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The Treatment of Pilonidal Disease: Guidelines of the Italian Society of Colorectal Surgery (SICCR)

Segre D, Pozzo M, Perinotti R, et al (2015)
Tech Coloproctol 19:607–13

The Italian Society of Colorectal Surgery (SICCR) has prepared clinical practice guidelines to help its members to optimize the treatment of pilonidal disease, a very common condition, especially among young people, and therefore of great importance on a socioeconomic level. The SICCR committee of experts on pilonidal disease analyzed the international literature and evaluated current evidence. Nonoperative management includes gluteal cleft shaving, laser epilation as well as fibrin glue and phenol injection: reported healing rates and recurrence incidence are satisfactory but the majority of studies are small series with low-quality evidence. Surgical therapy which can be divided into two categories: excision of diseased tissue with primary closure using different techniques or excision with healing by secondary intention. On the whole, no clear benefit is demonstrated for one technique over the other.

Commentaires : *La Société italienne de chirurgie colorectale a établi des recommandations concernant le traitement de la maladie pilonidale. Les auteurs concluent qu'aucune technique n'a d'avantage sur une autre. Ces recommandations, publiées dans* Techniques in ColoProctology *sont critiquables, une réponse aux auteurs ayant d'ailleurs été publiée par la suite par des collègues allemands. En effet, certains travaux n'ont pas été pris en compte par ces recommandations, notamment une revue de la* Cochrane Database *montrant que l'excision* lay open *suivie d'une cicatrisation dirigée était associée à un risque de récidive inférieur comparé aux techniques fermées (RR : 0,65, IC : [0,45–0,93]). Les auteurs de la lettre qui critiquent ces recommandations suggèrent que les Italiens revoient la méthodologie utilisée pour leurs guidelines en la conseillant de consulter le site Web du National Guideline System (SNLG)* http://www.snlg-iss.it/

Cotation : ☺

A. Senéjoux

Allogeneic Bone Marrow-Derived Mesenchymal Stromal Cells Promote Healing of Refractory Perianal Fistulas in Patients with Crohn's Disease

Molendijk I, Bonsing BA, Roelofs H, et al (2015)
Gastroenterology 149:918–27

Background & aims: Patients with perianal fistulizing Crohn's disease have a poor prognosis because these lesions do not heal well. We evaluated the effects of local administration of bone marrow-derived mesenchymal stromal cells (MSCs) to these patients from healthy donors in a double-blind, placebo-controlled study.

Methods: Twenty-one patients with refractory perianal fistulizing Crohn's disease were randomly assigned to groups given injections of $1 \times 10(7)$ [$N = 5$, group 1], $3 \times 10(7)$ ($N = 5$, group 2), or $9 \times 10(7)$ ($N = 5$, group 3) MSCs, or placebo (solution with no cells, $N = 6$), into the wall of curettaged fistula, around the trimmed and closed internal opening. The primary outcome, fistula healing, was determined by physical examination 6, 12, and 24 weeks later; healing was defined as absence of discharge and < 2 cm of fluid collection-the latter determined by magnetic resonance imaging at week 12. All procedures were performed at Leiden University Medical Center, The Netherlands, from June 2012 through July 2014.

Results: No adverse events were associated with local injection of any dose of MSCs. Healing at week 6 was observed in 3 patients in group 1 (60.0%), 4 patients in group 2 (80.0%), and 1 patient in group 3 (20.0%), vs 1 patient in the placebo group (16.7%) ($P = 0.08$ for group 2 vs placebo). At week 12, healing was observed in 2 patients in group 1 (40.0%), 4 patients in group 2 (80.0%), and 1 patient in group 3 (20.0%), vs 2 patients in the placebo group (33.3%); these effects were maintained until week 24 and even increased to 4 (80.0%) in group 1. At week six, 4 of 9 individual fistulas had healed in group 1 (44.4%), 6 of 7 had healed in group 2 (85.7%), and 2 of 7 had healed in group 3 (28.6%) vs 2 of 9 (22.2%) in the placebo group ($P = 0.04$ for group 2 vs placebo). At week twelve, 3 of 9 individual fistulas had healed in group 1 (33.3%), 6 of 7 had healed in group 2 (85.7%), 2 of 7 had healed in group 3 (28.6%), and 3 of 9 had healed in the placebo group (33.3%). These effects were stable through week 24

and even increased to 6 of 9 (66.7%) in group 1 ($P = 0.06$ group 2 vs placebo, weeks 12 and 24).

