REPORT
25th SOCIAL RETURN OF THE RESEARCH
CANCER

OPTIMISATION OF THE MANAGEMENT OF THE T1 COLORECTAL CANCER

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1. Project summary

The implementation of colorectal cancer (CRC) screening programs has led to a considerable increase in the prevalence of endoscopically treated polyps containing early-stage cancer. There is a lack of consensus and standardization regarding the management of these lesions. A significant proportion of patients undergo surgery without any demonstrated benefit in terms of survival.

2. Results

Subproject 1

A total of 3,649 patients were recruited from 27 centers across 13 Spanish autonomous communities, representing a representative sample from all of Spain and the most extensive and complete retrospective database of CRCpT1 cases in the world (550 variables including baseline and follow-up data). The patient sample tripled the estimate in the initial report, resulting in an increase in the effort and time required for data cleaning (more than 25,000 queries generated) and database exploitation. Interestingly, histological slides of 2,743 of these cases with sufficient clinical follow-up were retrieved and scanned. In total, 12,464 slides were scanned (200x magnification; Panoramic 250 Flash II, 3 DHistech), occupying more than 38TB and stored in a secure and confidential cloud system during the project's development. Thanks to synergy with the principal investigator of another grant from La Marató de TV3 on melanoma, software was created to visualize and annotate these images (DSA digital slide; https://dsa.athenatechai.com/#?dialog=login). During the last months of the project, a centralized review of all histological slides was achieved through close collaboration with a working group consisting of 20 pathologists from across Spain. Initially, a review of 11 representative cases was conducted to identify points of controversy among different pathologists and unify criteria. In the second phase, 72 cases were selected for review by all pathologists, serving to conduct an inter-observer agreement analysis that was presented as a communication at national and international congresses and is pending submission for publication. A new consensus meeting was held, followed by the centralized review of cases. During the last 6 months of the project, pathologists conducted the review of all slides (124 cases per pathologist) and completed the

centralized review. These data are currently being analyzed and incorporated into the overall survival analysis. Several clinical substudies are also in the analysis phase. During the grant period, two reviews on the management of T1 CRC were published, and various clinical substudies were presented at national and international conferences. At present, the manuscripts are in the final stages of writing or analysis. The main study is a propensity score that is undergoing modeling by the statistics team after completing the centralized histology review.

The clinical conclusions we have reached show that:

- 24% of T1 CRCs are initially treated with oncologic surgery and 76% are initially treated locally.

- Of those treated locally, 50% will undergo salvage oncologic surgery.

- The pre-treatment clinical suspicion of invasive cancer in polyps is low. It is suspected in only 40% of cases.

- Half of the polyps with CRCpT1 were smaller than 20mm, and 40% were pedunculated.

- Based on baseline histological criteria, 61% of CCRT1 cases were classified as low risk. Only 54% were treated locally.

- Of the 37% with high-risk histological criteria, 63% were treated with oncologic surgery and the rest only with local treatment.

- The overall recurrence rate was 3.5% (112 out of 3,161 patients): 8% regional lymph nodes; 20% endoluminal recurrence; 4.5% extraluminal recurrence; 61.6% distant metastasis; 2.7% distant lymph nodes; 3.6% peritoneal carcinomatosis.

- Overall mortality was 13.4%:
o Mortality from CRC: 2.2%
o Mortality from surgical complications: 0.93%
o Mortality from endoscopic complications: 0.17%

- A specific sub-study was conducted to analyze the extension study of rectal pT1 CRCs. This article highlights significant heterogeneity in real-world practice and underscores the poor performance of commonly used tests.

- A substudy comparing CRCs diagnosed within screening programs showed lower overall mortality, higher rates of local treatments, and similar cancer-associated survival rates.

- A collaborative substudy with the Dutch consortium showed that in T1 cases with good prognostic criteria treated locally, fragment treatment was associated with a higher recurrence rate at a distance.

