Palga-prijs 2024

Abstracts

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Voorwoord

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

De Palga-prijs wordt uitgereikt aan de onderzoeker met het beste abstract van onderzoek waarbij gebruik is gemaakt van Palga-gegevens.

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

Onderzoekers werden uitgenodigd om een abstract in te dienen. Het abstract kon zowel een huidig, nog niet gepubliceerd onderzoek betreffen als een onderzoek dat in 2022 of 2023 gepubliceerd is. 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.

Voor de Palga-prijs 2024 werden 26 abstracts ingediend.

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

- Originaliteit van de vraagstelling
- Heldere/duidelijke schrijfstijl
- Kwaliteit van de methodologie
- Klinische relevantie
- Goed gebruik van de Palga-databank als onderzoeksbron

In de eerste ronde werd elk abstract door één patholoog en één epidemioloog/KMBP'er beoordeeld. Dit resulteerde in negen best beoordeelde abstracts. Deze werden vervolgens in de tweede ronde door ieder lid van de CW opnieuw beoordeeld.

De winnaar van de Palga-prijs 2024 is **drs. Koen Zwart** met het abstract getiteld:

Increased risk of deficient mismatch repair colorectal cancer and its immediate precursor lesions after kidney transplantation

In dit boekje zijn 24 van de 26 beoordeelde abstracts gebundeld. Voor twee abstract werd geen toestemming verkregen om te publiceren op de Palga-website. De overige abstracts staan op alfabetische volgorde. Het winnende abstract is als eerste opgenomen.

Inhoud *Pagina*

Pagina

Increased risk of deficient mismatch repair colorectal cancer and its immediate precursor lesions after kidney transplantation

Koen Zwart, Rob C.M. van Kruijsdijk, Valentina Angerilli, Marije C. Baas, Miriam Koopman, Iris D. Nagtegaal*, Guus M. Bol*

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Background

Kidney transplant recipients have an increased colorectal cancer (CRC) risk. We hypothesize that impaired immunosurveillance allows progression of sessile serrated lesions (SSL), leading to a higher incidence of immunogenic mismatch repair deficient (dMMR), but not mismatch repair proficient (pMMR) CRC.

Methods

The Dutch pathology registry (PALGA) was linked with the national transplant and cancer registry by probabilistic matching. If mismatch repair (MMR) status was unknown, the tissue was collected centrally, and the MMR status was determined with immunohistochemistry. Combined with data from Statistics Netherlands (CBS), standardized incidence ratios (SIR) were calculated with adjustment for age, sex, and incidence year. Within the Dutch CRC screening program, kidney transplant patients were 1:4 matched to controls based on age, sex, and year of screening to assess premalignant lesions.

Results

20,181 kidney transplant patients were identified between 2000-2021. 218 CRCs were observed, resulting in an overall SIR of 1.11 (95%CI:0.96-1.26). dMMR CRC occurred in 27% of kidney transplant patients with CRC (49/181) compared to 13% in the general CRC population (5,640/42,982). This resulted in a relative risk of 2.1 (95%CI:1.6-2.6) which remained significant when stratified for stage. The dMMR SIR was 3.05 (95%CI:2.18-4.25) and pMMR SIR 0.97 (95%CI:0.78-1.22). 1,336 polyps were identified in 488 kidney transplant patients that participated in the Dutch CRC screening program. SSL with dysplasia occurred more often in the transplantation cohort compared to the matched cohort, relative risk 2.3 (95%CI:1.3-3.9).

Conclusion

This nationwide study linked four different registries to retrieve high-quality pathology and clinical data of all kidney transplant patients in the Netherlands over several decades. We show an increased risk to develop dMMR CRC after kidney transplantation but not pMMR CRC in this matched analysis. This is supported by the increased detection of SSL with dysplasia (the

immediate precursor of dMMR CRC) in kidney transplant patients at population screening. This would imply the need for adaptations in CRC screening for this patient group.

Penile Intraepitheliale Neoplasia (PeIN) in the Netherlands: A Comprehensive 15-Year Study on Incidence, Recurrence, and Progression to Invasive Malignancy

Ofir Avitan, Lucas van Maaren, Manon Vreeburg, Arno G J L H van Leenders, Elise Bekers, Henk van der Poel, Oscar Brouwer.

Background

Penile intraepithelial neoplasia (PeIN), primarily linked to high-risk Human papillomavirus (hrHPV) infection, has witnessed a notable surge in cases based on recent retrospective studies in Sweden, Denmark, and the Netherlands. However, existing literature lacks comprehensive insights into PeIN recurrence and its progression to invasive cancer.

Research question

This study aims to elucidate the trend in PeIN incidence, emphasizing associated recurrence and progression rates and establishing correlations with PeIN I-III, representing mild, moderate, and high dysplasia grades, respectively.

Methods

Utilizing data from the Netherlands nationwide histopathology registry (PALGA) spanning 2008 to 2022, this retrospective analysis focused on patients diagnosed with primary PeIN, classified as PeIN I-III. Incidence rates, age-standardized rates (ASR), recurrence rates, progression rates, HPV status, dysplasia grades, and lesion locations were calculated, with a correlation to PeIN I-III.

Results

Among 2,456 Dutch patients from 2008 to 2022, 1,705 primary PeIN cases were found, with a median age at diagnosis of 60. The overall incidence rose from 1.28 in 2008 to 1.84 in 2022 per 100,000 men, doubling for those over 60. Positive hrHPV cases exhibited a 16% recurrence rate, compared with 5% for negative cases. PeIN I, II, and III diagnoses were distributed at 12%, 10%, and 75%, respectively. A significant recurrence rate of 14%, particularly in high-grade PeIN. Progression occurred in 7.3% of cases, predominantly in PeIN III cases, with an average progression time of 10 months.

Conclusion

This study underscores the concerning rise in PeIN incidence, notably in older men, with a significant correlation to high-risk HPV infection. The substantial recurrence rate, especially in high-grade PeIN, emphasizes the need for vigilant follow-up, and the progression to invasive carcinoma, particularly in PeIN III cases, underscores the importance of early detection and consideration of more radical intervention.