Conclusions: Local administration of allogeneic MSCs was not associated with severe adverse events in patients with perianal fistulizing Crohn's disease. Injection of 3 × 10(7) MSCs appeared to promote healing of perianal fistulas. ClinicalTrials.gov ID NCT01144962.

Commentaires : *Le traitement des fistules anopérinéales au cours de la maladie de Crohn reste un challenge. En dépit de progrès dans la prise en charge médicale de cette affection, le traitement chirurgical reste fréquemment indiqué : drainage mais aussi traitement d'épargne sphinctérienne visant à obturer le ou les trajet(s) fistuleux. Les injections de colle biologique ont une efficacité très modeste, le plug de collagène n'est pas une alternative efficace. Les auteurs rapportent un essai contrôlé avec des résultats qui n'atteignent pas le seuil de significativité mais suggèrent une efficacité du traitement dans une revue prestigieuse. Des travaux concernant des injections de cellules souches autologues (le plus souvent dérivées de la graisse du patient) avaient déjà été publiés avec des résultats contradictoires. Si ces résultats encourageants se confirment, l'utilisation de donneurs sains simplifierait la technique qui reste de mise en œuvre délicate.*

Cotation : ☺

A. Senéjoux

Karydakis Flap versus Excision — only Technique in Pilonidal Disease

Keshvari A, Keramati MR, Fazeli MS, et al (2015)
J Surg Res Sep;198(1):260-6. doi: 10.1016/j.jss.2015.05.039. Epub 2015 May 28

Background: Karydakis flap (K-flap) and Excision with Healing by Secondary Intention (EHSI) are currently accepted methods for surgical management of sacrococcygeal pilonidal disease. This clinical trial study aimed to compare early and late outcomes of these two surgical techniques.

Materials and methods: In this controlled, prospective, randomized clinical trial, patients diagnosed with sacrococcygeal pilonidal disease were randomly allocated to two groups. Patients in the first group underwent Karydakis procedure, whereas EHSI was the surgical management in the second group. The two techniques were compared based on their overall time of wound healing, return to work, rate of complications, and recurrence.

Results: A total of 321 patients including 161 in the K-flap group and 160 in the EHSI group were included in the study. The median follow-up duration was 49 mo. The mean time of wound healing (16.44 versus 80.01 d, $P < 0.001$), return to work (14.44 versus 24.19, $P < 0.001$), rate of wound complications (18.7 versus 31.2%, $P = 0.006$), and recurrence (1.2 versus 7.5%, P = 0.005) were all significantly lower in the K-flap group. The mean operation time was significantly shorter in the EHSI group (15.87 versus 55.17 min, $P < 0.001$). The K-flap group showed significantly higher pain on their first postoperative day and significantly less pain after 1 wk ($P < 0.001$).

Conclusions: Although both techniques are safe, the K-flap is associated with significantly lower rates of complications and recurrence and significantly shorter time of wound healing and return to work.

Commentaires : *Je ne sais si c'est la consonance grecque du nom qui me rappelle mes vacances dans les Cyclades et/ou si c'est parce que je m'inquiète de réaliser une intervention qui, en France, est transmise de génération en génération depuis plus d'un demi-siècle et qui impose, de surcroît, des soins locaux infirmiers quotidiens durant 6 à 12 semaines. Quoi qu'il en soit, la technique de fermeture paramédiane mise au point en 1973 par le chirurgien grec George Karydakis m'a toujours intéressé.*

Par conséquent, même si je ne connaissais pas cette revue de chirurgie, je ne pouvais que rapporter cet essai contrôlé iranien ayant randomisé des patients après exérèse de leur sinus pilonidal infecté, laissée tel quel pour une cicatrisation dirigée à ciel ouvert versus une fermeture selon la technique de Karydakis. Ce d'autant plus que, excusez du peu, il y avait 160 patients dans chaque groupe et sans aucun perdu de vue après un suivi médian d'environ un an. Mieux encore, la comparaison en faveur du Karydakis a été édifiante avec notamment une cicatrisation écourtée, une reprise d'activité plus rapide et même un taux de récidive plus faible, et ce malgré une petite déhiscence de la suture chez 12 % des patients.