Finally, thanks to synergy with an FIS grant from the ISCIII, a study of molecular markers in paraffin samples was also conducted. It included 101 patients with locally resected T1 CRCs who had tumor recurrence at a distance within 3 years (n = 26) and no recurrence for more than 3 years (n = 75). Thirteen transcriptomic markers were identified and confirmed to correlate significantly with vascular invasion (area under the curve (AUC) = 0.81), which has significant clinical potential as it would allow the detection of lesions at risk not only of lymphatic but also hematogenous metastasis. The overall diagnostic accuracy for tumor recurrence was very solid (AUC = 0.84), and we were able to successfully validate its tumor recurrence prediction in an independent validation cohort (AUC = 0.82). Our risk prediction model had superior predictive accuracy for tumor recurrence (AUC = 0.91). Finally, the prognostic impact of this risk stratification model revealed that high-risk patients exhibited significantly worse disease-free survival than low-risk patients ($p<0.001$).

Subproject 2

This subproject has developed an online learning tool for gastroenterologists to learn to recognize the invasive pattern in colorectal polyps and has implemented a study of its clinical validation involving 191 gastroenterologists from 81 Spanish centers.
As far as the authors are aware, this is the first time that knowledge scattered across different articles and the experience of Japanese endoscopic schools has been systematized to make it accessible to everyone in the future. After studying the different possibilities, the research team considered Moodle to be the e-learning platform that best suited their needs. 3ipunt, a Moodle partner, was the selected

company through a tender to develop the technical and graphic aspects of the platform. The final result is a high-quality 26-hour online course to learn to recognize the endoscopic invasive pattern of colorectal polyps. The course is available at trainingopticaldiagnosis.com.

The features of the course that make it of high quality include:

- Implementation from the beginning of a communication plan entrusted to Galènia, a communication agency specialized in health, which then facilitated the recruitment of participants.

- Creation of a research group website and a pleasant graphic environment for the platform hosting the course.

- Selection of images obtained with magnification by international experts.

- Course structure and pedagogical strategy based on learning by doing. Participants progressively acquire layers of knowledge on the same topic through feedback on different types of exercises.

- Content editing with the collaboration of specialized doctors, programmers, and designers.

- Review of the content by a selected group of international experts (Spain, UK, USA, and Japan) through multiple meetings and a two-day workshop.

Once the contents of the online course were developed, the recruitment of participating gastroenterologists was initiated to validate its utility in clinical practice through a clinical trial. In this case, the participating subjects were gastroenterologists who agreed to record the optical diagnosis (test) and histology (gold standard), as well as the clinical outcomes, of patients with polyps > 20 mm for 12 months. At 6 months, they were randomized to take the course or not. Initially, 191 gastroenterologists from 81 Spanish centers who wanted to participate in the study were included, of whom 103 (from 59 centers) effectively started recording patient data. Of these, 58 participating gastroenterologists have already taken the course (some from the control group after

the 12-month period), while others still need to record more patient data before they can be randomized. At present, we have data on 1,956 registered patients when the sample size was 3,000. We will need to reach 3,000 lesions included according to the sample size calculation in order to evaluate if the sensitivity for predicting early cancer in colorectal polyps is higher in endoscopists who have received this training. It also aims to assess if the rate of complete resection (R0) in early colorectal cancer is higher in the group that has received this training. Although, in students who have taken the course, diagnostic accuracy based on a 20-image test was significantly higher after taking the course compared to the initial test (difference of 7.6%, p = 0.004), preliminary analysis in routine clinical practice has not shown significant differences with the current sample size.

3. Relevance with possible future implications

Subproject 1

The establishment of this cross-sectional interest group with clinicians and pathologists (EpiT1 consortium) is one of the important milestones of this grant, as it will standardize clinical practice and facilitate the implementation of other training and research projects that will help improve quality of care in this area. In addition, the creation of this extensive library of histological images stored on 5 hard drives occupying a total of 38TB and associated clinical data in the AEGRedCap database represents a significant wealth. In fact, three external collaborations have already emerged that will bear fruit in the coming years:

- Collaboration with the Institute for Cancer Genetics and Informatics at Oslo University Hospital and the Dutch pT1CRC consortium for the creation of an artificial intelligence algorithm for predicting survival and lymph node involvement in CRCpT1 from histological slides.