Improving the diagnosis of serous tubal intraepithelial carcinoma (STIC) using deep learning

Joep M A Bogaerts, John-Melle Bokhorst, Michiel Simons, Majke H D van Bommel, Miranda P Steenbeek, Joanne A de Hullu, Jeroen A W M van der Laak.

Background & objective

Reliable diagnosis of Serous Tubal Intraepithelial Carcinoma (STIC), a precursor of high-grade serous ovarian carcinoma, is critical for the safety of patients who opt for alternative risk-reducing surgery. Moreover, women with STIC seem to be at an increased risk of developing peritoneal carcinoma, raising issues about management and follow-up. Accurate detection of STIC is therefore essential, however, reproducibility of STIC among pathologists is suboptimal with many pathologists having limited experience with the diagnosis. Our goal is to develop a deep learning algorithm which can help pathologists diagnose these lesions.

Methods

A dataset of STIC (n=323) and controls (n=359) was collected and split into three sub-cohorts: A (n=169), B (n=327) and C (n=186). A reference standard was set for cohorts A and B, by an international panel review amongst 15 gynecologic pathologists. Cohort A was used to train and validate a deep-learning algorithm (U-Net with resnet50 backbone) to differentiate STIC from benign tubal epithelium. Cohorts B and C served as test sets.

Results

The model's performance was evaluated by ROC curve analysis, achieving an AUC of 0.98 (95% CI: 0.96-0.99) on cohort B, and 0.95 (95% CI: 0.90-0.99) on cohort C. Visual inspection of all cases confirmed accurate detection of STIC in relation to the morphology, immunohistochemistry, and the reference standard.

Conclusion

We present a deep-learning model that can automatically detect STIC/STIL in digitalized whole slide images of fallopian tube specimens. This model's output can aid pathologists in detecting STIC, and can contribute towards a more reliable and reproducible diagnoses.

Non–muscle-invasive bladder cancer molecular subtypes predict differential response to intravesical Bacillus Calmette-Guérin

Florus C. de Jong, Teemu D. Laajala , Robert F. Hoedemaeker, Kimberley R. Jordan, Angelique C. J. van der Made, Egbert R. Boevé, Deric K. E. van der Schoot, Bart Nieuwkamer, Emiel A. M. Janssen, Tokameh Mahmoudi, Joost L. Boormans, Dan Theodorescu, James C. Costello, Tahlita C. M. Zuiverloon

The recommended treatment for patients with high-risk non–muscle-invasive bladder cancer (HR-NMIBC) is tumor resection followed by adjuvant Bacillus Calmette-Guérin (BCG) bladder instillations. However, only 50% of patients benefit from this therapy. If progression to advanced disease occurs, then patients must undergo a radical cystectomy with risks of substantial morbidity and poor clinical outcome. Identifying tumors unlikely to respond to BCG can translate into alternative treatments, such as early radical cystectomy, targeted therapies, or immunotherapies. Here, we conducted molecular profiling of 132 patients with BCG-naive HR-NMIBC and 44 patients with recurrences after BCG (34 matched), which uncovered three distinct BCG response subtypes (BRS1, 2 and BRS3). Patients with BRS3 tumors had a reduced recurrence-free and progression-free survival compared with BRS1/2. BRS3 tumors expressed high epithelial-to-mesenchymal transition and basal markers and had an immunosuppressive profile, which was confirmed with spatial proteomics. Tumors that recurred after BCG were enriched for BRS3. BRS stratification was validated in a second cohort of 151 BCG-naive patients with HR-NMIBC, and the molecular subtypes outperformed guideline-recommended risk stratification based on clinicopathological variables. For clinical application, we confirmed that a commercially approved assay was able to predict BRS3 tumors with an area under the curve of 0.87. These BCG response subtypes will allow for improved identification of patients with HR-NMIBC at the highest risk of progression and have the potential to be used to select more appropriate treatments for patients unlikely to respond to BCG.

The limited value of sentinel lymph node biopsy in lentigo maligna melanoma: A nomogram based on the results of 29 years of the nationwide Dutch pathology registry (PALGA)

Yannick S Elshot, Tristan V M Bruijn, Wouter Ouwerkerk, Lies H Jaspars, Bart A van de Wiel, Biljana Zupan-Kajcovski, Menno A de Rie, Marcel W Bekkenk, Alfons J M Balm, W Martin C Klop

Background:

The value of sentinel lymph node biopsy (SLNB) for lentigo maligna melanoma (LMM) patients remains to be determined, as the reported average yield of positive lymph nodes is limited. In this nationwide cohort study, we wanted to identify LMM patients with an increased risk of SLNB-positivity.

Methods:

LMM with an SLNB indication according to the 8th AJCC melanoma guidelines were retrospectively identified from the nationwide PALGA Database. A penalized logistic regression analysis was performed to determine the optimal combination of clinicopathological factors predicting SLNB-positivity.

Results:

Between 1991 and 2020, 1989 LMM patients met our inclusion criteria. SLNB was performed in 16.7% (n = 333) and was positive in 7.5% (25/333). The false-negative rate was 21.9%. Clinically detectable regional lymph node (LN) metastases were found in 1.3% (n = 25). Clinicopathological characteristics best predictive for SLNB-positivity (Odds ratio; 95% CI) were ulceration 1.59 (0.444.83), T4-stage (1.81; 0.43-6.2), male sex (1.97; 0.79-5.27), (lymph)angioinvasion (5.07; 0.94-23.31), and microsatellites (7.23; 1.56-32.7) (C-statistic 0.75). Age was inversely associated with SLNB-positivity (P = 0.007), with a decreasing OR (95%. CI) of 0.1 (0.01–0.51) (P > 0.001) for the 51–60 age group to 0.09 (0.09–0.59) (P = 0.032) for the >80 age group. A minimal 2 and 5-year follow-up period was available for 85% (n = 1701) and 64.4% (n = 1281) of the patients, respectively. Regional LN recurrences were detected in 4.2% (n = 83) patients. Most (n = 74; 89.2%) cases had no evidence of regional LN metastases at baseline.

Conclusion:

Our findings indicate a limited positive yield of SLNB in LMM patients when performed according to current melanoma guideline recommended indications, especially with increasing age. Based on the PALGA data, we identified high-risk clinicopathological features and developed a nomogram to predict the risk of a positive SLNB.