Bref, même s'il est bien possible qu'il y ait un problème quelque part dans cet essai, même si la technique de Karydakis est certes plus longue de réalisation (35 à 120 minutes, 55 minutes en moyenne versus 16 minutes pour l'exérèse seule…), voici de bonnes raisons supplémentaires de s'intéresser à cette technique de fermeture après exérèse de sinus pilonidal.

Cotation : ☺ ☺ ☺

V. de Parades

Everolimus for the Treatment of Advanced, Non-Functional Neuroendocrine Tumours of the Lung or Gastrointestinal Tract (RADIANT-4): a Randomised, Placebo-Controlled, Phase III Study

Yao JC, Fazio N, Singh S, et al (2015)
Lancet Dec 15. pii: S0140-6736(15)00817-X.
doi:10.1016/S0140-6736(15)00817-X. [Epub ahead of print]

Background: Effective systemic therapies for patients with advanced, progressive neuroendocrine tumours of the lung or gastrointestinal tract are scarce. We aimed to assess the efficacy and safety of everolimus compared with placebo in this patient population.

Methods: In the randomised, double-blind, placebo-controlled, phase III RADIANT-4 trial, adult patients (aged ≥ 18 years) with advanced, progressive, well-differentiated, non-functional neuroendocrine tumours of lung or gastrointestinal origin were enrolled from 97 centres in 25 countries worldwide. Eligible patients were randomly assigned in a 2:1 ratio by an interactive voice response system to receive everolimus 10 mg per day orally or identical placebo, both with supportive care. Patients were stratified by tumour origin, performance status, and previous somatostatin analogue treatment. Patients, investigators, and the study sponsor were masked to treatment assignment. The primary endpoint was progression-free survival assessed by central radiology review, analysed by intention to treat. Overall survival was a key secondary endpoint. This trial is registered with ClinicalTrials.gov, number NCT01524783.

Results: Between April 3, 2012, and Aug 23, 2013, a total of 302 patients were enrolled, of whom 205 were allocated to everolimus 10 mg per day and 97 to placebo. Median progression-free survival was 11.0 months (95% CI: [9.2–13.3]) in the everolimus group and 3.9 months (3.6–7.4) in the placebo group. Everolimus was associated with a 52% reduction in the estimated risk of progression or death (hazard ratio [HR]: 0.48; 95% CI: [0.35–0.67], $P <$ [0.00001]). Although not statistically significant, the results of the first pre-planned interim overall survival analysis indicated that everolimus might be associated with a reduction in the risk of death (HR: 0.64; 95% CI: [0.40–1.05], one-sided $P = 0.037$, whereas the boundary for statistical significance was 0.0002). Grades 3 or 4 drug-related adverse events were infrequent and included stomatitis (in 18 [9%] of 202 patients in the everolimus group vs 0 of 98 in the placebo group), diarrhoea (15 [7%] vs 2 [2%]), infections (14 [7%] vs 0), anaemia (8 [4%] vs 1 [1%]), fatigue (7 [3%] vs 1 [1%]), and hyperglycaemia (7 [3%] vs 0).

Conclusions: Treatment with everolimus was associated with significant improvement in progression-free survival in patients with progressive lung or gastrointestinal neuroendocrine tumours. The safety findings were consistent with the known side-effect profile of everolimus. Everolimus is the first targeted agent to show robust anti-tumour activity with acceptable tolerability across a broad range of neuroendocrine tumours, including those arising from the pancreas, lung, and gastrointestinal tract.

Commentaires : *Les tumeurs neuroendocrines (TNE) sont un groupe de tumeurs hétérogènes dans leur présentation clinique et leur pronostic. L'évérolimus, suite à l'étude RADIANT-3, a une AMM uniquement contre les TNE pancréatiques métastatiques ou localement avancées, en deuxième ligne après échec d'une chimiothérapie cytotoxique. Des premiers résultats suggéraient une activité de l'évérolimus également sur d'autres primitifs de TNE. Les auteurs rapportent dans cette phase III randomisée que l'évérolimus augmente la survie sans progression chez des patients atteints d'une TNE de grades 1–2, du tube digestif et du poumon. Le profil de tolérance rapporté est similaire à ce qui est maintenant bien connu. L'évérolimus devrait élargir, suite à cette étude, son AMM à cette population. Cependant, des compétiteurs existent sur des populations proches : le sunitinib dans les TNE du pancréas et la radiothérapie vectorisée interne dans les TNE intestinales (essai de phase III, Netter-1, largement positif, présenté fin 2015 à l'ESMO).*

