Abstracts Palga-prijs 2022

Uitreiking Palga-prijs:
13 april 2023, Week van de Pathologie, Amersfoort

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Voorwoord

De Stichting Palga reikt vanaf 2012 jaarlijks de **Palga-prijs** uit. De Palga-prijs is in het leven geroepen om het gebruik van de Palga-databank voor wetenschappelijk onderzoek te stimuleren.

De Palga-prijs is een prijs voor het beste abstract met Palga-gegevens.

De winnaar wordt in de gelegenheid gesteld om na de uitreiking van de prijs een korte presentatie te geven over het onderzoek.

In 2022 zijn er 38 abstracts ingediend.

Het abstract kon zowel een huidig, nog niet gepubliceerd onderzoek betreffen als een onderzoek dat in 2021 of 2022 gepubliceerd is. Junioronderzoekers, AIOS en gepromoveerde onderzoekers werkzaam zowel binnen als buiten de pathologie werden uitgenodigd om een abstract in te dienen. Het abstract diende te voldoen aan de volgende voorwaarden:

- De gebruikte onderzoeksbron(nen) is/zijn: gegevens uit de landelijke Palga-databank, PA-materiaal opgevraagd via Palga en/of klinische gegevens van de behandelaar verkregen via Palga
- De onderzoeker is bereid een presentatie te geven op de Week van de Pathologie.
- Het abstract dient Engelstalig te zijn, maximaal 300 woorden te bevatten en de volgende indeling te hebben: titel, auteurs, achtergrond, vraagstelling, methode, resultaten, conclusie.

De Commissie Wetenschap van Palga (CW), bestaande uit 3 pathologen en 2 epidemiologen, en één KMBP heeft aan elk abstract punten toegekend voor de volgende onderdelen:

- originaliteit van de vraagstelling
- heldere/duidelijke schrijfstijl
- kwaliteit methodologie
- goed gebruik van de Palga-databank als onderzoeksbron

Elk abstract is door 1 patholoog en 1 epidemioloog/KMBP beoordeeld. Dit resulteerde in 9 best beoordeelde abstracts. Ieder lid van de CW heeft deze 9 abstracts opnieuw beoordeeld.

De winnaars van de Palga-prijs 2022 zijn **Vincent de Jong** en **Juwei Wang** met het abstract getiteld:

Prognostic Value of Stromal Tumor-Infiltrating Lymphocytes in Young, Node-Negative, Triple-Negative Breast Cancer Patients Who Did Not Receive (neo)Adjuvant Systemic Therapy

In dit boekje zijn alle 38 beoordeelde abstracts gebundeld.
Het winnende abstract is als eerste opgenomen. De volgorde van de overige abstracts is op alfabet.

Inhoud *Pagina*

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Pagina

Prognostic Value of Stromal Tumor-Infiltrating Lymphocytes in Young, Node-Negative, Triple-Negative Breast Cancer Patients Who Did Not Receive (neo)Adjuvant Systemic Therapy

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Objective: Triple-negative breast cancer (TNBC) is considered aggressive and therefore, virtually all young patients with TNBC receive (neo)adjuvant chemotherapy. Increased stromal tumor-infiltrating lymphocytes (sTILs) have been associated with a favorable prognosis in TNBC. However, whether this association holds for patients who are node-negative (N0), young (<40 years), and chemotherapy-naïve, and thus can be used for chemotherapy de-escalation strategies, is unknown.

Methods: We selected all patients with N0 TNBC diagnosed between 1989 and 2000 from a Dutch population-based registry. Patients were <40 years at diagnosis and had not received (neo)adjuvant systemic therapy, as was standard practice at the time. FFPE blocks were retrieved (PALGA: Dutch Pathology Registry) and a pathology review including sTILs was performed. Patients were categorized according to sTILs (<30%, 30-75%, ≥75%). Multivariable Cox regression was performed for overall survival, with or without sTILs as a covariate. Cumulative incidence of distant metastasis or death was analyzed in a competing risk model, with second primary tumors as competing risk.

Results: Stromal TILs were scored for 441 patients. High sTILs (≥ 75%; 21%) translated into an excellent prognosis with a 15-year cumulative incidence of a distant metastasis or death of only 2.1% (95%CI 0-5.0), whereas low sTILs (<30%; 52%) had an unfavorable prognosis with a 15-year cumulative incidence of a distant metastasis or death of 38.4% (32.1–44.6). In addition, every 10% increment of sTILs decreased the risk of dying by 19% (adjusted hazard ratio: 0.81; 95%CI 0.76 to 0.87), which are an independent predictor adding prognostic information to standard clinicopathological variables ($\chi 2=46.7$, $p<0.001$).

Conclusions: Chemotherapy-naïve, young, N0 TNBC patients with high sTILs (≥ 75%) have an excellent long-term prognosis. Therefore, sTILs should be considered for prospective clinical trials investigating (neo)adjuvant chemotherapy de-escalation strategies.

Prophylactic medication for the prevention of endoscopic recurrence in Crohn's disease: a prospective study based on clinical risk stratification

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On behalf of the Dutch Initiative on Crohn's and Colitis (ICC)

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Background: To prevent recurrence after ileocolonic resection (ICR) in Crohn's disease (CD), postoperative prophylaxis based on risk stratification is recommended in international guidelines. This study aimed to evaluate postoperative CD recurrence after implementation of a clinical management algorithm and determine the predictive value of clinical and histological risk factors (RF).

Methods: In this multicenter, prospective cohort study, CD patients (≥16 years) scheduled for ICR were included. The algorithm advised no postoperative medication for low-risk patients, and treatment with prophylaxis (immunosuppressant/biological) for high-risk patients (≥1 RF: active smoking, penetrating disease, prior ICR). Three experienced gastrointestinal pathologist analyzed haematoxylin-eosin (H&E) stained histology slides of the surgical resection specimen in a blinded and random manner according to a standardized assessment schedule. Clinical and histologic RF (active inflammation, granulomas, plexitis in resection margins) for endoscopic recurrence (Rutgeerts' score ≥i2b at 6 months) were assessed using logistic regression and ROC curves based on predicted probabilities.

Results: 213 CD patients after ICR were included (age 34.5 years; 65% women) (93[44%] low-risk;120[56%] high-risk [45[38%] smoking; 51[43%] penetrating disease; 51[43%] prior ICR]). Adherence to the algorithm was 82% in low-risk (no prophylaxis) and 51% in high-risk patients (prophylaxis). Endoscopic recurrence was higher in patients treated without prophylaxis than with prophylaxis in both low (45% vs 16%, p=.012) and high-risk (49% vs 26%, p=.019). Clinical risk stratification including the prescription of prophylaxis corresponded with an area under the curve (AUC) of 0.70 (95%CI 0.61-0.79). Clinical RF combined with histological RF increased the AUC to 0.73 (95%CI 0.64-0.81).

Conclusion: Adherence to this management algorithm is 65%. Prophylactic medication after ICR prevents endoscopic recurrence in low and high-risk patients. The addition of histologic factors to the clinical risk factors has limited added predictive value. Further refinement of risk factors, is needed.

Nationwide impact of centralization, neoadjuvant therapy, minimally invasive surgery, and standardized pathology reporting on R0 resection and overall survival in pancreatoduodenectomy for pancreatic cancer

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#Shared first authorship, *Shared senior authorship

Background: R0 resection in patients with pancreatic cancer is associated with better overall survival. However, it is unclear whether changes such as centralization, increased use of neoadjuvant therapy, minimal invasive surgery, and standardized pathology reporting have influenced R0 resections.

Methods: This nationwide retrospective cohort study combined data from the Netherlands Cancer Registry and the Dutch Nationwide Pathology Database. All consecutive patients after pancreatoduodenectomy (PD) for pancreatic cancer (2009-2019) were included. R0 resection was defined as >1mm tumor clearance at the pancreatic- and arterial resection margins, and posterior- and venous surfaces. Completeness of pathology reporting was scored based on six elements: histological diagnosis, tumor origin, radicality, tumor size, extent of invasion and lymph node examination.

Results: Among 2,955 patients after PD for pancreatic cancer the rate R0 resection was 49%, and decreased from 68% in 2009 to 43% in 2019 (P<0.001). The rate of resections in high volume hospitals, minimal invasive surgery, neoadjuvant therapy, and complete pathology reports significantly increased over time. More complete pathology reporting was independently associated with lower R0 rates (OR 0.77, 95%CI: 0.69-0.85, p<0.001), whereas hospital volume, neoadjuvant therapy, and minimally invasive surgery were not. R0 resection was independently associated with improved overall survival (HR 0.71, 95%CI 0.65-0.77, p<0.001). Also in the 214 patients receiving neoadjuvant treatment (HR 0.61, 95%CI: 0.42-0.87, p=0.007).

Conclusions: Nationwide, the rate of R0 resections have decreased over time, mostly related to complete pathology reporting. R0 resection was not influenced by centralization, neoadjuvant therapy, or minimal invasive surgery, and remained associated with overall survival.

Development and external validation of a prediction model for overall survival after resection of distal cholangiocarcinoma

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Objective: To develop and validate a prediction model for 3-year overall survival (OS) after pancreatoduodenectomy for distal cholangiocarcinoma (dCCA).

Methods: The derivation cohort consisted of all patients who underwent pancreatoduodenectomy for dCCA in the Netherlands (2009–2016). Clinically relevant variables were selected based on the Akaike information criterion using a multivariate Cox proportional hazards regression model, with model performance being assessed by concordance index (C-index) and calibration plots. External validation was performed using patients from the Belgium Cancer Registry (2008–2016), and patients from two university hospitals of Southampton (U.K.) and Verona (Italy).

Results: Independent prognostic factors for OS in the derivation cohort of 454 patients after pancreatoduodenectomy for dCCA were age (HR 1.02, 95% CI 1.01–1.03), pT (HR 1.43, 95% CI 1.07–1.90) and pN category (pN1: HR 1.78, 95% CI 1.37–2.32; pN2: HR 2.21, 95% CI 1.63–3.01), resection margin status (HR 1.79, 95% CI 1.39–2.29) and tumour differentiation (HR 2.02, 95% CI 1.62–2.53). The prediction model was based on these prognostic factors. The optimism-adjusted C-indices were similar in the derivation cohort (0.69), and in the Belgian (0.66) and Southampton-Verona (0.68) validation cohorts. Calibration was accurate in the Belgian validation cohort (slope = 0.93, intercept = 0.12), but slightly less optimal in the Southampton-Verona validation cohort (slope = 0.88, intercept = 0.32). Based on this model, three risk groups with different prognoses were identified (3-year OS of 65.4%, 33.2% and 11.8%).

Conclusions: The prediction model for 3-year OS after resection of dCCA had reasonable performance in both the derivation and geographically external validation cohort. Calibration slightly differed between validation cohorts. The model is readily available via www. pancreascalculator.com to inform patients from Western European countries on their prognosis, and may be used to stratify patients for clinical trials.

A Dutch prediction tool to assess the risk of incidental gallbladder cancers after cholecystectomies for benign gallstone disease

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Background: Despite the increasing implementation of selective histopathologic policies for post-cholecystectomy evaluation of gallbladder specimens in low-incidence countries, the fear of missing incidental gallbladder cancer (GBC) persists. This study aimed to develop a diagnostic prediction model for selecting gallbladders that require additional histopathological examination after cholecystectomy.