Colorectal carcinomas from path_MSH6 carriers display a lower degree of microsatellite instability and evoke weaker immune responses

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Introduction:

Lynch syndrome (LS) displays considerable phenotypic and molecular variation among carriers of pathogenic mismatch repair gene variants (path_MMR). Our recent study highlighted that colorectal carcinomas (CRCs) in path_MSH6 carriers exhibit fewer insertion/deletion mutations compared to other MMR mutation groups, suggesting a potentially lower degree of microsatellite instability (MSI) and weaker immune responses.

Methods:

We assessed the degree of MSI by analyzing mutations in twenty coding microsatellites (cMS) in 95 LS CRCs (39 MSH6, 18 MLH1, 16 MSH2, and 22 PMS2 CRCs) and 35 sporadic MSI CRCs. We compared mutation frequencies and mutant allele ratios among MMR groups and investigated associations between identified mutation profiles, HLA-A*02:01 status, and the predicted immunogenicity of cMS mutation-derived frameshift peptides. Immune cell frequencies and spatial context were examined using imaging mass cytometry.

Results:

MSH6 CRCs exhibited significantly lower mutation frequencies and mutant allele ratios across most cMS compared to other MMR groups. These CRCs also displayed the lowest T cell infiltration levels, with infiltrating T cells showing decreased expression of granzyme B and PD-1. Mutant allele ratios in MSH6 CRCs showed a negative correlation with the predicted immunogenicity of frameshift peptides, indicating potential counterselection against highly immunogenic peptides.

Conclusions:

Our findings suggest that MSH6 CRCs display a lower degree of MSI, resulting in weaker immune responses compared to CRCs in other MMR groups. These insights may impact patient management, particularly in immunotherapy and preventive cancer vaccine strategies, and if confirmed, would support the classification of LS as distinct syndromes associated with specific MMR genes.

Considerable interlaboratory variation in PD-L1 positivity for head and neck squamous cell carcinoma in the Netherlands – a nationwide evaluation study

Maaike Anna Hempenius, Bregje M. Koomen, Ivette A. G. Deckers, Sjoukje F. Oosting, Stefan M. Willems, Bert van der Vegt

Introduction:

Patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) are eligible for first-line immune checkpoint inhibition if their tumour is positive for programmed death-ligand 1 (PD-L1) determined by the combined positive score (CPS). This nationwide study, using real-world data, investigated the developing PD-L1 testing landscape in the first three years after introduction of the test in HNSCC and examined interlaboratory variation in PD-L1 positivity rates.

Methods:

Pathology reports of HNSCC patients mentioning PD-L1 were extracted from the Dutch Pathology Registry (Palga). Tumour and PD-L1 testing characteristics were analysed per year and interlaboratory variation in PD-L1 positivity rates was assessed using funnel plots with 95% confidence limits around the overall mean.

Results:

817 PD-L1 tests were reported in 702 patients across 19 laboratories. 85.2% of the tests on histological material were stated to be positive. The national PD-L1 positivity rate differed significantly per year during the study period (79.7% - 89.9%). The use of the recommended 22C3 antibody increased from 59.9% to 74.3%. 673 PD-L1 tests on histological material from 12 laboratories were analysed to investigate interlaboratory variation. Four (33%) significantly deviated from the national mean of PD-L1 positive cases using CPS ≥1 cutoff, while 2 (17%) significantly deviated for CPS ≥20 cutoff.

Conclusion:

In the first three years of PD-L1 assessment in HNSCC, the testing landscape became more uniform. However, interlaboratory variation in PD-L1 positivity rates between Dutch laboratories was substantial. This implies there is a need for further test standardization to reduce this variation.

Demographics and additional haematologic cancers of patients with histiocytic/dendritic cell neoplasms

Paul G Kemps, Lennart Kester, Marijn A Scheijde-Vermeulen, Carel J M van Noesel, Robert M Verdijk, Arjan Diepstra, Ariënne M W van Marion, Natasja Dors, Cor van den Bos, Annette H Bruggink, Pancras C W Hogendoorn, Astrid G S van Halteren

Aims:

The discovery of somatic genetic alterations established many histiocytic disorders as haematologic neoplasms. We aimed to investigate the demographic characteristics and additional haematologic cancers of patients diagnosed with histiocytic disorders in The Netherlands.

Methods and results:

We retrieved data on histiocytosis patients from the Dutch Nationwide Pathology Databank (Palga). During 1993 to 2022, more than 4000 patients with a pathologist-assigned diagnosis of a histiocytic disorder were registered in Palga. Xanthogranulomas were the most common subtype, challenging the prevailing assumption that Langerhans cell histiocytosis (LCH) is the most common histiocytic disorder. LCH and juvenile xanthogranuloma (JXG) had a peak incidence in the first years of life; males were overrepresented among all histiocytosis subgroups. 118 patients had a histiocytic disorder and an additional haematologic malignancy, including 107 (91%) adults at the time of histiocytosis diagnosis. In 16/118 patients, both entities had been analysed for the same genetic alteration(s). In 11 of these 16 patients, identical genetic alterations had been detected in both haematologic neoplasms. This included two patients with PAX5 p.P80R mutated B cell acute lymphoblastic leukaemia and secondary histiocytic sarcoma, further supporting that PAX5 alterations may predispose (precursor) B cells to differentiate into the myeloid lineage. All 4/11 patients with myeloid neoplasms as their additional haematologic malignancy had shared N/KRAS mutations.

Conclusions:

This population-based study highlights the frequency of xanthogranulomas. Furthermore, our data add to the growing evidence supporting clonal relationships between histiocytic/dendritic cell neoplasms and additional myeloid or lymphoid malignancies. Particularly adult histiocytosis patients should be carefully evaluated for the development of these associated haematologic cancers.

Evaluating the effectiveness of ovarian tumour risk assessment strategies in a real-world national setting

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Background

Predicting whether an ovarian tumour (OT) is malignant remains a challenge. Risk assessment strategies are used to select which patients with an OT should be referred to oncologic centres. However, their predictive value depends on the prevalence within a population. On hospital level, this prevalence is often known, but on a national level, these data are more difficult to obtain. Significant differences in prevalence exist between individual hospitals and single-centre study results should be generalised with caution. Therefore, we aimed to evaluate the prevalence of malignancy among surgically removed OTs and the accuracy of referral to oncologic centres in the Netherlands.

