rectal malignancies are scarce, findings in this present study can be useful in clinical decision-making.

Author’s contribution

J.M. van Rees: Conceptualization, Methodology, Formal analysis, Writing — original draft, Visualization.

M.A.G. Elferink: Methodology, Formal analysis, Resources, Writing — review & editing, Visualization, Supervision.

P.J. Tanis: Writing — review & editing, Methodology.

J.H.W. de Wilt: Writing — review & editing, Methodology.

J.W.A. Burger: Writing — review & editing, Methodology.

Verhoef M.D: Conceptualization, Methodology, Writing — original draft, Writing — review & editing, Supervision, Project administration.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.04.036.

References