- Collaboration with the Computer Vision Center, Josep Carreras Leukemia Research Institute for the co-development of the subproject "Deep learning algorithms in the diagnosis of early colorectal cancer pT1" in the context of the project "deeP lEarning AlgoRithmS in the diagnosis of adenomas and early colorectal cancer (PEARSON)",

funded by the call "Strategic projects aimed at ecological transition and digital transition 2021".

- Collaboration with Dr. Carolina Martinez and Prof. Andrés Cervantes from the Research Foundation of the Hospital Clínic of the Valencian Community and the Telecommunications Service of the Polytechnic University of Valencia for the project "Generation of an artificial intelligence algorithm through analysis of digital histopathological image of lymph nodes for prediction of recurrence in patients with localized colorectal cancer. AGIL-CCR Project.

Moreover, our risk model based on transcriptomics could provide an individualized clinical approach to identify high-risk patients who require adjuvant oncologic therapy for CRC T1 and be the starting point for future validation projects.

Subproject 2

The endoscopic distinction of polyps that have early cancer from those that do not could help overcome the limitations of current clinical practice:

- Unnecessary surgery in patients with complex polyps without risk of lymph node metastasis who could have been endoscopically treated using advanced therapeutic procedures.

- Unnecessary endoscopic treatments in lesions with cancer and risk of lymph node metastasis that still require surgery.

- Inappropriate choice of endoscopic treatment, such as fragment mucosectomy in lesions suspicious of containing cancer and where histological analysis will not allow measurement of submucosal invasion and resection margins.

- Advanced endoscopic therapies such as submucosal dissection in very benign lesions like low-grade dysplasia, where the integrity and orientation of the sample are not very important.

- Scheduling new colonoscopies to try to endoscopically remove lesions that are seen to have cancer in the second colonoscopy and need surgery.

- Making decisions based on biopsies, which underestimate histology due to sampling error.

- Unnecessary referrals to a tertiary center.

- Heterogeneity of treatments according to the center.

4. Scientific bibliography generated / References

Articles

1. Oswaldo Ortiz, Maria Daca-Alvarez, Liseth Rivero-Sánchez, Karmele Saez De Gordoa, Rebeca Moreira, Miriam Cuatrecasas, Francesc Balague, Maria Pellisé. Linked-color imaging versus high-definition white-light endoscopy for evaluation of post-polypectomy scars of nonpedunculated lesions: LCI-Scar study. Endoscopy 2024; DOI 10.1055/a-2204-3236

2. Quintanilla I, Jung G, Jimeno M, Lozano JJ, Sidorova J, Camps J, Carballal S, Bujanda L, Vera MI, Quintero E, Carrillo-Palau M, Cuatrecasas M, Castells A, Panés J, Ricart E, Moreira L, Balaguer F, Pellisé M. Differentially Deregulated MicroRNAs as Novel Biomarkers for Neoplastic Progression in Ulcerative Colitis. *Clin Transl Gastroenterol* (IF: 3.97; Q1). 2022 Jul 1;13(7):e00489. doi:10.14309/ctg.0000000000000489. Epub 2022 Apr 8. PMID: 35404333

3. Saez de Gordoa K, Rodrigo-Calvo MT, Archilla I, Lopez-Prades S, Diaz A, Tarragona J, Machado I, Ruiz Martín J, Zaffalon D, Daca-Alvarez M, Pellisé M, Camps J, Cuatrecasas M. Lymph Node Molecular Analysis with OSNA Enables the Identification of pT1 CRC Patients at Risk of Recurrence: A Multicentre Study. *Cancers (Basel)* (IF: 6.13; Q1). 2023 Nov 20;15(22):5481. doi: 10.3390/cancers15225481.PMID: 38001742

4. Brunori A, Daca-Alvarez M, Pellisé M. pT1 colorectal cancer: A treatment dilemma. *Best Pract Res Clin Gastroenterol* (IF: 3.04; Q3). 2023Oct; 66:101854. doi: 10.1016/j.bpg.2023.101854. Epub 2023 Aug 7. PMID: 37852711.