Methods

Histological reports on surgically removed OTs in 2019 were retrieved from the Dutch Pathology Registry PALGA (Pathologic-Anatomic National Computerized Archive). Reports on prophylactic removed ovaries, recurrent ovarian cancer (OC) and reports of patients below 18 years were excluded. Data on stage, subtype and surgical procedure of malignant and borderline OTs from the same year were obtained from the Dutch Gynaecological Oncology Audit (DGOA).

Results

A total of 17469 reports were retrieved from PALGA of which 6122 reports were eligible, including 4867 benign (79.5%), 870 malignant (14.3%) and 385 borderline OTs (BOT, 6.3%). From DGOA, 1344 reports were retrieved. Referral for cytoreductive surgery for advanced OC was 100%. Early-stage OC and BOTs were also mainly operated in oncological centres and 66 OCs were operated in non-oncologic centres.

Conclusion

Correct classification of OTs is crucial for treatment planning, patients' well-being and optimal use of health care resources. In the Netherlands, the majority of patients with early-stage OC are correctly referred. Because only 66 OCs were missed out of a total group of 6122 OTs, current risk assessment strategies generally selected the correct patients for referral. However, there is still room to improve preoperative risk assessment.

A multidimensional analysis reveals distinct immune phenotypes and tertiary lymphoid structure-like aggregates in the bone marrow of pediatric acute myeloid leukemia

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# equal contribution

Background Due to the low mutational burden and the anticipated poor immunogenicity of pediatric cancers such as acute myeloid leukemia (AML), children are thought to be suboptimal candidates for T cell-directed immunotherapies. However, the immune compartment in the bone marrow (BM) of pediatric AML remains poorly understood. To explore the potential success of T cell-directed immunotherapies in pediatric AML, we conducted a multidimensional analysis of the BM immune microenvironment in pediatric AML and non-leukemic controls.

Methods We collected 82 formalin-fixed and paraffin-embedded BM biopsies from pediatric patients with treatment-naïve de novo AML (n=72; acquired via the Dutch National Tissue Portal, the Princess Máxima Center biobank, and Aarhus University Hospital) and age- and sex matched non-leukemic controls (n=10). We employed immunohistochemistry, immune-related gene expression profiling (PanCancer IO 360TM Panel), and spatial transcriptomics (GeoMxTM). In addition, we obtained immune-related gene expression data from pre-treatment BM of 30 relapsed or refractory adult AML cases treated with flotetuzumab (CD3 x CD123; NCT02152956) and analyzed immunofluorescence data from pre- and/or post-treatment BM and extramedullary biopsies of 11 adult AML cases treated with ipilimumab-based therapy in two clinical trials (NCT02890329, NCT01822509).

Results On a cohort level, we demonstrate wide variation in T cell infiltration with nearly one-third of cases harboring an immune-infiltrated BM. These immune-infiltrated cases are characterized by a decreased abundance of M2-like macrophages, which we find to be associated with response to flotetuzumab in adult AML. On an organizational level, we reveal the composition of spatially organized immune aggregates in pediatric AML, and show that in the adult setting such aggregates in post-treatment BM and extramedullary sites associate with response to ipilimumab-based therapy.

Conclusion Altogether, our study provides immune correlates of response to T cell-directed immunotherapies and encourages the clinical evaluation of T cell-directed immunotherapies in immune-infiltrated pediatric AML.

Nationwide retrospective cohort study on oncological outcomes after laparotomic, laparoscopic and robot-assisted laparoscopic staging for early stage high-intermediate or high-risk endometrial cancer

Ruben C.G. Koek, Hans H.B. Wenzel, Trudy N. Jonges, Christianne A.R. Lok, Ronald P. Zweemer, Cornelis G. Gerestein

Aim

To compare oncological outcomes in patients with early stage high-intermediate or high-risk endometrial cancer undergoing surgical staging via laparotomy, conventional laparoscopy or robot-assisted laparoscopy.

Methods

Patients that underwent laparotomic, laparoscopic or robot-assisted laparoscopic staging surgery for stage I-II (FIGO 2009), high-intermediate or high-risk endometrial cancer between 2015 and 2021 were identified in the Netherlands cancer registry. 5-year disease free survival and overall survival were calculated using Kaplan-Meier method, and equality between groups was evaluated using log-rank testing. Disease-free survival and overall survival was also analysed by histological subtype. The effect of surgical modality on the risk of recurrence and all-cause death was assessed by performing Cox-regression analysis with inverse probability treatment weighting. Hazard ratios with 95% confidence intervals were calculated.

Results

No difference in disease-free survival (75.0% vs 71.2% vs 79.0% p = 0.35) or overall survival (72.7% vs 72.3% vs 71.2% p=0.98) was observed between laparotomy, laparoscopy and robot-assisted laparoscopy. Sub-analyses by histologic subtype showed comparable disease-free survival and overall survival between surgical approaches. There was no significantly increased risk of recurrence or risk of death of all cause for laparoscopy or robot-assisted laparoscopy compared to laparotomy.

Conclusion

Laparoscopic and robot-assisted laparoscopic staging surgery in women with early stage high-intermediate or high-risk endometrial cancer is a safe alternative to laparotomic staging surgery.

Trends in management of benign ovarian tumours in the Netherlands; do we more often opt for conservative management? – a nationwide cohort study

Esther Lems*, Anna H. Koch*, Sam Armbrust, Jaklien C. Leemans, Marlies Y. Bongers, Alicia Leon – Castillo, Christianne A. R. Lok, Peggy M.A.J. Geomini

*Both authors contributed equally

Introduction

Increasing evidence shows that conservative management of specific benign-looking ovarian tumours is safe. Therefore, conservative management of benign-looking ovarian tumours was adopted as a treatment option in the Dutch guideline in 2013. The aim of this study is to examine the possible changes in the number of surgically removed benign ovarian tumours over an eight-year period, while the national guideline was updated concurrently.