Cotation : ☺ ☺

T. Walter

Features of Late Recurrence Following Transanal Local Excision for Early Rectal Cancer

Oh BY, Yun HR, Kim SH, et al (2015)
Dis Colon Rectum 58:1041-7

Background: Transanal local excision has recently received attention as an alternative to radical surgery for early rectal cancer. Recurrence usually occurs within 5 years after surgery, but recurrences later than this have also been reported.

Objective: The aim of this study was to investigate the incidence and risk factors of recurrence in patients who have early rectal cancer 10 years after transanal local excision.

Design: Patients with early rectal cancer who underwent transanal local excision from October 1994 to December 2010 were retrospectively reviewed. We reviewed the demographics and clinicopathologic features of primary lesions and analyzed the incidence and risk factors of recurrence.

Settings: This investigation was conducted at a tertiary university hospital.

Patients: A total of 295 patients who underwent transanal local excision for pTis ($N = 155$) or pT1 ($N = 140$) early rectal cancer were included in the analysis.

Intervention: Transanal local excision was performed for each patient to excise primary rectal lesions.

Main outcome measures: The primary end point of this study was the incidence of recurrence, especially late recurrence. The secondary end point was risk factors for recurrence.

Results: The 10-year cumulative local recurrence rate was 6.7% in pTis and 18.0% in pT1 patients. The rate of late local recurrence was 2.8% in pTis and 3.7% in pT1 patients. There was no evidence of late systemic recurrence 5 years after transanal local excision. In pT1 patients, a higher risk of recurrence was associated with an invasion depth of sm3, the presence of lymphovascular invasion, and a positive resection margin.

Conclusions: Late recurrence can occur in patients with early rectal cancer who have undergone transanal local excision. Transanal local excision can be performed in selective patients with biologically favorable tumors, and 10-year postoperative surveillance should be considered for these patients.

Commentaires : *Bien que de méthodologie critiquable, cette série coréenne d'électro-résections transanales (ERTA) de petites tumeurs rectales (pTis et pT1) attire l'attention :*

- *tout d'abord, par la taille de son effectif (295 patients inclus sur un total de 413 avant exclusion pour maladie récidivante, suivi inférieur à deux ans…) ;*
- *ensuite, par son message : des risques non négligeables de récidives tardives, au-delà des cinq ans habituellement retenus comme délai de guérison. En effet, le taux de récidive locale à dix ans était de près de 7 % pour les tumeurs pTis et de 18 % pour les pT1 !*

Près de 3 et 4 % de récidives tardives entre cinq et dix ans de suivi, respectivement pour les tumeurs pTis et pT1. Mais attention, en lisant entre les lignes, seulement 43 patients ont été suivis jusqu'à dix ans, et le délai moyen de suivi de l'étude était seulement de six ans.

De quoi réfléchir malgré tout à allonger la surveillance de nos patients…

Trois facteurs de risque de récidive étaient identifiés pour les tumeurs pT1 : envahissement sm3, invasion lymphatique, marge de résection positive. Il n'était pas mis en évidence de facteur prédictif de récidive en analyse multivariée pour les tumeurs pTis.

Ce dernier item (envahissement de la marge opératoire) laisse planer un doute sur la prise en charge : les patients à marge envahie n'auraient-ils pas dû bénéficier d'un traitement complémentaire ? Pas de précision à ce sujet disponible dans cet article…

Cotation : ☺☺

D. Bouchard

Impact of Surgery on Relationship Quality in Patients with Ulcerative Colitis and Their Partners

Cohan JN, Rhee JY, Finlayson E, et al (2015)
Dis Colon Rectum 58:1144-50

Background: Although social support is important for quality of life in patients undergoing surgery for ulcerative colitis, the impact of surgery on patient relationships is not known.

Objective: We examined relationship parameters in patients with ulcerative colitis and their partners before and 6 months after surgery.