Methods: A registration-based retrospective cohort study of nine Dutch hospitals was conducted between January 2004 and December 2014. Data were collected using a novel secure linkage of three patient databases (nationwide network and registry of histo- and cytopathology in the Netherlands, Netherlands Cancer Registry and Dutch Hospital Database), and potential clinical predictors of gallbladder cancer were selected. The prediction model was validated internally by using bootstrapping. Its discriminative capacity and accuracy were tested by assessing the area under the receiver operating characteristic curve (AUC), Nagelkerke's pseudo-R2, and Brier score.

Results: Using a cohort of 22025 gallbladders, including 75 GBC cases, a prediction model with the following variables was developed: age, sex, urgency, type of surgery, and indication for surgery. After correction for optimism, Nagelkerke's R2 and Brier score were 0.32 and 88%, respectively, indicating a moderate model fit. The AUC was 90.3% (95% confidence interval, 86.2%–94.4%), indicating good discriminative ability.

Discussion: We developed a good clinical prediction model for selecting gallbladder specimens for histopathologic examination after cholecystectomy to rule out GBC.

Endoscopic and surgical treatment outcomes of colitis-associated advanced neoplasia: a multicenter cohort study

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a. Shared first authorship
b. Shared last authorship

Objective: To (1) assess synchronous and metachronous neoplasia following (sub)total or proctocolectomy, partial colectomy or endoscopic resection for advanced neoplasia (AN) in inflammatory bowel disease (IBD) and (2) identify factors associated with treatment choice.

Summary Background Data: IBD patients are at increased risk of AN (high-grade dysplasia (HGD) or colorectal cancer (CRC)).

Methods: In this retrospective multicenter cohort study, we used the Dutch nationwide pathology databank (PALGA) to identify patients diagnosed with IBD and colonic AN between 1991 and 2020 in seven hospitals in the Netherlands. Logistic and Fine&Gray's subdistribution hazard models were used to assess adjusted subdistribution hazard ratios (asHR) for metachronous neoplasia and associations with treatment choice.

Results: We included 189 patients (HGD n=81; CRC n=108). Patients were treated with proctocolectomy (n=33), (sub)total colectomy (n=45), partial colectomy (n=56) and endoscopic resection (n=38). Synchronous neoplasia was found in 43 patients (25.0%; (sub)total or proctocolectomy n=22, partial colectomy n=8, endoscopic resection n=13). We found a metachronous neoplasia rate of 6.1, 11.5 and 13.7 per 100 patient-years after (sub)total colectomy, partial colectomy and endoscopic resection, respectively. Endoscopic resection, but not partial colectomy, was associated with an increased metachronous neoplasia risk (asHR 4.16, 95% CI 1.64-10.54, p<0.01, figure 1) compared to (sub)total colectomy. Partial colectomy was more frequently performed in patients with limited disease and older age, with similar patient characteristics between Crohn's disease and ulcerative colitis.

Conclusions: After confounder adjustment, partial colectomy yielded a similar metachronous neoplasia risk compared to (sub)total colectomy. High metachronous neoplasia rates after endoscopic resection underline the importance of strict subsequent endoscopic surveillance.

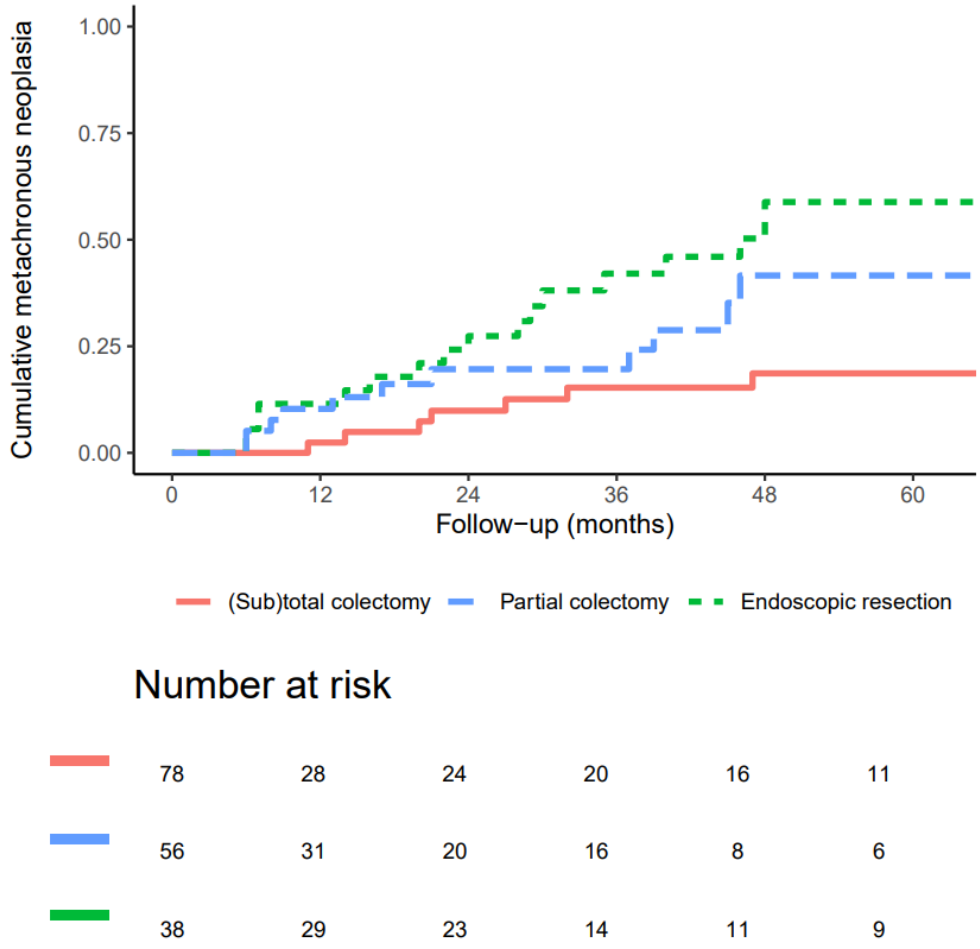

Figure 1. Cumulative incidence of metachronous neoplasia by treatment modality

Long-term impact of the COVID-19 pandemic on inflammatory bowel disease healthcare utilization: A two-year nationwide update

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a. Shared first authorship

Background: The COVID-19 pandemic has profoundly impacted utilization of inflammatory bowel disease (IBD) healthcare, with a large reduction in scheduled procedures in the early phase of the pandemic. In this nationwide study, we aimed to determine the impact of consecutive COVID-19 waves on IBD healthcare utilization including IBD-related diagnoses and procedures during the first two years of the COVID-19 pandemic.

Methods: We conducted a search in the Dutch nationwide pathology databank (PALGA) to identify IBD-related endoscopies or surgery, and new diagnoses of IBD or IBD-related neoplasia. We compared the incidence of these procedures and diagnoses during the first two years of the COVID-19 pandemic in the Netherlands (March 2020 – February 2022) with the mean incidence of the previous two years (March 2018 – February 2020).

Results: Our search yielded 89,401 (94.2%) endoscopic and 5,462 (5.8%) surgical procedures. We calculated a net reduction of 2.9% (1,391 procedures) after the first two years of the COVID-19 pandemic compared to the two pre-pandemic years (figure 1). For both endoscopic and surgical procedures, an initial net decrease after the first pandemic year was followed by a net increase after the second year (-6.2% (n=1,413) versus +0.02% (n=4) and -1.3% (n=18) versus +2.7% (n=36), respectively). We observed a net reduction of 0.9% (n=54) in new IBD diagnoses (first year: -0.8%, n=24; second year: -1.0%, n=30) and 1.9% (n=74) in IND/LGD diagnoses (first year: -10.9%, n=213; second year: +7.1%, n=139) after the two-year pandemic period. No net decrease was seen for HGD and CRC diagnoses.

Conclusion: In this nationwide cohort study covering the first two pandemic years, we observed a mitigation of the initial reduction of IBD-related procedures after the first COVID-19 wave. This illustrates the rapid adaptation of the national IBD healthcare system during subsequent COVID-19 peaks.

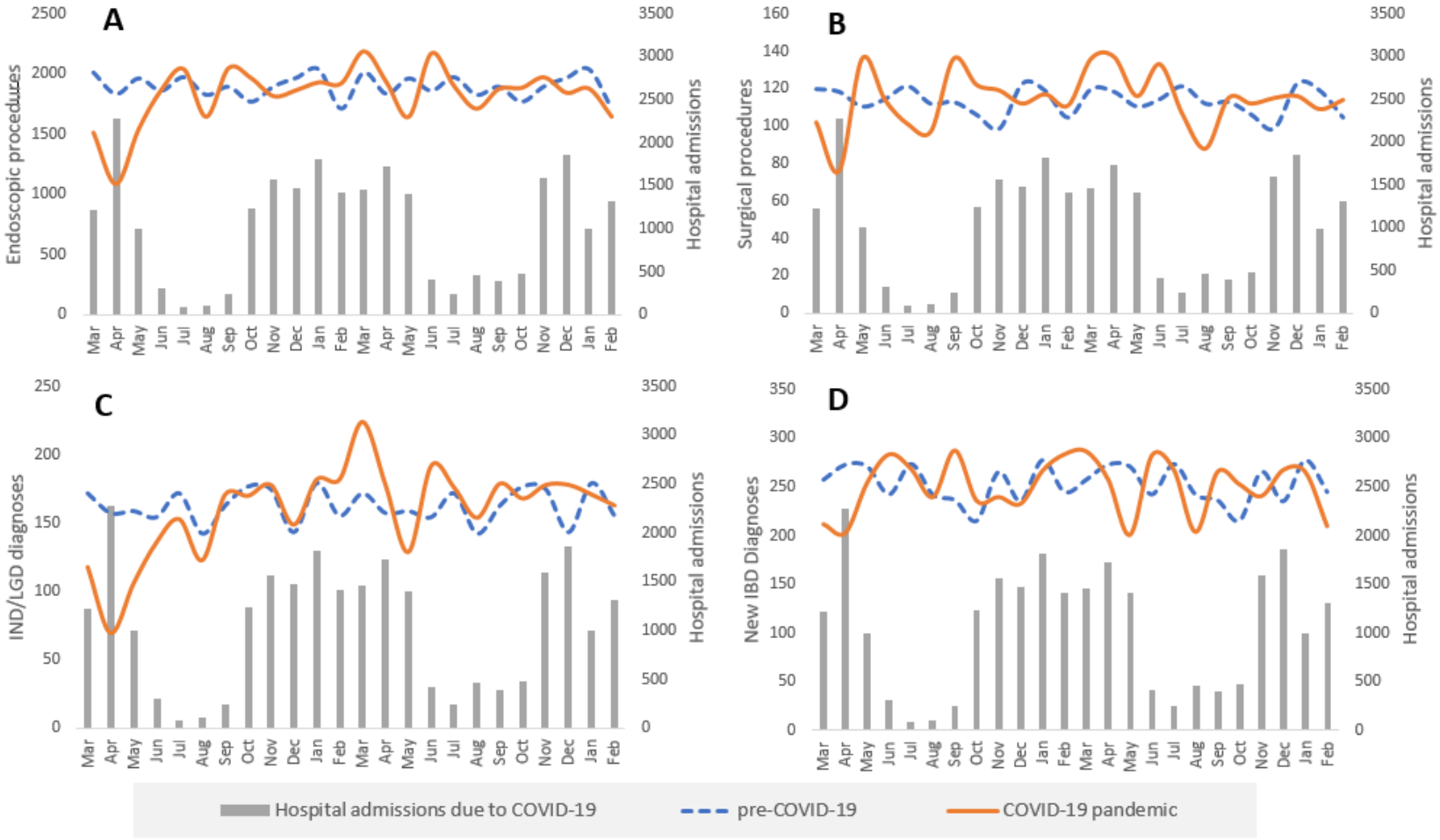

Figure 1. Total IBD-related endoscopic procedures *(A)*, surgical procedures *(B)*, indefinite and low-grade dysplasia diagnoses (IND and LGD) *(C)*, and new IBD diagnoses *(D)*. The grey bars represent the mean number of hospital beds occupied by COVID-19 patients in the Netherlands per month.