Materials and methods

All reports on surgically removed adnexa and tubes in 2011 (before guideline adaptation) and in 2019 (after guideline adaptation) were requested from PALGA, the Dutch nationwide pathology databank. Reports of patients below 18 years old, on prophylactic removed adnexa or on adnexa removed for other benign gynaecological indications were excluded. The histopathological diagnosis from all included reports was recorded. Interobserver variability between researchers was checked with Cohen's Kappa.

Results

A total of 34,932 reports were retrieved, of which 13,917 reports were included. In 2011 and 2019, respectively 6452 (83.1%) vs 4861 (79.0%) benign ovarian tumours were registered, and 1311 (16.9%) vs 1293 (21.0%) borderline and malignant tumours. The number of surgically removed benign ovarian tumours declined with 24.7% (p=0.000). The most substantial decrease between 2011 and 2019 was observed among the following benign subtypes: serous cysteadenomas (-37.5%; n=1392 vs n=870), endometriomas (-29.6%; n=982 vs n=691), simple epithelial cysts (-54.9%; n=566 vs n=255) and corpus luteum cysts (-55.6%; n=269 vs n=122). Cohen's Kappa for the analysed variables was 0.96.

Conclusions

Despite a growing population, the number of surgically removed benign ovarian tumours has significantly decreased in the Netherlands over the past eight years. The absolute number of malignant and borderline tumours remained stable. These findings, therefore, suggest a successful implementation of the updated guideline including an increased adoption of conservative management for benign-looking ovarian tumours.

Incidence and centralization of chordoma in the Netherlands: a nationwide study between 1991 and 2020

A. Lipplaa, R.J.P. van der Wal, A.D.G. Krol, W.C. Peul, J.V.M.G. Bovée, H. Gelderblom

Introduction:

Chordomas are rare malignant bone tumors arising in the axial skeleton, with an incidence of 0.3-0.88 per million inhabitants. We studied the annual incidence rate and centralization of treatment for chordoma in the Netherlands.

Methods:

We retrieved pathology excerpts from the PALGA nationwide Dutch Pathology Registry between 1991 and 2019 for patients with a chordoma to calculate incidence rates. From pathology reports we extracted patient age at diagnosis, sex, year of diagnosis, localization of primary tumor, histologic chordoma subtype (conventional including chondroid, poorly differentiated or dedifferentiated), center of diagnosis (bone tumor referral center (BTC) or other hospital), and partial identification of the BTCs.

Results:

A total of 420 individual chordoma patients were identified in the given time period. The incidence of chordoma increased from 0.593 per million inhabitants between 1991-1995 to 1.111 from 2015-2019 (P=0.002). Median age at diagnosis was 63 years (interquartile range 49-72), 252 patients (60%) were male. The proportion of samples analyzed in a BTC either primarily or secondary, as a consultation, revision or referral, increased significantly from 29.3% to 84.4% (P<0.001). Most primary and secondary samples were analyzed at the Leiden University Medical Center (LUMC, 54.4 and 57% respectively).

Conclusions:

This study shows an increase in the standardized incidence of pathology proven chordoma in the Netherlands. We observed an increase in samples being analysed in the specialized BTCs as well, which is in line with current guidelines and will hopefully lead to more accurate diagnoses and optimal treatment plans for chordoma patients in specialized treatment centers.

COVID-19 in the Netherlands: Lessons from a Nationwide Registry of Dutch Autopsy, Histology and Cytology Pathological Reports.

Boaz Lopuhaä, Q.J.M. Voorham, Folkert J. van Kemenade, Jan H. von der Thüsen.

Background

Since the onset of the COVID-19 pandemic, autopsies have played a valuable role in understanding the pathophysiology of COVID-19. In this study, we have analyzed COVID-19 related pathology reports from autopsies, histology and cytology on a nationwide level.

Methods

Pathology reports from all 43 pathology laboratories in the Netherlands stating “COVID”, “Corona” and/or “SARS” were queried from the Dutch Nationwide Pathology Database (Palga). Consecutive reports of the included patients were also retrieved. Out of 5,065 entries, a total of 1,803 eligible COVID-19-related pathology reports between January 2020 and June 2021 were included in this registry.

Results

Lung histopathology reports reflected differences in severity of abnormalities (acute diffuse alveolar damage, alveolar histiocytes and thrombi during the first three pandemic waves (Wuhan variant) versus the fourth wave (alpha variant)). Autopsy reports from 2020 state significantly shorter disease duration and younger age of death compared to autopsy reports from 2021. All reports together reflected a more granular pathology with comorbidities such as chronic histiocytic intervillositis, perniosis and thrombi found in a variety of organs (lungs, kidneys and small- and large intestines).

Conclusion

This nationwide registry provides data concerning COVID-19 related deaths as well as comorbidities in a clinical setting. Tagging of report IDs allows for inclusion of follow-up reports to this registry, enabling it to serve as a post-viral surveillance tool future studies regarding long term effects of COVID-19 as well as identifying effects of different SARS-CoV-2 variants.

The value of case reports in rare oncological scenarios: mixed method analysis of colorectal metastases from breast cancer

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Objective

With improved survival of cancer patients, we increasingly encounter infrequent metastatic locations. While for the common metastatic locations both prognostic information as well as evidence-based guidelines are available, for rare locations we have to rely on anecdotal case reports, the value of which is currently unknown. To establish their value and determine relevant features, we compared data from case reports with a national real-life cohort focusing on breast cancer patients with colorectal metastases.

Methods

We performed a systematic literature search and all identified cases were analyzed as individual patients. Autopsy studies were excluded. Data on stage, histological factors, treatment and outcome were extracted. The real-life cohort was extracted from the nationwide Dutch pathology databank. Linkage with the Netherlands Cancer Registry provided clinical characteristics, treatment and outcome data. Survival analyses and univariate regression were performed to identify relevant features for future treatment decisions.

Results

We identified 308 patients from 207 studies in the literature, and 454 patients in the real-life cohort. Colorectal metastases were the first metastatic event in 42.5% and 47.0% respectively. Cohorts were comparable for age, gender, location and hormone status, but differed in tumour type, stage and treatment. The time to colorectal metastases was similar in both cohorts (median of 68 months), and was dependent on presence of other metastases, nodal status, and primary breast surgery. The median overall survival after development of colorectal metastases was 20.6 months (95%CI 18.0-23.1 months).