5. Diana Zaffalon, Maria Daca-Alvarez, Karmele Saez de Gordoa, María Pellisé. Dilemmas in the Clinical Management of pT1 Colorectal Cancer.PMID: 37444621 PMCID: PMC10341121 DOI: 10.3390/cancers15133511.

6. Llach J, Pellisé M, Monahan K. "Lynch syndrome; towards more personalized management?" In Hereditary Disorders'. *Best Pract Res Clin Gastroenterol* (IF: 3.04; Q3). 2022 Jun-Aug;58-59:101790. doi: 10.1016/j.bpg.2022.101790. Epub 2022 Mar 26. PMID: 35988964.

7. Carballal S, Sánchez A, Moreira L, Cuellar-Monterrubio JE, Bernuy J, Daca M, Ortiz O, Ocaña T, Rivero-Sánchez L, Jung G, Serradesanferm A, Pozo A, Grau J, Torá I, Zaffalon D, Castells A, Pellisé M, Balaguer F; PROCOLON Group. *Prevalence of adenomatous polyposis in a fecal immunochemical test-based colorectal cancer screening program and risk of advanced neoplasia during follow-up.* Endoscopy. 2021 Oct 4. doi: 10.1055/a-1660-5353. Online ahead of print.

8. Rodríguez de Santiago E, Hernández-Tejero M, Rivero-Sánchez L, Ortiz O, García de la Filia-Molina I, Foruny-Olcina JR, Prieto HMM, García-Prada M, González-Cotorruelo A, De Jorge Turrión MA, Jiménez-Jurado A, Rodríguez-Escaja C, Castaño-García A, Outomuro AG, Ferre-Aracil C, de-Frutos-Rosa D, Pellisé M; Endoscopy Group of the Spanish Gastroenterology Association. Management and Outcomes of Bleeding Within 30 Days of Colonic Polypectomy in a Large, Real-Life, Multicenter Cohort Study. *Clin Gastroenterol Hepatol* (IF: 8.549; Q1). 2021 Apr;19(4):732-742.e6. doi: 10.1016/j.cgh.2020.03.068. Epub 2020 Apr 6.PMID: 32272252.

9. M. Jimeno, A. Domingo, I. Salas, MR Sánchez, C. González, C. Salas, MJ Paúles, X. Sanjuán, I. Quintanilla, S. Carballal, G. Molist, M. Cuatrecasas, M. Pellisé. Pathologist experience and concordance in the diagnosis of dysplasia in long standing inflammatory bowel disease. The American Journal of Surgical Pathology 2020;44(7):955-61. *Ranking*: Patología 6/76 (D1); Cirugía 7/203 (D1)

Presentations at congresses

1. Cáncer colorectal pt1 diagnosticados en contexto de cribado de CCR. 43 Congreso de la Sociedad Española de Endoscopia Digestiva. 25-27 de Septiembre 2021, Malaga. (Comunicación Oral)

2. Cáncer colorectal pt1 diagnosticados en contexto de cribado de CCR". XXXI Congrés de la Societat Catalana de Digestologia 2022

3. Impacto del programa de cribado poblacional de CCR basado en TSOH en el tratamiento del cáncer colorrectal pT1. 25 Reunión Anual de la Asociación Española de Gastroenterología (AEG),23 al 25 de marzo de 2022, Madrid. (Comunicación Oral)

4. Impact of FIT-based CRC population screening program on the management of pt1 colorectal cancer". Digestive Disease Week 2022. May 21-24. San Diego, CA. (Oral Presentation)

5. Impact of FIT-Based CRC Population Screening Program on The Management of PT1 Colorectal Cancer. ESGE days 2022; Prague 28-29 April 2022.