Development and Validation of an Algorithm to Identify Patients with Advanced Cutaneous Squamous Cell Carcinoma from Pathology Reports

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Background: The exceedingly high incidence rates of cutaneous squamous cell carcinoma (cSCC) result in a large number of patients with advanced cSCC (i.e., locally advanced, recurrent, and metastatic cSCC), who are at risk of death. However, nationwide data on advanced cSCC is scarce since few cancer registries include cSCC, and those that do only include the primary tumor without collecting data on follow-up.

Objective: To facilitate nationwide epidemiological research on advanced cSCC, we sought to develop and validate an algorithm that identifies advanced cSCC from free-text pathology reports.

Methods: The algorithm was based on both hierarchical histopathological codes and free text from pathology reports recorded in the National Pathology Registry (PALGA). Medical files from the Erasmus Medical Center of 186 patients with stage III/IV/recurrent cSCC and 184 patients with stage I/II cSCC between May 18, 2018 and October 9, 2020 were selected and served as the gold standard to assess the performance of the algorithm.

Results: The rule-based algorithm demonstrated a sensitivity of 91.9% (95% confidence interval (CI) 88.0-95.9), a specificity of 96.8% (95% CI: 94.2-99.3), and a positive predictive value (PPV) of 78.5% (95% CI: 74.2-82.8) for all advanced cSCC combined. The sensitivity was lower per subgroup; locally advanced (52.3-86.2%), recurrent cSCC (23.3%) and metastatic cSCC (70.0%). The specificity per subgroup was above 97%, and the PPV was above 78%, except for metastatic cSCC, which had a PPV of 62%.

Conclusion: This algorithm can be used to identify advanced cSCC patients from pathology reports and will facilitate large-scale epidemiological studies of advanced cSCC in the Netherlands and internationally after external validation.

Metachronous Colorectal Cancer Risk in Lynch Syndrome: is Extensive Colectomy Necessary for all Carriers?

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Introduction: Extensive surgery (subtotal /total colectomy) is often performed in Lynch syndrome (LS) carriers with colorectal cancer (CRC). However, MSH6 and PMS2 carriers have a lower CRC risk (low risk) than MLH1 and MSH2 LS carriers (high risk). Consequently, MSH6 and PMS2 carriers might benefit partial colectomy while metachronous CRC (mCRC) risk is acceptable.

Methods: LS carriers registered in the Dutch National Prospective LS database were linked to the Dutch National Pathology registry to identify carriers with CRC. Time-to-event analyses were performed to assess mCRC risks in the following subgroups: high risk/extensive surgery, high risk/partial colectomy, low risk/extensive surgery, and low risk/partial colectomy. Patients were censored at time of mCRC, death or assembly of database (February 28th 2022). mCRC was defined as second CRC at least six months after primary CRC.

Results: Of 1908 LS carriers, 527 (mean age 48.7, 52% male) underwent surgery for primary CRC. 121 LS carriers (23.0%) developed mCRCs (median duration 132 months after primary CRC). Ten-year mCRC incidence was 5.2% for high risk/extensive surgery, 15.7% for high risk/partial colectomy, 0% for low risk/extensive surgery, and 8.6% for low risk/partial colectomy subgroups. High risk carriers with partial colectomy had a significantly higher mCRC risk than those with extensive colectomy (HR = 2.54; 95% CI 1.39 – 4.65; p = 0.003). mCRC risk did not differ significantly between low risk/partial colectomy and high risk/extensive surgery subgroups (HR = 1.38; 95% CI 0.69 – 2.76; p = 0.37).

Conclusion: In high risk LS carriers, extensive surgery gives a significantly lower mCRC risk than partial colectomy. mCRC risk did not differ significantly between low risk carriers with partial colectomy and high risk carriers with extensive colectomy. This suggests that partial colectomy, followed by regular endoscopic surveillance, is an acceptable CRC treatment option with favorable functional outcome in MSH6 and PMS2 carriers.

MSI-H/dMMR tumours are more ubiquitous in patients with Lynch syndrome than previously anticipated

Lisa Elze, MSc; Rachel S. van der Post, MD, PhD#; Janet R. Vos, PhD#; Arjen R. Mensenkamp, PhD; Mirjam S.C. de Hullu, BSc; Iris D. Nagtegaal, MD, PhD; Nicoline Hoogerbrugge, MD, PhD; Richarda M. de Voer, PhD; Marjolijn J.L. Ligtenberg, PhD

# These authors contributed equally

Background: Individuals with Lynch syndrome are at increased hereditary risk of colorectal and endometrial carcinomas with microsatellite instability (MSI-H) and mismatch repair-deficiency (dMMR), which make these tumors vulnerable to therapy with immune checkpoint inhibitors. Our aim is to assess how often other tumor types in these individuals share these characteristics.

Methods: We retrieved the full tumor history of a historical clinic-based cohort of 1,745 individuals with Lynch syndrome via the Dutch nationwide pathology databank and calculated the standard incidence ratio (SIR) for all tumor types. MSI status, somatic second hit alterations and immunohistochemistry-based MMR status were analyzed in 236 malignancies other than colorectal and endometrial carcinomas.

Results: In individuals with Lynch syndrome MSI-H/dMMR occurred both in Lynch-spectrum and in non-Lynch-spectrum malignancies (84% vs. 39%, P<0.01). MSI-H/dMMR malignancies were found in nearly all non-Lynch-spectrum tumor types. Almost all breast carcinomas had medullary features and most of them were MSI-H/dMMR. Breast carcinoma with medullary features were shown to be associated with Lynch syndrome (SIR: 38.8, 95%CI 16.7-76.5).

Conclusions: In individuals with Lynch syndrome MSI-H/dMMR occurs in more than half of the malignancies other than colorectal and endometrial carcinomas including tumor types without increased incidence. The Lynch-spectrum tumors should be expanded to breast carcinomas with medullary features. All malignancies in patients with Lynch syndrome, independent of subtype, should be tested for MSI-H/dMMR in case therapy with immune checkpoint inhibitors is considered. Moreover, Lynch syndrome should be considered as underlying cause of all MSI- H/dMMR malignancies other than colorectal and endometrial carcinomas.

Functional Estrogen Receptor Signal Transduction Pathway Activity and Anti-Hormonal Therapy Response in Low-Grade Ovarian Carcinoma

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Background: Advanced Low-Grade Ovarian Carcinoma (LGOC) is difficult to treat. In several studies, high Estrogen Receptor (ER) protein expression was observed in LGOC, which suggests that Anti-Hormonal Therapy (AHT) is a treatment option. However, only a subgroup of patients responds to AHT and this response cannot be adequately predicted by currently used immunohistochemistry (IHC). A possible explanation is that IHC only takes the ligand, but not the activity of the whole signal transduction pathway (STP) into account. Therefore, in this study we assessed whether functional STP activity can be an alternative tool to predict response to AHT in LGOC.

Methods: Reports of patients between 1999-2019 with an ovarian mass, were identified through a PALGA (Dutch Pathology Registry) search. FFPE tumor tissue samples of patients with primary or recurrent LGOC subsequently treated with AHT were obtained (n=27). Histoscores of ER and progesterone receptors (PR) were determined. Additionally, STP activity of the ER and six other STPs known to play a role in ovarian cancer was assessed and compared to STP activity of healthy post-menopausal fallopian tube epithelium.

Results: Patients with a normal functional ER STP activity had a progression-free survival (PFS) of 16.1 months. This was significantly shorter in patients with a low and very high ER STP activity with a median PFS of 6.0 and 2.1 months respectively ($p<0.001$). Unlike ER, the PR histoscores were strongly correlated to the ER STP activity and therefore to PFS.

Conclusion: Aberrant low and very high functional ER STP activity and low PR histoscores in LGOC indicate decreased respons.

Shifting risk-stratified early prostate cancer detection to a primary healthcare setting

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Objective: To evaluate the feasibility of risk-stratified early prostate cancer (PCa) detection in a primary healthcare diagnostic facility regarding its effects on referral rate and PCa diagnoses compared to the current PSA referral threshold of 3.0 ng/mL.

Methods: In 2014, the Erasmus MC Cancer Institute and the primary healthcare diagnostic facility STAR-SHL (located in Rotterdam city centre) initiated this observational study. General practitioners (GPs) could refer men with a PCa screening wish to STAR-SHL for consultation by specially trained personnel. Referral recommendations to secondary healthcare were based on the Rotterdam Prostate Cancer Risk Calculator (RPCRC) outcome and were compared to the current Dutch GPs' PSA referral threshold of 3.0 ng/mL. Data on Pca diagnosis were extracted from the Dutch nationwide pathology databank (PALGA).

Results: Between January 2014 and February 2021, 507 men were referred for consultation and in 495 men PSA was tested (fig 1.). The median (IQR) follow-up from consultation to PALGA linkage was 43 (25-65) months. PSA was elevated in 279 men (56%), of whom 68% (95%-CI 63-74) were considered at low risk according to the RPCRC. Within 1 year after consultation, one (0.52%; 95%-CI 0.092-2.9) was diagnosed with clinically significant (cs)PCa (i.e., International Society of Urological Pathology Grade Group ≥2). Thereafter, another four (2.1%; 95%-CI 0.82-5.3) low-risk men were diagnosed with csPCa. Of the high-risk men who were biopsied within 1 year after consultation (n=61), 77% (95%-CI 65-86) were diagnosed with PCa and 49% (95%-CI 37-61) with csPCa.

Conclusion: In a primary healthcare diagnostic facility, the RPCRC could reduce up to 68% of referrals o secondary healthcare, as compared to a PSA referral threshold of 3.0 ng/mL. Deploying the RPCRC in this setting resulted in a high csPCa detection rate in those men biopsied. This strategy can be considered safe since observational data showed low proportions of csPCa among low-risk men.

Real-world data of HER2-low metastatic breast cancer: a population based cohort study

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Background: With the introduction of investigational human epidermal growth factor receptor 2 (HER2) targeting treatments, thorough understanding of breast cancer with different HER2 expression levels is critical. The aim of this study was to compare clinicopathologic characteristics and survival of patients with metastatic breast cancer according to the level of HER2 expression.

Methods: Women with distant metastatic breast cancer during 2008-2016 were selected from PALGA, the Dutch Pathology Registry, and linked to the PHARMO Database Network. Breast cancer samples were categorized as HER2 immunohistochemistry score 0 (IHC0), HER2-low or HER2+.