Conclusions

Despite a potential publication bias and lack of complete data for patients in the case report series, we have shown that an extensive systematic review can provide data that are comparable to real-life data, which can be used for decision-making and patient counselling. Colorectal metastases are a late event in breast cancer patients, that is not associated with a detrimental survival.

Exploring Associated Malignancies in Mycosis Fungoides Patients: Findings from a Dutch Nationwide Retrospective Cohort Study

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Background:

The prognosis of patients with mycosis fungoides (MF) is variable and largely depends on the disease stage. Recent evidence shows a higher incidence of other primary malignancies (OPMs) in MF patients but have shown mixed results.

Objectives:

This study investigates the incidence of OPMs in MF patients in the Netherlands and compared with the Dutch population.

Methods:

A retrospective, nationwide, population-based cohort study was performed with data from the Dutch Cutaneous Lymphomas Registry including patients with a diagnosis of MF between 2000-2020. All histopathology reports were requested from the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands and screened for diagnoses of OPMs. Life-long incidence rates were used to compare the incidence of malignancies in MF patients and the general population based on data from the Netherlands Cancer Registry and Statistics Netherlands.

Results:

In total 1024 patients were included with an average age of 60 years(SD 17) and mean follow-up of 10 years(SD 6). A total of 294 cases of other primary malignancies were found with 28% of the MF patients developing at least one OPM. Only cutaneous(OR 2.54 (CI 2.0-3.2) and hematological malignancies(OR 2.62 (CI 2.00-3.42) had a statistically significant higher incidence than the Dutch population. For cutaneous malignancies there was a significantly increased risk of developing melanomas(OR 2.76; CI 2.11-3.59) and cutaneous squamous cell carcinomas(OR 2.34; CI 1.58-3.45). For hematological OPMs Lymphomatoid papulosis and Hodgkin lymphoma were more frequently found than in the reference population, with respective ORs of 76.22(CI 50.35-115.32) and 6.28(CI 2.02-19.55).

Conclusion:

Our study shows no association between MF and other solid organ tumors, however patients with MF are significantly at risk for developing other hematological and cutaneous malignancies

compared to the general population. Clinicians should be aware of this increased risk when conducting total body skin inspections during routine che-ups.

Development of radiomics-based models on mammograms with mass lesions to predict prognostically relevant characteristics of invasive breast cancer in a screening cohort

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Background:

To optimize breast screening performance, both overdiagnosis of prognostically favorable invasive breast cancer (IBC) that does not need immediate recall and underdiagnosis of prognostically unfavorable IBC that is not recalled timely should be reduced. We investigated whether mammographic features of masses can predict prognostically relevant IBC characteristics.

Methods:

In a screening cohort, we identified 1,587 IBCs presenting as a mass through linkage with the Netherlands Cancer Registry and obtained pathological information from excerpts or review of FFPE samples (Palga: Dutch Pathology Registry). We used radiomics features to develop mammography-based prediction models. Models were based on 1,095 positive mammograms (possible overdiagnosis of favorable IBC), and on 603 last negative mammograms with an in retrospect visible mass (possible underdiagnosis of unfavorable IBC). We defined two outcomes: 1) whether IBC was prognostically favorable, defined as T1N0M0 luminal A-like, or prognostically unfavorable, and 2) 15-year risk of breast cancer death predicted by the PREDICT tool ('PREDICTrisk'). We calculated performance metrics using repeated nested cross-validation.

Results:

23.5% of masses were prognostically favorable IBC. Using 1,095 positive mammograms, the model generated predictions in the 10th-90th percentile range of 8.7-47.0% to have prognostically favorable IBC and 10.9-27.7% for PREDICT-risk. Model performance was moderate: AUC 0.75 (SD across repeats 0.01) and slope 1.16 (SD 0.07) to predict prognostically favorable IBC and an explained variation (R2) of 22.3% (SD 0.91) for PREDICT-risk. Performance in 603 last negative screening mammograms with masses was poor: AUC 0.60 (SD 0.02), slope 0.85 (SD 0.28) and R2 6.3% (SD 0.83).

Discussion:

Models based on mammographic features from masses representing IBC at the time of recall (possible overdiagnosis) predict prognostically relevant IBC characteristics. Models based on in

retrospect visible masses (possible underdiagnosis) performed poorly. To optimize screening through a prognostic assessment of potential IBCs presenting as mass, further model improvements are needed.

Pathologic complete response of ductal carcinoma in situ to neoadjuvant systemic therapy in HER2-positive invasive breast cancer patients: a nationwide analysis

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Background: Neoadjuvant systemic therapy (NST) is increasingly applied in HER2-positive invasive breast cancer (IBC). In approximately 50% of HER2-positive IBC, a ductal carcinoma in situ (DCIS) component is present. DCIS was previously considered to be poorly responsive to NST. Recent studies show that DCIS accompanying HER2-positive IBC can be completely eradicated by NST, however study populations were small.

Aim: Our aim was to determine the percentage of pathologic complete response of the DCIS component accompanying HER2-positive IBC in a nationwide cohort, and to determine associated clinicopathologic variables. Furthermore, the impact of DCIS on surgical treatment after NST was investigated.

Methods: Women diagnosed with HER2-positive IBC, treated with NST and surgery, between 2010-2020, were selected from the Netherlands Cancer Registry. Pre-NST biopsy and postoperative pathology reports were obtained from the Dutch Nationwide Pathology Databank and the presence of DCIS was reviewed. Clinicopathologic factors associated with complete response of DCIS were assessed using logistic regression analyses.

Results: A total of 5598 patients were included, of whom 1403 (25.1%) had a DCIS component present in the pre-NST biopsy. Pathologic complete response of the DCIS component was achieved in 730 patients (52.0%) after NST. Complete response of DCIS occurred more frequently in case of complete response of IBC (63.4% versus 33.8%, $p<0.001$). ER-negative IBC (OR 1.79; 95%CI 1.33–2.42) and more recent years of diagnosis (2017-2019 OR 1.76; 95%CI 1.34–2.34) were associated with complete response of DCIS in multivariable logistic regression analysis. Patients with IBC+DCIS had a significantly higher mastectomy rate when compared to IBC only (53.6% versus 41.0%, $p<0.001$).