Design: This was a prospective cohort in which we performed an exploratory analysis.

Settings: Patients were enrolled from an academic medical center.

Patients: Surgical patients with ulcerative colitis and their partners were invited to participate.

Interventions: Patients underwent proctocolectomy in 1, 2, or 3 stages.

Main outcome measures: We measured quality of life and sexual function in patients, as well as relationship quality, empathy, and sexual satisfaction in patients and partners before and 6 months after surgery using validated questionnaires.

Results: The study sample consisted of 74 participants, including 37 patients (25 men and 12 women) and their opposite-sex partners. Quality of life improved significantly in male and female patients after surgery. Sexual function scores also improved after surgery in male and female patients; however, the changes reached statistical significance in male patients only. Sexual satisfaction scores improved significantly after surgery in female patients and their partners. There was little change in relationship quality or empathy after surgery, with the exception of slightly improved relationship quality reported by male partners. In general, patients and partners reported levels of relationship quality and empathy similar to normative populations.

Conclusions: Male and female patients with ulcerative colitis have high-quality relationships that are not negatively affected by surgical treatment. Changes in sexual function do not necessarily coincide with changes in sexual satisfaction in this patient population. Future studies should evaluate the effect of high-quality relationships on surgical outcomes.

Commentaires : *Un sujet très à la mode : la qualité de vie des patients atteints de MICI au sens large et les PRO (*Patients Related Outcomes*) en particulier.*

Cette série se focalise sur le domaine sexuel des patients ayant subi une proctocolectomie pour RCH : fonction sexuelle, satisfaction sexuelle, relation avec leur partenaire

stable (qu'ils avaient avant et qu'ils ont toujours six mois après la chirurgie).

Trente-sept patients et leurs partenaires ont été interrogés sur le sujet :

- *message n°°1 : amélioration significative de la qualité de vie après chirurgie dans les deux sexes : c'est rassurant et heureusement pas nouveau !*
- *message n°°2 : fonction sexuelle améliorée après chirurgie dans les deux sexes mais seulement chez les hommes de manière statistiquement significative : compréhensible sans doute pour des raisons anatomofonctionnelles…*
- *message n°°3 : il existe une inadéquation entre l'amélioration de la fonction sexuelle et de la satisfaction sexuelle : les hommes ont une amélioration significative du score fonctionnel mais une amélioration non significative de la satisfaction sexuelle, alors que c'est l'inverse pour les femmes… Les femmes auraient-elles une libido plus complexe que celle des hommes ?*
- *message n°°4 : pas de dégradation significative de la relation de couple avant–après chirurgie, évaluation fondée sur deux scores spécifiques.*

Voilà des messages rassurants à donner à nos patients atteints de RCH sévères avant qu'ils ne rencontrent le chirurgien, ce d'autant que d'autres études récentes concluaient à une altération de la relation de couple des patients de même profil.

On attend avec impatience des études de plus grande envergure.

Cotation : ☺ ☺ ☺

D. Bouchard

The Risk of Definitive Stoma Formation at 10 Years after Low and Ultralow Anterior Resection for Rectal Cancer

Celerier B, Denost Q, Van Geluwe B, et al (2016)
Colorectal Disease 18:59–66

Aim: The long-term risk of definitive stoma after sphincter-saving resection (SSR) for rectal cancer is underestimated and has never been reported for ultra-low conservative surgery. We report the 10-year risk of definitive stoma after SSR for low rectal cancer.

Method: From 1994 to 2008, patients with low rectal cancer who were suitable for SSR were analysed retrospectively. Patients were divided into the following four groups: low colorectal anastomosis (LCRA); coloanal anastomosis (CAA); partial intersphincteric resection (pISR); and total intersphincteric resection (tISR). The end-point was the risk of a definitive stoma according to the type of anastomosis.

Results: During the study period, 297 patients had SSR for low rectal cancer. The incidence of definitive stoma increased from 11% at 1 year to 22% at 10 years. The reasons were no closure of the loop ileostomy (4.7%), anastomotic morbidity (6.5%), anal incontinence (8%) and local recurrence (5.2%). The risk of definitive stoma was not influenced by type of surgery: 26 vs 18% vs 18 vs 19% ($P = 0.578$) for LCRA, CAA, pISR and tISR, respectively. Independent risk factors for definitive stoma were age > 65 years and surgical morbidity.