Results: Among women with hormone receptor (HR) positive metastatic breast cancer (n=989), 373 (38%) cancers were HER2 IHC0, 472 (48%) were HER2-low and 144 (15%) were HER2+. Among HR negative patients (n=272), the proportion of HER2 IHC0, HER2-low and HER2+ was 110 (40%),104 (38%) and 58 (21%) respectively.

Within the HR+ cohort, patients with HER2 IHC0 or HER2-low cancer were significantly older compared to HER2+ patients. This age difference was not seen in the HR- cohort. The localisation of distant metastases differed significantly between HER2 IHC0 or HER2-low versus HER2+ cases. Survival rates did not differ markedly by subtypes.

Conclusion: Substantial proportion of patients had a HER2-low breast cancer. No clear differences in survival were found when comparing HER2 and HR status. Getting more granular insights in the level of HER2 expression and addressing HER2-low as a separate category could help to assess the impact of emerging treatment strategies. Therefore, more detailed information on HER2 expression should be routinely reported.

Sex differences in survival of pediatric high-grade gliomas: a population-based cohort study

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Background: Pediatric high-grade gliomas (pHGGs) are among the most devastating childhood cancers. Girls (0-9 years) with a malignant glioma have been reported to have worse survival compared to boys. In this study, we investigated sex differences in survival for midline and hemispheric pHGGs.

Methods: Population-based data of the Netherlands Cancer Registry (NCR) was linked with the Dutch Pathology Registry (PALGA) for all children (<18 years) diagnosed with a pHGG in the Netherlands during the period 2003-2017. Site of pHGGs were revised and were categorized in a clinically relevant manner (i.e. midline and hemispheric tumors) based on the full pathology reports delivered by PALGA, and radiological data for non-biopsied cases collected by the NCR. Within these groups, sex differences in characteristics were examined utilizing Chi-squared or Fisher-exact test. Median survival time was determined by Kaplan-Meier method. Cox Proportional-Hazards models were computed to test whether differences in first-line therapy, and patient and tumor characteristics were associated with sex differences in survival.

Results: In total, 272 pHGG patients (midline n=217, 80%, hemispheric n=55, 20%) were diagnosed during 2003-2017. Twenty cases (7%) were reclassified after reviewing the full pathology report or radiological diagnosis. For midline pHGGs no significant differences were found in first-line therapy (i.e., neurosurgery, radiotherapy and systemic therapy) or patient and tumor characteristics (i.e., age, tumor location and WHO CNS grade) between boys and girls. Median survival for girls with midline pHGGs was worse compared to boys (8.8 versus 9.7 months, p=0.04). Worse outcomes for girls remained intact when adjusting for first line treatment in multivariable analysis (HR1.4 (95%CI1-1.8)). However, outcomes became comparable between boys and girls when also adding patient and tumor characteristics (HR1.2 (95%CI0.9-1.6)).

Conclusion: Our study reports that girls had a higher chance to die from a midline pHGG compared to boys, which is mostly due to differences in patient and tumor characteristics.

The diverse use of cytology and histology for diagnosis of axillary metastasis in breast cancer patients in the Netherlands

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Background: Patients with suspicion of breast cancer and axillary metastasis are examined with histology or cytology from both locations. In literature, there is a difference between these techniques in diagnostic value, cost and patient impact. In practice, these methods are used intertwined, without a national standardized protocol. In this study, the primary objective is focused on stratifying the use of cytology and histology for the diagnosis of axillary metastasis in mamma carcinoma patients in the Netherlands at primary presentation.

Methods: This is a retrospective observational study. Data is retrieved from PALGA, Dutch Pathology Registry. These include both females and males from all ages with pathological lymph node and breast examination through histology and/or cytology. Examinations are performed on the left or right side or bilaterally. The main exclusion criterium is if the lymph node examination is not of the axilla or not in 2019. The data is analysed using IBM SPSS statistics 27.

Results: Intermediate results of 714 patients show that cytology of the breast (n=128 17,9%) is less often performed then histology of the breast (n=627 87,8%). Vice versa, cytology of the axilla (n=543 76%) is more often conducted than histology of the axilla (n=238 33%). The results of the exam in the axilla differs; no possible diagnosis is given in 9,2% of cytology vs 4,2% of histology. A benign or atypical cell result is given in respectively 48,4% vs 40,0% and suspicious or malignant in 42,4% vs 58,8%.

Conclusion: In patients with suspicion of breast cancer with lymph node metastasis, cytology of the axilla and histology of the breast is more common. There is a higher rate of malignancy when histological examination of the lymph node is performed.

Disease relapse in relation to extent of lymph node sampling in patients with resected pulmonary carcinoid tumors: a population-based study

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Introduction: The predictive value of extent of per-operative lymph node (LN) sampling in relation to disease relapse in patients with pulmonary carcinoid (PC) is unknown. Furthermore, post-surgery follow-up recommendations rely on institutional retrospective studies with rather short followup. We aimed to address these short-comings by examining the relation between LN sampling and relapse in a population-based cohort with long-term follow-up.

Methods: By combining the Dutch nation-wide pathology registry (PALGA) and Netherlands Cancer Registry (NCR), all patients with surgically resected PC (2003-2012) were included in this analysis (last update 2020). Extent of surgical LN dissection was scored for number of LN sampled, location (hilar/mediastinal), and completeness of resection according to European Society of Thoracic Surgeons (ESTS) guidelines. Relapse free interval (RFI) was evaluated using Kaplan Meier and multivariate regression analysis.

Results: 662 patients were included. Median follow-up was 87.5 months. Relapse occurred in 10% of patients, mostly liver (51.8%) and locoregional sites (45%). Median RFI was 48.1 months (95% CI 36.8-59.4). Poor prognostic factors were atypical carcinoid, pN1/2 and R1/R2 resection. In 546 patients LN dissection data could be retrieved; at least one N2 LN was examined in 44% and completeness according to ESTS in merely 7%. In 477 cN0 patients, 5.9% had pN1 and 2.5% pN2 disease.

Conclusions: In this population-based cohort, relapse occurred in 10% of PC patients with a median RFI of 48.1 months thereby underscoring the necessity of long-term follow-up. Extended mediastinal LN sampling was rarely performed but systematic nodal evaluation is recommended as it provides prognostic information on distant relapse.

OTP, CD44, and Ki-67: A prognostic marker panel for relapse free survival in patients with surgically resected pulmonary carcinoid

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Introduction: Relapse occurs in 10% of patients with resected pulmonary carcinoid (PC). While typical carcinoids (TC) show low relapse rates, safe exclusion from long-term follow-up (FU, 10-15 years) is impossible partly due to high interobserver variation in the WHO classification criteria. Here, we examined if an immunohistochemical (IHC) marker panel (OTP, CD44, Ki67) improves 1) uniformity among pathologists and 2) prediction of relapse free survival (RFS) in a population-based cohort.

Material and Methods: All surgically resected PC (2003-2012) were identified from the Dutch nation-wide pathology registry (PALGA) and Netherlands Cancer Registry (NCR) registry. A casecontrol cohort (2:1 for relapse, N=170) was established. 4 pathologists independently revised all cases and assessed IHC-markers (OTP & CD44 H-score, Ki67 eyeball method). IHC cut-off values were determined using ROC curve analysis. Agreement between pathologists for diagnostic classification and IHC was determined using kappa. The remaining total cohort (N=396/566) was scored similarly.

Results: Median FU of 2:1 cohort was 86.7 months and 61% (n=35/57) of relapsed patients had TC diagnosis. Revision showed poor kappa among pathologists (mitotic count: 0.38, necrosis: 0.48), whereas IHC markers showed high kappa (Ki67: 0.92, OTP: 0.98, CD44: 0.98). ROC analysis for relapse identified optimal cut-off for OTP (<50), CD44 (<30), and Ki67 (≥5). Mean negative predictive value (NPV) for relapse increased from 0.74 (TC diagnosis) to 0.85 (IHC low-risk (OTP≥50 & CD44≥30 & Ki67<5)). IHC risk stratification for relapse of the total cohort (high-risk (n=220) and low-risk (n=314)) showed a NPV of 96%.

Conclusion: An IHC OTP/CD44/Ki67 panel increases diagnostic uniformity among pathologists and reveals a high NPV (96%) for relapse, indicating that a biomarker driven FU management for PC patients may be used to identify patients who can be excluded from long-term FU.

Long-term consequences of juvenile vulvar lichen sclerosus: a cohort study and survey of 81 adults with a histologically confirmed historical diagnosis in childhood or adolescence

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Objective: The long-term consequences of vulvar lichen sclerosus in childhood and adolescence are unknown. This study aims to analyze an unbiased cohort of adult women with a histologically confirmed diagnosis of juvenile vulvar lichen sclerosus, evaluating repercussions in adulthood.

Methods: All cases of histologically diagnosed juvenile vulvar lichen sclerosus in the Netherlands 1991-2015 were identified. Pathology material was retrieved and reviewed in a structured and semi-quantitative manner. Subjects were traced through the respective hospitals and surveyed online using the DLQI, Skindex-29, FSFI and FSDS-R and asked additional questions regarding their experience with the disease.

Results: Material was available for 313 of all 328 cases of vulvar lichen sclerosus in females 18 years old or younger registered in the Dutch Nationwide Pathology Databank (PALGA). The histological diagnosis was confirmed in 252 cases, of which 220 are currently adults. One-hundred and six of these adult women were traceable. In all, 81 women participated, median age 29.0 years, median follow-up 19.5 years. An association was found between recent complaints and the presence of spongiosis, basal apoptotic keratinocytes or high apoptotic cells in the childhood biopsy. Both quality of life and sexuality were somewhat affected in at least half of the cases. Less than half (45%) reported having regular check-ups. Forty-five (56%) had complaints within the past year, and of those with complaints 14 (31%) were not under surveillance. Sixteen respondents (20%) were not aware of the childhood diagnosis prior to this study.

Conclusions: Quality of life and sexuality are affected in a majority of adult women who had been diagnosed with juvenile vulvar lichen sclerosus, to what degree has yet to be elucidated. Once the diagnosis of juvenile vulvar lichen sclerosus has been established clinicians have a responsibility to actively council juveniles and their caretakers regarding continuing surveillance and maintenance treatment.

The immune landscape of primary stage III non-small cell lung carcinoma that developed metastasis to brain

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Background: Despite radical concurrent chemoradiotherapy, approximately 30% of patients with stage III non-small cell lung cancer (NSCLC) will develop brain metastases (BM). Previously, we highlighted the importance of the immune-response in regulating the development of organ-specific metastasis. This study aimed at investigating the (immune)microenvironment of primary stage III NSCLC in patients who developed BM.

Materials and Methods: From two multicenter clinical trials (NCT01282437, NL3335) and one retrospective series (PMID 23518381), ~200 FFPE samples of primary NSCLC were collected. Pathology reports of these patients were derived from PALGA. Gene expression of 59 primary NSCLC (13 developed BM) was measured using the PanCancer IO 360™ Panel that includes 770 cancer-related genes. The independent spatial multi-omics validation was done using 16 primary NSCLC samples (8 developed BM). Quantitative measurements of 70 immune-related antibodies were generated from one FFPE tissue section. Tumor- and immune-rich areas (ROIs) were profiled separately using the novel GeoMx™ Digital Spatial Profiler (DSP) of NanoString Technology. Each ROI was measured in three replicates in all the samples. Data analyses were performed using NanoString nSolver advanced analysis and DSP software.