Conclusion: Pathologic complete response of DCIS occurred in 52.0% of HER2-positive IBC patients and was associated with ER-negative IBC and more recent years of diagnosis. Future studies should investigate the possibility of monitoring DCIS response on imaging to improve surgical decision-making after NST.

Association of Biological Age with Tumor Microenvironment in Patients with Esophageal Adenocarcinoma

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Esophageal cancer is the seventh most common cancer worldwide and typically tends to manifest at an older age. Marked heterogeneity in time-dependent functional decline in older adults results in varying grades of clinically manifest patient fitness or frailty. The biological age-related adaptations that accompany functional decline have been shown to modulate the non-malignant cells comprising the tumor microenvironment (TME). In the current work, we studied the association between biological age and TME characteristics in patients with esophageal adenocarcinoma. We comparatively assessed intratumoral histologic stroma quantity, tumor immune cell infiltrate, and blood leukocyte and thrombocyte count in 72 patients stratified over 3 strata of biological age (younger <70 years, fit older ≥70 years, and frail older adults ≥70 years), as defined by a geriatric assessment. Frailty in older adults was predictive of decreased intratumoral stroma quantity (B = -14.66% stroma, P = 0.022) relative to tumors in chronological-age-matched fit older adults. Moreover, in comparison to younger adults, frail older adults (P = 0.032), but not fit older adults (P = 0.302), demonstrated a lower blood thrombocyte count at the time of diagnosis. Lastly, we found an increased proportion of tumors with a histologic desert TME histotype, comprising low stroma quantity and low immune cell infiltration, in frail older adults. Our results illustrate the stromal-reprogramming effects of biological age and provide a biological underpinning for the clinical relevance of assessing frailty in patients with esophageal adenocarcinoma, further justifying the need for standardized geriatric assessment in geriatric cancer patients.

Clinical validity of post-surgery circulating tumor DNA testing in stage III colon cancer patients treated with adjuvant chemotherapy: the PROVENC3 study

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Introduction: Surgery followed by adjuvant chemotherapy (ACT) is standard of care in stage III colon cancer. However, only 15-20% of patients benefit from ACT. Detection of circulating tumor DNA (ctDNA) in plasma after resection of the primary tumor is a strong prognostic biomarker in non-metastatic colon cancer and offers a promising approach to better stratify stage III colon cancer patients for ACT treatment decisions. Furthermore, tumor-informed ctDNA detection tests increase the sensitivity and specificity compared to plasma-only tests.

Aim: The PROVENC3 study aims to determine the clinical validity of tumor-informed whole genome sequencing (WGS)-based post-surgery ctDNA detection in stage III colon cancer patients treated with ACT.

Methods: Patients were included in the Prospective Dutch ColoRectal Cancer cohort (PLCRC). The PLCRC-Palga databases linkage enabled the evaluation of the pathology reports available, and the request of formalin-fixed paraffin-embedded (FFPE) tumor blocks from 26 participating hospitals. Tumor-informed ctDNA detection was performed through integrated WGS analyses of FFPE tumor-tissue DNA (80x), germline DNA (40x), and plasma cell-free DNA (30x).

Results: Results from 209 patients (median follow-up: 40 months) show that ctDNA-positive patients post-surgery (n=28) had a higher risk of developing a recurrence within 3 years than ctDNA-negative patients (HR: 6.3, [95%CI: 3.5-11.3], P<10-8). Combination of post-surgery ctDNA status with established clinicopathological risk classification of low-risk (T1-3-N1) and high-risk (T4 and/or N2) resulted in a 3-year cumulative recurrence risk of 82% for high-risk ctDNA-positive patients compared to 7% for low-risk ctDNA-negative patients (HR 28.9 [95%CI: 10.6-78.2]; P<10-10).

Conclusion: Post-surgery ctDNA detection by tumor-informed WGS is a strong prognostic biomarker in stage III colon cancer patients. Importantly, the post-surgery ctDNA-positive disease-free patients were likely cured by ACT. These data enable the design of clinical practice-changing ctDNA-guided interventional trials in stage III colon cancer to personalize adjuvant treatment decisions.

B-cells and regulatory T-cells in the microenvironment of HER2+ breast cancer are associated with decreased survival: a real-world analysis of women with HER2+ metastatic breast cancer

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Background:

Despite major improvements in treatment of HER2-positive metastatic breast cancer (MBC), only few patients achieve complete remission and remain progression-free for a prolonged time. The tumor microenvironment (TME) plays an important role in the response to treatment in HER2-positive breast cancer and could contain valuable prognostic information. Detailed information on the cancer-immune cell interactions in HER2-positive MBC is however lacking. By characterizing the TME of HER2-positive MBC, we aimed to get a better understanding why overall survival (OS) differs so widely and which alternative treatment approaches may improve outcome.

Methods:

We included all patients with HER2-positive MBC, who were treated with trastuzumab-based therapy in the Netherlands Cancer Institute between 2000 and 2014 and for whom pre-treatment tissue from the primary tumor or metastases was available via the nationwide pathology network (PALGA). Infiltrating immune cells and their spatial relationships to one another and to tumor cells were characterized by immunohistochemistry and multiplex immunofluorescence. We also evaluated immune signatures and other key pathways using nextgeneration RNA-sequencing data. With nine years median follow-up from initial MBC diagnosis, we investigated the association between tumor and immune characteristics and outcome.

Results:

124 patients with 147 samples were included and evaluated. The different technologies showed high correlations between each other. T-cells were less prevalent in metastases compared to primary tumors, whereas B-cells and regulatory T-cells (Tregs) were comparable between primary tumors and metastases. Stromal tumorinfiltrating lymphocytes in general were not associated with OS. The infiltration of B-cells and Tregs in primary tumors was associated with unfavorable OS. Four signatures classifying the ECM of primary tumors showed differential survival.

Conclusions:

In real-world patients with HER2-positive MBC, B-cells and Tregs in primary tumors are associated with unfavorable survival. We provide a comprehensive insight of the TME that could guide further research into development of novel immunomodulatory strategies.