6. Karmele Saez de Gordoa, Iván Archilla, Maite Rodrigo, Jose Javier Aguirre, Maria Camara Jurado, Adriana Canosa, Francisco Giner, Mireya Jimeno, Ismael Jurado, Stefania Landolfi, Adrià Lloret, Isidro Machado,Carolina Martínez-Ciarpaglini, Eva Musulen, Dolores Naranjo, Natalia Papaleo, Òria Rosiñol, Rosario Sánchez-Yuste, Greissy Tibisay Vázquez Benítez, Miriam Cuatrecasas Inter-observer concordance in the measurement of histological risk factors in pT1 colorectal adenocarcinomas. 34th Congress of the ESP, 3-7 September 2022, Basel, Switzerland.

7. Estadiaje pre-tratamiento en el cáncer rectal pT1 _Estudio EpiT1". 43 Congreso Nacional de la Sociedad Española de Endoscopia Digestiva. 2022

8. Utilización del tatuaje en el cáncer de recto con estadio T1 y sus implicaciones en la cirugía". XXXII Congrés de la Societat Catalana de Digestología 2023

9. Karmele Saez de Gordoa, Maite Rodrigo, Iván Archilla, María Daca, Jose Javier Aguirre, Lorena Alarcón, Maria Camara Jurado, Adriana Canosa, Francisco Giner, Carmen González, Mireya Jimeno, Ismael Jurado, Isidro Machado, Carolina Martínez-Ciarpaglini, Eva Musulen, Dolores Naranjo, Natalia Papaleo, Cristina Peña, Òria Rosiñol, Rosario Sánchez-Yuste, Greissy Tibisay Vázquez Benítez, María Pellisé, Miriam Cuatrecasas, EpiT1 Consortium. Improving the Pathological Assessment of Histological Risk Factors in pT1 Colorectal Carcinoma. An Inter-Observer Concordance Study

Congreso: 112th USCAP Annual Meeting, 11-16 March 2023, New Orleans, Louisiana, USA.

10. Estadiaje pre-tratamiento en el cáncer rectal pT1 _Estudio EpiT1Poster con relevancia para la práctica clínica. 26 Reunión Anual de la Asociación Española de Gastroenterología (AEG).2023

11. Pronóstico de los CCRpT1 de bajo riesgo resecados localmente en bloque y en fragmentos - Estudio comparativo con dos cohortes internacionales: Consorcio Epit1 y Dutch pT1CRC study group" ESGE Days 2023

12. Importancia de un diagnóstico histológico de precisión para evaluar el riesgo de metástasis ganglionares en el carcinoma colorrectal pT1. Karmele Saez de Gordoa, Maite Rodrigo, Ivan Archilla, María Daca, Jose Javier Aguirre, Lorena Alarcón-Molero, María Cámara Jurado, Francisco Giner, Mireya Jimeno, Ismael Jurado, Isidro Machado, Carolina Martínez-Ciarpaglini, Eva Musulen, Dolores Naranjo Natalia Papaleo, Cristina Peña, Òria Rosiñol, Greissy Tibisay Vázquez Benítez, María Pellisé, Miriam Cuatrecasas, EpiT1 Consortium. XXXI Congreso Nacional de la SEAP-IAP, XXVI Congreso SEC y VII Congreso SEPAF, 03-05 Mayo 2023, Sevilla.

13. Staging of pt1 rectal cancer in a nationwide population-based cohort Epit1 consortium". Digestive Disease Week (DDW) 2023

14. Prognosis of low-risk pT1 CRC locally resected en bloc and in piecemeal - Comparative study with two international cohorts: Epit1 Consortium and Dutch T1 group. UEG Week 2023. UEG Week 2023.

15. Staging of pt1 rectal cancer in a nationwide population-based cohort Epit1consortium". UEG Week 2023.

16. Prognosis of low-risk pT1 CRC locally resected en bloc and in piecemeal - Comparative study with two international cohorts: Epit1 Consortium and Dutch T1 group. ESGE Days 2024.