Results: Twenty differentially expressed genes were identified, and higher abundance of Mast and T cells were found in primary NSCLC of patients who developed BM. Quantification by DSP showed that CD3+ cells highly infiltrated the desmoplastic ROIs of the same group (adj.p ≤ 0.05). In the same line, tumor areas expressed higher levels of CD25, FOXP3 and CD14 (adj.p ≤ 0.05), suggesting the involvement of T regulatory and myeloid-derived cells in the development of BM.

Conclusions: This is the first study that describes immune differences in primary NSCLC samples in relation to subsequent brain-specific metastasis. Spatial profiling revealed the specific organization of immune cells across the tissue landscape. The presented results will be validated in a bigger independent cohort of samples.

Cancer in patients with Inclusion Body Myositis: A nationwide study in the Netherlands: 1991-2019

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Objective: Patients with inclusion body myositis (IBM) may have a higher risk of cancer. We aimed to investigate the incidence of malignancies in IBM patients using Dutch nationwide data.

Methods: We did a retrospective nationwide cohort study using reports on muscle biopsies in PALGA's Public Pathology Database from 1991-2019. We searched for patients with a certain IBM diagnosis in combination with one or more malignancies. Malignancies were coded according to Dutch Cancer Registration (NKR) guidelines. We calculated incidence of malignancies and computed the standardized incidence ratio (SIR) for all malignancies and subgroups, where possible, by comparing our IBM population data with Dutch population data (NKR).

Results: Following screening of 16.889 muscle biopsies 368 IBM patients were included (35.1% females). Mean age at IBM diagnosis was 68.4 years (SD 8.5). 96 (26.1%) patients had one or more malignancies; in total 120 malignancies were found. Mean time between IBM diagnosis and malignancy diagnosis was 0.6 (4.7) years; we observed a peak in malignancies (n=13) in the first year following IBM diagnosis. SIR for all cancers together was 1.4 (0.5-2.3) for females and 0.6 (0.1-1.1) for males, which did not differ with the Dutch population. Out of five malignancy subgroups (n=62 malignancies) males and females showed relatively high SIRs (1.4 and 3.0) for hematopoietic and lymphoid malignancies (n=12), although not statistically significant.

Conclusion and discussion: We did not show an increased overall incidence of malignancies in IBM patients compared to the Dutch population. We found a relatively high number of malignancy diagnoses immediately following IBM diagnosis. In combination with a high SIR for hematopoietic and lymphoid malignancies (this may be an underestimation as we only evaluated tissue), which is in agreement with findings by others, these results show that careful evaluation of nationwide data in rare disorders, provide valuable insights for further research.

Development and validation of a clinico-pathological model to estimate the absolute metastatic risk in patients with cutaneous squamous cell carcinoma

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Aim: Cutaneous squamous cell carcinoma (cSCC) is a common skin cancer, and it metastasizes in 2-5% of the patients. However, current staging systems do not provide personalized estimates of the absolute metastatic risk, and are insufficient to identify high-risk patients. We developed a model to estimate the probability of metastasis in cSCC patients to support decisions on treatment and surveillance.

Methods: A nested case-control study was conducted on a cohort of 12,325 patients with a first primary cSCC registered in the Netherlands Cancer Registry (NCR), and linked to a nationwide network and registry of histo- and cytopathology (PALGA). Metastatic cases were identified (n=195), and matched to 195 non-metastatic controls. A weighted Cox regression model with Kaplan-Meier type of weights and backward selection was used to predict the probability of metastasis based on eleven routinely available clinico-pathological variables. Model performance was assessed using weighted c-index, calibration slope in 100 bootstrapped samples and decision curve analysis. The model will be validated in a cohort from England.

Results: Eight out of 11 variables remained in the prediction model. The model showed good discrimination (optimism-corrected c-index of 0.81 (95% confidence interval (CI) 0.76-0.85)), a calibration slope of 0.83 (95% CI 0.64-1.02) and higher clinical utility compared to current staging systems. As an example, the metastatic risk probability predicted by the model for a patient with the following characteristics: 70-year old male, 2cm poorly differentiated first cSCC on the face, located in the dermis, without perineural/lymphovascular invasion, is 5%. The model is available as a web-based calculator (provisional link: https://barentroia.shinyapps.io/rshinyapp/).

Conclusions: The developed clinico-pathological model provides absolute risk predictions for cSCC patients using routinely available risk factors. Once independently validated, the model could help with the management of cSCC patients.

Recurrence rates of cervical adenocarcinoma in situ patients following LLETZ, conisation or hysterectomy

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Aim: In the Netherlands the recommended treatment for cervical adenocarcinoma in situ (AIS) is either a conisation or hysterectomy1. In contrast, several international guidelines2,3,4 recommend a completing hysterectomy, even after initially fertility-sparing treatment. In order to provide supporting evidence for future guidelines, this study is the first nation-wide evaluation of recurrence rates in AIS patients following large loop excision of the transformation zone (LLETZ), conisation, and hysterectomy.

Methods: From the Dutch nation-wide pathology databank (PALGA) AIS patients were identified, who underwent treatment between 2011 and 2021 in the Netherlands. Patients who developed cervical cancer within 3 months following AIS diagnosis were excluded. AIS recurrence rates and the progression rate to adenocarcinoma were compared between the primary treatment modalities by Kaplan-Meier analyses.

Results: In total 2,486 AIS patients were identified, of whom primary treatment consisted of 1064 LLETZs, 1121 conisations and 301 hysterectomies. Recurrent AIS was diagnosed in 122 patients and progression to adenocarcinoma was diagnosed in 11 patients. The recurrence rate was 3.4% (95% confidence interval (CI): 2.2-4.5) following LLETZ, 1.3% (95% CI: 0.6-2.0) following conisation and 0% following hysterectomy. The progression rate to adenocarcinoma was 0.7% (95% CI: 0.1-1.2), 0.4% (95% CI: 0.0-0.7) and 0.4% (95% CI: 0.0-1.2) following LLETZ, conisation and hysterectomy, respectively. The AIS recurrence rate differed following LLETZ vs. hysterectomy (p=0.002) and following LLETZ vs. conisation (p=0.004), but not between conisation and hysterectomy (p=0.05). The progression to adenocarcinoma after initial treatment for AIS did not differ between treatment groups.

Conclusion: Conisation performed equally to hysterectomy, indicating it is a good alternative to hysterectomy for AIS treatment. Following LLETZ AIS recurrences were more prevalent compared to hysterectomy and conisation, but the progression rate to adenocarcinoma remained similar. Taking into account the improved fertility-outcomes following LLETZ compared to conisation, LLETZ may still be considered as fertility-sparing treatment for AIS patients.

Recurrences following fertility-sparing surgery in early-stage cervical cancer patients based on cytology and HPV in follow-up – a population-based cohort study

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Aim: This study aims to determine the prognostic value of cytology and HPV testing to detect recurrent disease in the follow-up after fertility-sparing surgery for cervical cancer.

Methods: From the Dutch National Pathology Database (PALGA) and the Netherlands Cancer Registry, data was retrieved of FIGO 2009 stage I cervical cancer patients aged 18 to 40 years, who underwent fertility-sparing surgery between 2000 and 2020 in the Netherlands. Cytology was subdivided into normal, mild dysplasia (MD), and moderate/severe dysplasia (SD)) based on the first Pap smear within 12 months of follow-up. HPV status was based on the first HPV result within 12 months of follow-up. The cumulative incidence of recurrent cervical intraepithelial neoplasia grade 2 or higher (rCIN2+) and of recurrent cervical cancer (rCXCA) was calculated by performing Kaplan-Meier analyses. Patients were censored if they were lost to follow-up or if they received a hysterectomy.

Results: In total, 1462 patients were included, of whom 1379 and 512 patients had available cytology and/or HPV within the first 12 months of follow-up, respectively. rCIN2+ was diagnosed in 128 patients (cumulative incidence: 15%), of whom 52 patients (cumulative incidence: 5.4%) developed rCXCA. After five years follow-up the cumulative incidence of rCIN2+ was 4.9%, 10.4% and 41.4% after normal cytology, MD and SD within 12 months, respectively, and the cumulative incidence of rCXCA was 2.4%, 4.1% and 22.6%, respectively. Furthermore, the 5-year cumulative incidence of rCIN2+ and rCXCA was 5.1% and 2.2% for HPV negative patients and 18.7% and 9% for HPV positive patients.

Conclusion: By using nation-wide pathology data this study was able to evaluate cytology and HPV in the follow-up of early-stage cervical cancer patients who received fertility-sparing surgery. The results demonstrate that cytology and HPV testing at the first follow-up visit within 12 months may already discriminate patients at high risk for rCIN2+ and rCXCA.

Association of margin status and DCIS size with subsequent breast cancer risk after DCIS treatment in a multinational pooled cohort comprising 47,695 women

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Background: As Ductal Carcinoma In Situ (DCIS) is a potential precursor to breast cancer (IBC), women with DCIS are treated with (breast conserving) surgery (BCS) +/- radiotherapy (RT) and/or endocrine treatment (ET). However, most DCIS-lesions will never progress to IBC, leaving many women treated without benefit. To allow informed treatment decisions, risk estimates based on large, unbiased cohorts are needed. Our aim was to study the effect of margins and DCIS-size on the risk of subsequent ipsilateral invasive breast cancer (iIBC) and ipsilateral DCIS (iDCIS).

Methods: Patient-level data of 47,695 DCIS-patients diagnosed between 1999 and 2017 in the Netherlands, UK and USA, was pooled. For the Dutch patients, data on margins and DCIS-size was largely unavailable in the cancer registry and thus manually extracted from over 12,000 pathology reports using the Dutch pathology registry (PALGA) yielding 80% and 60% availability, respectively. To account for additional missing data on DCIS-grade, margins and DCIS-size, multiple imputation was performed. Cox regression analyses were performed assessing the associations of margins and DCIS-size with the risks of iIBC and iDCIS.

Results: Risks of iIBC and iDCIS after primary DCIS were low. Involved margins was a risk factor for both iIBC and for iDCIS in women receiving BCS+/-RT. Larger DCIS-size (20-49mm and ≥50mm) increased the risk of iDCIS, but not iIBC. Furthermore, ET after BCS was not significantly associated with a lower risk of iIBC compared to BCS-only.

Conclusions: DCIS-size and margins-associated risks of iIBC and iDCIS, although independent of treatment, are low. We therefore conclude that clinicopathological factors alone don't provide sufficient clinical utility to decide which women might be suitable for less invasive treatment. Nonetheless, there is a very low risk for iIBC and iDCIS after DCIS-treatment and a modest effect at best of ET, paving the way to consider de-escalation of DCIS management.

Using TK1-expression to predict response to trifluridine/tipiracil in metastatic colorectal cancer

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Goal: Trifluridine/tipiracil (FTD/TPI) is a treatment available for refractory metastatic colorectal cancer patients. The RECOURSE trial demonstrated a modest survival benefit1, resulting in an urgent need for predictive biomarkers to avoid unnecessary toxicity. TK1 may be of prognostic value for response to FTD/TPI as it has a role in the metabolism of trifluridine. Our goal is to evaluate the predictive value of TK1-expression for response to FTD/TPI.