Long-term outcomes of young, node-negative, chemotherapy-naïve, triple-negative breast cancer patients according to BRCA1 status

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Background: This study investigated the unbiased prognostic values of BRCA1-related biomarkers in young, node-negative, chemotherapy-naïve, triple-negative breast cancer (TNBC) patients, and explored their potential interaction with the established prognostic marker of stromal tumor-infiltrating lymphocytes (sTILs).

Methods: We included 485 Dutch women diagnosed with node-negative TNBC under age 40 between 1989 and 2000. During this period, these women were considered low-risk and did not receive chemotherapy. BRCA1 status, including pathogenic germline BRCA1 mutation (gBRCA1m), somatic BRCA1 mutation (sBRCA1m), and tumor BRCA1 promoter methylation (BRCA1-PM), was assessed using DNA from formalin-fixed paraffin-embedded tissue. sTILs were assessed according to the international guideline. Patients' outcomes were compared using Cox regression and competing risk models.

Results: Among 399 patients with BRCA1 status, 26.3% had a gBRCA1m, 5.3% had a sBRCA1m, 36.6% had tumor BRCA1-PM, and 31.8% had BRCA1-non-altered tumors. Compared to BRCA1-non-alteration, gBRCA1m was associated with a worse 15-year overall survival (OS) from the fourth year after diagnosis (adjusted HR=2.11, 95%CI:1.18-3.75), and this association attenuated after adjustment for second primary tumors. Every 10% sTILs increment was associated with 16% higher 15-year OS (adjusted HR=0.84, 95%CI:0.78-0.90) in gBRCA1m, sBRCA1m or BRCA1-non-altered patients, and 31% higher 15-year OS in tumor BRCA1-PM patients. Among the 66 patients with tumor BRCA1-PM and ≥ 50% sTILs, we observed excellent 15-year OS (97.0%, 95%CI:92.9%-100%). Conversely, among the 61 patients with gBRCA1m and < 50% sTILs, we observed poor 15-year OS (50.8%, 95%CI:39.7%-65.0%). Furthermore, gBRCA1m was associated with higher (adjusted subdistribution HR=4.04, 95%CI:2.29-7.13) and tumor BRCA1-PM with lower (adjusted subdistribution HR=0.42, 95%CI:0.19-0.95) incidence of second primary tumors, compared to BRCA1-non-alteration.

Conclusions: Tumor BRCA1-PM and gBRCA1m are associated with different outcomes in young, node-negative, chemotherapy-naïve TNBC patients. By combining sTILs and BRCA1 status for risk classification, we were able to identify potential subgroups in this population to intensify and de-escalate adjuvant treatment.

The multitarget FIT for improving programmatic stool-based colorectal cancer screening: a population-based paired-design intervention study

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Background

The present study (NCT05314309) aimed to prospectively validate the multitarget FIT (mtFIT, measuring haemoglobin, calprotectin, and serpinF2 versus FIT the faecal immunochemical test (FIT), for colorectal cancer (CRC) screening.

Methods

Individuals eligible for the Dutch national FIT-based CRC screening programme were invited to submit both a FIT and mtFIT sample collected from the same bowel movement. Positive FIT (47 µg/g haemoglobin cut-off) and/or mtFIT (based on decision tree algorithm) led to colonoscopy referral. Primary outcome was the relative detection rate of advanced neoplasia (AN) across multiple test positivity rates. Key secondary outcomes were the relative detection rates of CRC, AA and ASP across multiple test positivity rates. Long-term health and economic impacts were determined with microsimulation modelling.

Findings

Among 35,786 invitees, 15,283 (42·7%) consented, and of these, 13,187 (86·3%) provided both tests with valid results. mtFIT showed a 9·11% positivity rate and 2·27% AN detection rate, compared to 4·08% and 1·21%, respectively, for FIT. CRC, AA, and ASP detection rates of mtFIT versus FIT were 0·20% versus 0·17%, 1·64% versus 0·86%, and 0·43% versus 0·17%, respectively. Modelling demonstrated that mtFIT-based screening could cost-effectively reduce CRC incidence and CRC-related mortality by 21% and 18%, respectively, compared to the current Dutch CRC screening programme. At equally low positivity rate of 3·60%, AN detection rate of mtFIT was 1·36% versus 1·22% of FIT (p=0·071), and CRC, AA, and ASP detection rates of mtFIT versus FIT were 0.17% versus 0.18%, 1.02% versus 0.87%, and 0.18 versus 0.17%, respectively. Here, mtFIT-based screening was predicted to decrease CRC incidence and CRC-related mortality compared to FIT by 5% and 4%, respectively.

Interpretation

The higher detection rate of mtFIT for AA compared to FIT holds potential to translate into

additional and clinically meaningful long-term CRC incidence and CRC-related mortality reductions in programmatic CRC screening.

The effect of intrauterine manipulator on oncological outcome in early stage, low grade endometrial cancer: A retrospective cohort study

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Objective: To evaluate the influence of intrauterine (IU) or non-IU manipulators on oncological outcome in early-stage, low-grade endometrial endometrioid cancer (EEC).

Design: Retrospective cohort study

Setting: Nationwide population-based study in the Netherlands

Population: Women with FIGO stage I, low-grade EEC who received total laparoscopic hysterectomy between 2010 and 2020.

Methods: Patient data were identified from the Netherlands Cancer Registry. Data regarding hospital manipulator preferences were retrieved through an online survey. Patients were categorized based on hospital manipulator preference. Survival analyses were performed using univariable and multivariable cox regression analysis.

Main outcome measures: Recurrence of cancer, disease-free survival (DFS), overall survival (OS), site of recurrence, and manipulator preference according to type of hospital.

Results: Of the total study population (N = 5,205), 1524 (29.3%) patients underwent surgery in hospitals that used non-IU manipulators and 3681 (70.7%) in hospitals that used IU manipulators. Recurrence of cancer was experienced by 195 patients, 49 (3.2%) in the non-IU group and 146 (4.0%) in the IU group. No significant difference in site of recurrence was observed (p=0.778). After adjusting for potential confounders, type of uterus manipulator did not affect DFS (hazard ratio [HR] 0.93, 95% confidence interval [CI] 0.78–1.11) and OS (HR 0.90, 95% CI 0.75–1.09).

Conclusion: IU manipulators are not inferior to non-IU manipulators with respect to oncological outcome in early-stage, low-grade EEC.