Methods: We examined the association between TK1-expression in tumour tissue and survival in FTD/TPI-treated patients. TK1-expression was analysed in 146 archival formalin-fixed, paraffin-embedded (FFPE) tumour samples of 110 patients, including 93 primary, 51 metastatic, and 2 recurrence samples. Immunohistochemical staining of TK1 was performed. TK1-expression was quantified using tumour cell percentage with a moderate-strong degree of staining and H-score in QuPath. Differences in patient survival per TK1-expression category based on exploratory cut-off values were compared using log-rank tests.

Results: TK1-expression varied substantially between 36 paired primary and metastatic tissue. In all patients, TK1-expression was significantly higher in primary tumor samples compared to metastatic samples. Median progression-free suvival (PFS) was significantly different across several TK1 cut-off values, e.g. longer in patients with <2.5% TK1-expressing tumour cells (104 versus 84 days). The results remained significant when analysing only primary samples. A similar trend was seen for metastatic samples, but only significant at a higher cut-off value. For overall survival (OS), no prognostic value was seen.

Conclusion: TK1-expression in metastatic samples was lower than in primary tumor samples. TK1-expression was associated with PFS but not with OS. TK1-expression was identified in previous literature as a prognostic biomarker for FTD/TPI2,3, although results were conflicting. This discordance might be explained by different cut-off values and quantification methods. The feasibility of TK1 as a biomarker is limited considering the conflicting results and varying cut-off values per tissue type.

Identification of Clinical and Histopathological Risk Factors for Radioactive Iodine Refractory Disease in Patients With Follicular Thyroid Carcinoma And Hürthle Cell Carcinoma

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Introduction: Radioactive iodine (RAI) is the preferred adjuvant treatment for patients with follicular (FTC) and Hürthle cell (HCC) thyroid carcinoma. Both tumors are rare (incidence: 1:100.000 person-years) and have relatively good prognosis (10-year survival 80-94%). However, this changes dramatically once RAI-refractory disease occurs with limited treatment options available thereafter. Data on risk factors for RAI-refractory disease are lacking, as well as studies with histopathological revision, which is crucial because of existence of high heterogeneity and complexity in correctly diagnosing these tumors. Our aim was identification clinicopathological risk factors for developing RAI-refractory disease in FTC and HCC patients.

Methods: All adult FTC and HCC patients treated at the Erasmus MC between 2000 and 2016 were included. Histopathological tissue of all patients was obtained through PALGA (Dutch Pathology Registry) and extensive revision was performed independently by two pathologists to systematically assess all variables in standardized manner. Risk factors were identified using univariate logistic regression.

Results: A total of 142 patients were included, of whom 36 became RAI-refractory (25.4%) after 2 years and 2 RAI therapies. Patients with RAI-refractory disease had significantly worse 10-year survival (62.4% vs 95.9%). Risk factors for RAI-refractory disease were high age (OR 1.05; 95%CI 1.02-1.08), N1-stage (OR 17.2; 95%CI 4.49-65.6), M1-stage (OR 4.99; 95%CI 2.03-12.3), extrathyroidal extension (OR 5.43; 95%CI 2.12-13.9), no encapsulation (OR 6.79; 95%CI 2.65-18.3), extensive vascular invasion (OR 8.29; 95%CI 2.60-26.4), and Hürthle cell histology (OR 3.98; 95%CI 1.80-8.79).

Conclusions: In this large cohort of FTC and HCC patients, 1 in 4 patients developed RAI-refractory disease after 2 years, resulting in poor prognosis. Using the unique opportunity of pathological data retrieval through PALGA, we were able to systematically revise tissue and for the first time identify important risk factors associated with RAI-refractory disease. This study lays the foundation for further research to better predict RAI-refractory disease in FTC and HCC patients.

Nationwide implementation of a multifaceted tailored strategy to improve uptake of standardized structured reporting in oncological pathology: an effect and process evaluation

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Background: Use of standardized structured reporting (SSR) is stated in national and international oncology guidelines. However, actual SSR usage varies widely in pathology. Implementation strategies improve guideline adherence. Effect and process evaluations are conducted to provide insights into success or failure of implementation strategies. We conducted both evaluations to determine the nationwide implementation of standardized structured reporting (SSR) in pathology.

Methods: We conducted an interrupted time series analysis to evaluate the effect of a nationwide implementation strategy on SSR use in pathology laboratories: All Dutch pathology laboratories send their diagnostic reports to the pathology database (PALGA), which are then automatically flagged. We retrieved this aggregated data and collected data on SSR usage on a weekly basis, 26 time points before and 26 time points after the dissemination period of the toolbox. We further conducted a process evaluation to evaluate the exposure to the strategy elements and the experiences of the users with the implementation strategy. We also tested whether being exposed to a specific element of the strategy resulted in more increase of SSR use.

Results: There was a significant increase in SSR use after the strategy introduction for reporting of gastrointestinal (p=.018) and urological (p=.003) oncological diagnoses. The “Feedback button”, an option within the templates used for standardized structured reporting to provide feedback to the provider and one of the elements of the implementation strategy, was most frequently used by the SSR users and effectiveness results showed that it increased average SSR use after strategy introduction.

Conclusions: Nationwide SSR implementation improved for specific tumor types. Next step will be to further improve the use of SSR, and simultaneously, to further develop potential benefits of high SSR use, focusing on re-using discrete pathology data. In this way, we can eventually facilitate proper treatment decisions in oncology.

Revision and expert pathologist consensus of high-grade dysplasia in IBD impacts the advanced neoplasia rate: a multicenter study

Maarten te Groen, Monica EW Derks, Iris D Nagtegaal, Charlotte P Peters, Annemarie C de Vries, Gerard Dijkstra, Tessa EH Romkens, Carmen S Horjus, Nanne K de Boer, Michiel E de Jong, Britt van Ruijven, Frank Hoentjen, Shoko Vos[a], Lauranne AAP Derikx[a] on behalf of the Dutch Initiative on Crohn's and Colitis (ICC) and the Dutch Nationwide Pathology Databank (PALGA) group

Background and aims: The diagnosis of inflammatory bowel disease (IBD) associated high-grade dysplasia (HGD) has a significant impact on clinical management, including colectomy. However, the prognosis of HGD remains unclear due to diagnostic uncertainty and low-quality data on subsequent synchronous and metachronous neoplasia. We aimed to evaluate a diagnostic strategy with revision and expert pathologist consensus of HGD and the impact on synchronous and metachronous neoplasia.

Methods: In this retrospective multicenter cohort study, we used the Dutch Nationwide Pathology Databank to identify IBD patients with HGD in seven hospitals. Histopathological specimens of the initial HGD were independently revised by two expert gastrointestinal pathologists. Inter-observer variability was assessed with Cohen's Kappa. Definitive diagnosis was established in a consensus-meeting. Synchronous and metachronous neoplasia incidences were assessed with a competing risk analysis.

Results: We included 54 IBD patients with HGD, of whom 33 (61.1%) with ulcerative colitis and 42 (77.8%) with extensive disease. Inter-observer agreement for histologic revision was fair (Kappa 0.31). After consensus, 18 (33.3%) lesions were downgraded to indefinite/low-grade dysplasia, and 6 (11.1%) were revised to colorectal cancer (CRC). Seven patients (13.0%) had synchronous CRC. Patients with downgraded lesions showed a lower cumulative advanced neoplasia (HGD/CRC) incidence compared to confirmed HGD ((Gray's test $p<0.01$), 5 year cumulative incidence 0.0% vs 26.6%, figure 1).

Conclusions: We demonstrated frequent downgrading of HGD, associated with lower metachronous neoplasia rates. This underlines the potential impact of revision and expert pathologist consensus. The high and synchronous and metachronous neoplasia rates after HGD underline the need for close surveillance.

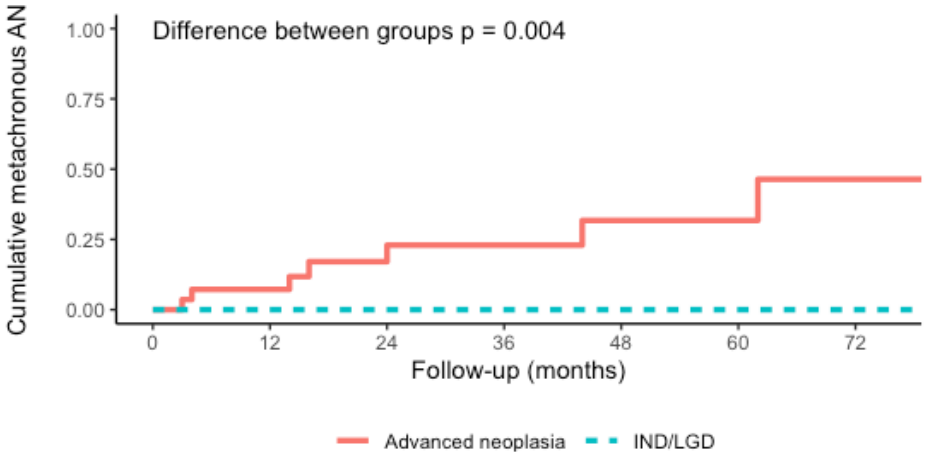


Figure 1. Metachronous AN after treatment, stratified by revised diagnosis

Quality of surveillance impacts the colitis-associated advanced neoplasia risk: a multicenter case-control study

Maarten te Groen[a], Monica Derks[a], Nathan. den Broeder, Charlotte Peters, Gerard Dijkstra, Annemarie de Vries, Tessa Romkens, Carmen Horjus, Nanne de Boer, Michiel de Jong, Iris Nagtegaal, Lauranne Derikx[b], Frank Hoentjen[b]

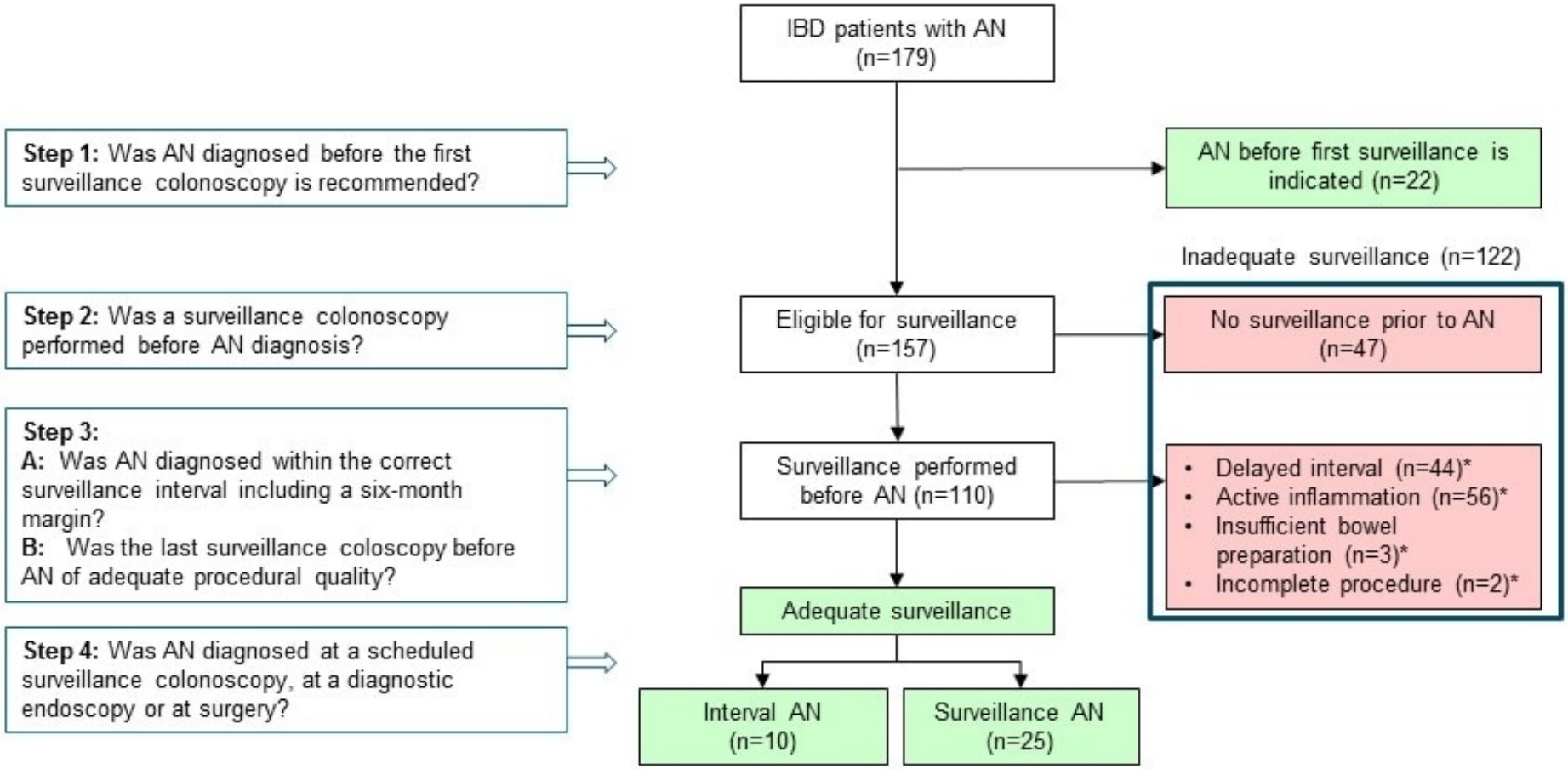
a Shared first authorship
b Shared last authorship

Background and aims: Although colorectal cancer (CRC) surveillance is embedded in clinical IBD practice, a subset of patients still develops advanced neoplasia (AN; high-grade dysplasia (HGD) and/or CRC). We aimed to assess the impact of surveillance quality on AN risk in IBD.

Methods: In this multi-center case-control study, we searched the Dutch nationwide pathology databank to identify IBD cases with AN, and controls with indefinite or low-grade dysplasia. The surveillance colonoscopy preceding the index lesion (first IND/LGD or AN) was used to assess the impact of surveillance quality. We assessed intervals, bowel preparation, cecal intubation and absence of inflammation as primary quality indicators. In addition, we assessed chromo-endoscopy, endoscopist expertise, setting and biopsy strategy. Associations of quality indicators with AN risk were determined with multivariable logistic regression analyses with Firth's correction.

Results: We included 137 cases and 138 controls. Delayed intervals (58.2% vs 39.6%) and active inflammation (65.3% vs 41.8%) were frequently present in cases and controls and were associated with AN (delayed interval: adjusted odds ratio (aOR) 2.00, 95% CI 1.07-3.81, p=0.03; active inflammation: aOR 2.46, 95% CI 1.33-4.61, p<0.01, figure 1). Surveillance compliant with primary quality indicators was associated with a reduced AN risk (aOR 0.43, 95% CI 0.22-0.91, p=0.03), similar to chromo-endoscopy (OR 0.11, 95% CI 0.01-0.89, p=0.01). Other indicators were not significantly associated with AN.

Conclusions: Surveillance compliant with quality indicators is associated with a reduced colitis-associated AN risk. Delayed surveillance intervals and active inflammation were associated with an increased AN risk. This underlines the importance of procedural quality, including endoscopic remission to optimize the effectiveness of endoscopic surveillance.


IBD patients with AN (n=179)
Step 1: Was AN diagnosed before the first surveillance colonoscopy is recommended?
AN before first surveillance is indicated (n=22)
Inadequate surveillance (n=122)
Step 2: Was a surveillance colonoscopy performed before AN diagnosis?
Eligible for surveillance (n=157)
No surveillance prior to AN (n=47)
Step 3:
A: Was AN diagnosed within the correct surveillance interval including a six-month margin?
B: Was the last surveillance coloscopy before AN of adequate procedural quality?
Surveillance performed before AN (n=110)
Delayed interval (n=44)*
Active inflammation (n=56)*
Insufficient bowel preparation (n=3)*
Incomplete procedure (n=2)*
Adequate surveillance
Step 4: Was AN diagnosed at a scheduled surveillance colonoscopy, at a diagnostic endoscopy or at surgery?
Interval AN (n=10)
Surveillance AN (n=25)

High-grade vulvar intraepithelial neoplasia: comprehensive characterization and long-term vulvar carcinoma risk

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Aims: Given the distinct vulvar squamous cell carcinoma (VSCC) risk between high-grade squamous intraepithelial lesion (HSIL) and differentiated vulvar intraepithelial neoplasia (dVIN), adequate diagnosis is essential but can be challenging. We comprehensively characterized a large population-based series of high-grade VIN and assessed the cancer risk.

Methods and Results: Vulvar lesions of 751 patients, originally reported as high-grade VIN, were categorized by revision, integrating p16INK4a, p53 and MIB-1 immunostaining, and HPV DNA results. Cancer risk was calculated by Kaplan-Meier analysis. Integrated analyses resulted in 88.5% HPV-associated lesions (76.6% HSIL, 11.6% ≤LSIL and 0.4% VSCC), 10.1% HPV-independent lesions (5.9% dVIN, 4.1% non-dysplastic lesions, and 0.1% VSCC) and 1.3% inconclusive lesions. HSIL demonstrated block-positivity for p16INK4a in 99.0% and HPV positivity in 99.6%. In HPV-associated lesions, a p53 wild-type mid-epithelial staining pattern was common (48.4%) while this pattern was not observed in HPV-independent lesions. DVIN showed a heterogeneous morphologic spectrum with a mutant p53 pattern in 77.3% and HPV positivity in 11.4%, the latter always combined with mutant p53 and negative p16INK4a. Strikingly, 84% of dVIN was originally not reported as dVIN, while for HSIL this was 0%. The 10-year cumulative VSCC risk was 8.2% for HSIL and 53.4% for dVIN ($p<0.001$).

Conclusions: To conclude, dVIN is poorly recognized despite of the high cancer risk, emphasizing the need to use additional diagnostic biomarkers. Immunohistochemistry by p16INK4a and p53 is strongly recommended for optimal categorization into HPV-associated and HPV-independent VIN. One should be aware of the common patterns and pitfalls when using those biomarkers.

Concordance between primary colorectal cancer and ovarian metastases for genetic mutations and mismatch repair status: a Dutch cohort study

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Objective: The genetic characteristics and mismatch repair (MMR) status of the primary tumor and corresponding metastases in colorectal cancer (CRC) are generally considered to be highly concordant. This implies that either the primary or metastatic tumor can be used for testing gene mutation and MMR status. However, whether this is also true for CRC and their ovarian metastases is currently unknown. Ovarian metastases generally show a poorer response to systemic therapy compared to other metastatic sites. Differences in genetic characteristics or discordance in the MMR status between primary CRC and ovarian metastases could possibly explain this difference in therapy response.

Methods: The study cohort was selected from CRC patients treated in two Dutch hospitals. Eligible patients with CRC and ovarian metastasis who were surgically treated between 2011 and 2018 were included. CRC and corresponding ovarian metastatic tissues were paired. Gene mutation status was established using next generation sequencing, while the MMR status was established using either immunohistochemistry or microsatellite instability analysis.

Results: Matched samples of CRC and ovarian metastasis from 26 patients were available for analysis. A concordance of 100% was detected for both gene mutation and MMR status.

Conclusions: Complete concordance in gene mutation and MMR status was found between MMR proficient CRC and their matching ovarian metastasis. Consequently, it can be concluded that biomarker testing of MMR proficient CRC tissue is sufficient, and that additional testing of metastatic ovarian tissue is not necessary. Differences in therapy response between ovarian metastases and other metastases from CRC are thus unlikely to be caused by differences in the genetic status.

Occult lymph node metastases in patients without residual muscle-invasive bladder cancer at radical cystectomy with or without neoadjuvant chemotherapy: a nationwide study of 5417 patients

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PURPOSE: Little is known about the prevalence of occult lymph node metastases (LNM) in muscle-invasive bladder cancer (MIBC) patients with pathological downstaging of the primary tumor. We aimed to estimate the prevalence of occult LNM in patients without residual MIBC at radical cystectomy (RC) with or without neoadjuvant chemotherapy (NAC) or neoadjuvant radiotherapy (NAR), and to assess overall survival (OS).

METHODS: Patients with cT2-T4aN0M0 urothelial MIBC who underwent RC plus pelvic lymph node dissection (PLND) with curative intent between January 1995–December 2013 (retrospective Netherlands Cancer Registry (NCR) cohort) and November 2017–October 2019 (prospective NCR-BlaZIB cohort (acronym in Dutch: BlaaskankerZorg In Beeld; English: Insight into bladder cancer care)) were identified from the nationwide NCR. The prevalence of occult LNM was calculated and OS of patients with <(y)pT2N0 vs. <(y)pT2N+ disease was estimated by the Kaplan–Meier method.

RESULTS: In total, 4657 patients from the NCR-cohort and 760 patients from the NCR-BlaZIB cohort were included. Of 1374 patients downstaged to <(y)pT2, 4.3% (N=59) had occult LNM; 4.1% (N=49) of patients with cT2-disease and 5.6% (N=10) with cT3-4a-disease. This was 4.0% (N=44) in patients without NAC or NAR, 4.5% (N=10) in patients with NAC, and 13.5% (N=5) in patients with NAR but number of patients treated with NAR and downstaged disease was small. The prevalence of <(y)pT2N+ disease was 4.2% (N=48) in the NCR-cohort and 4.6% (N=11) in the NCR-BlaZIB cohort. For patients with <(y)pT2N+ and <(y)pT2N0, median OS was 3.5 years (95%CI 2.5–8.9) versus 12.9 years (95%CI 11.7–14.0), respectively.

CONCLUSION: Occult LNM were found in 4.3% of patients with cT2-4aN0M0 MIBC with (near-)complete downstaging of the primary tumor following RC plus PLND. This was regardless of NAC or clinical T-stage. Patients with occult LNM showed considerable worse survival. These results can help in counseling patients for bladder-sparing treatments.

Nasopharyngeal carcinoma: nationwide trends in subtype specific incidence and survival over three decades in a non-endemic area

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Background: Nasopharyngeal carcinoma (NPC) is rare in western countries. In endemic areas, non-keratinizing NPCs, which are associated with Epstein-Barr virus (EBV), comprise >95% of cases, and incidence decreases. Less is known about changes in incidence and clinical outcome in non-endemic regions. We aimed to identify trends in incidence and survival of NPC, subdivided by EBV status and histopathological subtype, over a 30-year period in the Netherlands.

Methods: Anonymized data from the Netherlands Cancer Registry and the Dutch Nationwide Pathology Databank (PALGA) for the period 1989-2018 were linked to identify and classify NPC cases.

Results: Incidence of NPC remained stable, with an annual percentage change (APC) of -0.2. (95% CI -0.9; 0.5). EBV testing became routine only in the last decade, the incidence of EBV positive tumors remained stable over this period (APC 1.2, 95% CI -1.3; 3.8). An increase in EBV negative tumors (APC: 7.1, 95% CI 2.5; 11.9) and a decrease in untested tumors was found (APC: -10.7, 95% CI -15.7; -5.7). The incidence of non-keratinizing, differentiated tumors increased (APC: 3.8, (95% CI 2.2; 5.5) while the incidence of other histological subtypes remained stable. Overall survival was better in patients diagnosed after 1998 (hazard ratio 0.8, 95% CI 0.6; 0.9).

Conclusion: Testing for EBV increased over time, and a stable incidence of EBV positive NPC over the last 10 years. The rising incidence of non-keratinizing, differentiated NPC mirrors data from the US and suggests a shift in non-endemic regions.

Peripheral blood cytopenias in the ageing general population and risk of incident hematological disease and mortality

Isabelle A. van Zeventer, Aniek O. de Graaf, Melanie M. van der Klauw, Edo Vellenga, Bert A. van der Reijden, Jan Jacob Schuringa, Arjan Diepstra, Luca Malcovati, Joop H. Jansen, Gerwin Huls

Peripheral blood cytopenias may precede development of hematological malignancies and frequently pose clinical challenges in the elderly. The natural course of (mild) cytopenias during ageing and association with hematological disorders in community-dwelling individuals are not well studied. Within the population-based Lifelines cohort (n=167729), we studied changes in peripheral blood counts, occurrence of cytopenias and associated hematological outcomes in the context of ageing. Development of hematological malignancies and (cause-specific) mortality were evaluated by linkage to nationwide registries. Anemia and thrombocytopenia emerged with higher age, in line with a general age-related decline in these blood counts. For neutropenia, no increase in prevalence upon higher age was observed. Using standard reference limits to define cytopenias, anemia (HR 1.84, 95%CI 1.59-2.12) and thrombocytopenia (HR 1.58, 95%CI 1.32-1.89) and especially the concomitant presence of anemia and thrombocytopenia (HR 4.75, 95%CI 2.98-7.55) associated with inferior overall survival. Only a minor proportion of deaths was explained by diagnosed hematological malignancies, with the majority attributable to other causes. Neutropenia, either isolated (HR 0.88, 95%CI 0.73-1.06) or combined with another cytopenia, did not affect overall survival. For individuals ≥60 years, 5-year cumulative incidence of hematological malignancies was 0.60% (95%CI 0.50%-0.70%), with higher incidences among those with anemia (P<0.001) or thrombocytopenia (P<0.001) but not neutropenia (P=0.201). Highest cumulative incidences of diagnosis and mortality from hematological malignancies were observed for individuals with >1 cytopenia. We conclude that anemia and thrombocytopenia but not neutropenia associate with inferior overall survival of community-dwelling individuals. Hematological malignancies develop in a small fraction of these cases.

Upregulation of Filaggrin-2 in Scleritis Using Tissue Mass Spectrometry

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Purpose: Scleritis is a severe inflammatory ocular disorder with unknown pathogenesis. We investigated healthy sclera as well as sclera affected by non-infectious scleritis for differentially expressed proteins using a mass spectrometry approach.

Methods: We collected scleral samples of enucleated eyes due to severe non-infectious scleritis (n=3), and control scleral tissues (n=5), all exenterated eyes for eyelid carcinomas without scleral invasion. Samples were prepared for the nano LC-MS mass spectrometer, data was analyzed using proteomics software (Scaffold), and is available via ProteomeXchange (identifier PXD038727). Samples were also stained for immuno-histopathological evaluation.

Results: Mass spectrometry identified 629 proteins within the healthy and diseased scleral tissues, whereof collagen type I was the most abundantly expressed protein. Collagen type II-XII was also present. Filaggrin-2, a protein that plays a crucial role in epidermal barrier function, was found upregulated in all scleritis cases. In addition, other epithelial associated proteins were upregulated (such as keratin 33b, 34 and 85, epiplakin, transglutaminase-3, galectin 7, and caspase-14) in scleritis. Further, upregulated proteins involved in regulation of the cytoskeleton (vinculin and myosin 9), and housekeeping proteins were found (elongation factor-2 and cytoplasmic dynein 1) in our study. Upregulation of filaggrin-2 and myosin-9 was confirmed with immunohistochemistry, the latter protein showing co-localization with the endothelial cell marker ETC-related gene (ERG), indicating neovascularization in scleral tissue affected in scleritis.

Conclusions: We found upregulation of filaggrin-2 and signs of neovascularization in scleral tissue of patients with non-infectious scleritis. Further research, ideally including more scleritis cases, is needed to validate our findings.

DNA methylation analysis for the triage of HPV-positive women in cervical cancer screening: results from the IMPROVE trial

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Background. Triage strategies are needed for primary HPV-based cervical cancer screening to identify women requiring colposcopy. With increasing interest in self-sampling, triage strategies preferably should both be directly applicable to clinician-collected and self-collected screening samples. We assessed the performance of DNA methylation analysis on clinician- and self-collected cervical samples to triage HPV-positive women.

Methods. We conducted a post-hoc analysis within a Dutch population-based HPV-positive cohort derived from the IMPROVE trial (NTR5078). The paired-screen positive trial design allowed for analysis of clinician- and self-collected samples of the same HPV-positive women. Histology results were retrieved from pathology laboratories through PALGA, and corresponding formalin-fixed paraffin-embedded (FFPE) tissue blocks were collected through the DNTP infrastructure. Clinician-collected (n=715), self-collected (n=593) and tissue samples (n=116) were evaluated for methylation markers ASCL1 and LHX8 by quantitative methylation-specific PCR. The sensitivity and specificity for the detection of cervical intraepithelial neoplasia grade 3 and cancer (CIN3+) were determined with Wald 95% confidence intervals (95%CI). Spearman's rank correlation coefficient was used to analyse correlations between methylation levels in paired samples.

Results. Methylation levels in both clinician- and self-collected samples increased with severity of the underlying cervical disease ($p<0.0001$). A moderate correlation between ASCL1/LHX8 methylation levels in paired clinician-collected, self-collected, and FFPE samples was observed (Spearman's Rho range 0.359-0.563). The ASCL1/LHX8 marker panel yielded a CIN3+ sensitivity of 76.9% (70/91; 95%CI 68.3-85.6%) at a specificity of 74.5% (465/624; 95%CI 71.1-77.9%) for clinician-collected samples, and a CIN3+ sensitivity 73.3% (63/86; 95%CI 63.9-82.6%) with corresponding specificity of 61.1% (310/507; 95%CI 56.9-65.4%) for self-collected samples. The relative sensitivity and specificity for detecting CIN3+ were 0.95 (95%CI 0.82-1.10) and 0.82 (95%CI 0.75-0.90) for self- versus clinician-collected sampling.

Conclusions. The ASCL1/LHX8 methylation marker panel constitutes a feasible direct triage method for detecting CIN3+ in HPV-positive women participating in routine HPV-based screening using either clinician-collection or self-sampling.

Ambiguous melanocytic lesions: A retrospective cohort study of incidence and outcome of melanocytic tumor of uncertain malignant potential (MELTUMP) and superficial atypical melanocytic proliferation of uncertain significance (SAMPUS) in the Netherlands

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Background: Melanocytic tumor of uncertain malignant potential (MELTUMP) and superficial atypical melanocytic proliferation of uncertain significance (SAMPUS) are descriptive and provisional terms for melanocytic tumors with ambiguous histopathological features that are not easily classified as either benign or malignant.

Objective: To investigate the incidence and clinical outcome of MELTUMP and SAMPUS in the Netherlands.

Methods: In this retrospective cohort study, we reviewed all diagnoses of MELTUMP and SAMPUS from PALGA: the Dutch Nationwide Pathology Databank from 1991 to October 1, 2021. Clinical outcome was studied for cases diagnosed until October 1, 2018.

Results: A total of 1685 MELTUMP and 1957 SAMPUS were identified with an annual incidence of 150 to 300 cases. Metastatic behavior was seen in 0.7% of all initially diagnosed MELTUMP. All SAMPUS remained free of metastases.

Limitations: Reassessment of pathology slides and confirmation of clonality between primary and metastatic lesions remained outside the scope of this study.

Conclusion: Despite the ‘uncertainty’ in the nomenclature, our results demonstrate a low malignant potential for MELTUMP and no malignant potential for SAMPUS. We emphasize the importance of consultation for ambiguous melanocytic lesions and to limit the MELTUMP/SAMPUS terminology to legitimately uncertain or unclassifiable cases.

The measured distance between tumor cells and the peritoneal surface predicts the risk of peritoneal metastases and offers an objective means to differentiate between pT3 and pT4a colon cancer

Emma S. Zwanenburg, Daniel D. Wisselink, Charlotte E. L. Klaver, Jarmila D. W. van der Bilt, Pieter J. Tanis, Petur Snaebjornsson, on behalf of the COLOPEC trial collaborators.

Background: Substantial variability exists in what pathologists consider as pT4a in colorectal cancer when tumor cells are within 1 mm to the free peritoneal surface. This study aimed to determine if the measured sub-millimeter distance between tumor cells and the free peritoneal surface would offer an objective means of stratifying patients according to the risk of developing peritoneal metastases.

Methods: Histological slides of patients included in the COLOPEC trial, with resectable primary c/pT4N0-2M0 colon cancer, were centrally reassessed. Specific tumor morphological variables were collected, including distance from tumor to free peritoneal surface, measured in micrometers (µm). The primary outcome, 3-year peritoneal metastasis rate, was compared between four groups of patients stratified for relation of tumor cells to the peritoneum: 1) Full peritoneal penetration with tumor cells on the peritoneal surface, 2) 0-99 µm distance to the peritoneum, 3) 100-999 µm to the peritoneum, and 4) ≥1000 µm to the peritoneum, by using Kaplan-Meier analysis.

Results: In total, 189 cases were included in the present analysis. Cases with full peritoneal penetration (n=89), 0-99 µm distance to the peritoneal surface (n=34), 100-999 µm distance (n=33), and ≥1000 µm distance (n=33), showed significantly different 3-year peritoneal metastases rates of 25% vs 29% vs 6% vs 12%, respectively (Log Rank, p=0.044). N-category did not influence the risk of peritoneal metastases in patients with a tumor distance beyond 100 µm, while only the N2 category seemed to result in an additive risk in patients with a distance of 0-99 µm.

Conclusion: The findings of this study suggest that the measured shortest distance between tumor cells and the free peritoneal surface is useful as an objective means of stratifying patients according to the risk of developing peritoneal metastases. This simple measurement is practical and may help in providing a precise definition of pT4a.