Conclusion: The risk of a definitive stoma after SSR increased two-fold between 1 and 10 years after surgery, from 11 to 22%. Ultralow conservative surgery (pISR and tISR) did not increase the risk of definitive stoma compared with conventional CAA or LCRA.

Commentaires : *S'il existe de nombreuses publications faisant état du risque de stomie définitive pour « échec » d'anastomose colorectale basse ou coloanale, ces articles ont le plus souvent un suivi assez court et s'adressent principalement aux échecs dus aux fistules anastomotiques et au sepsis pelvien chronique postopératoire. L'intérêt de cette nouvelle publication de l'équipe d'Éric Rullier est non seulement de donner des résultats à dix ans, sur une série importante de patients opérés, mais aussi de donner ce taux d'échec tardif quelle que soit la raison de la stomie définitive. On voit ainsi que ce risque de stomie, qui atteint 22 % à dix ans, n'est pas lié à la hauteur de l'anastomose (la résection intersphinctérienne n'augmente donc pas ce risque de stomie définitive), et concerne dans près de la moitié des cas un échec fonctionnel. Cette information est importante évidemment à donner au patient en préopératoire.*

Cotation : ☺ ☺ ☺

Y. Panis

Long-Term Outcomes after Initial Presentation of Diverticulitis

Rose J, Parina RP, Faiz O, et al (2015)
Ann Surg 262:1046–53

Objective: This study aims to determine the long-term outcomes of diverticulitis and to apply the findings to current practice patterns.

Background: The long-term morbidity and mortality of diverticulitis are not well defined. Current practice guidelines for diverticulitis are based on limited evidence.

Methods: The California Office of Statewide Health Planning and Development database was queried for longitudinal observations across all hospitals from 1995 to 2009. Recurrence up to 15 years, medical versus surgical

treatment, and mortality after recurrence were analyzed for patients after emergent admission for diverticulitis.

Results: Among the 210,268 patients admitted emergently with diverticulitis, 179,649 (85%) were managed medically at their index admission. Of these medically managed patients, 27,450 (16.3%) suffered a second diverticulitis episode. On multivariable analysis, predictors of mortality with recurrence included the following [hazard ratio (95% confidence interval)]: age more than 50 years [5.19 (3.05–8.29)]; previous tobacco use [1.40 (1.18–1.66)]; and complicated initial presentation with obstruction [1.33 (1.06–1.65)], abscess [2.18 (1.60–2.97)], peritonitis [3.14 (1.99–4.97)], sepsis [1.88 (1.29–2.73)], and fistula [3.50 (2.17–5.66)]. The mortality of delayed elective surgical intervention after the first episode of emergent diverticulitis was 0.3% compared to 4.6% for emergent resection during a second episode.

Conclusions: Eighty-five percent of emergent diverticulitis patients do not recur after initial medical treatment. However, in view of significantly worse outcomes associated with diverticulitis recurrence, resection should be strongly considered for diverticulitis patients older than 50 years or those who present with a complicated clinical picture.

Commentaires : *Voilà une publication portant sur la bagatelle de 210 000 patients qui devrait (du moins j'espère…) parvenir à calmer les ardeurs des tenants d'un discours par trop simpliste qu'on pourrait résumer de la façon suivante : « la diverticulite, ça ne récidive jamais. Ce n'est jamais grave. Et de toutes les façons, il ne faut jamais opérer à froid ».*

Comme chacun sait, « en médecine, comme en amour, ni de jamais ni de toujours ». Ces staliniens ont donc évidemment tort, comme le laisse à penser cette étude de population qui, au contraire, plaide pour la chirurgie élective, notamment en cas de forme compliquée lors de la première poussée. Cela tombe bien, c'est écrit dans les recommandations françaises… Le débat sur les jeunes de moins de 50 ans reste lui encore ouvert et non réglé par ce papier.

Cotation : ☺ ☺ ☺

Y. Panis

Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study

André T, de Gramont A, Vernerey D, et al (2015)
J Clin Oncol 33:4176–87

Purpose: The MOSAIC (Multicenter International Study of oxaliplatin/fluorouracil/leucovorin in the Adjuvant Treatment of Colon Cancer) study has demonstrated 3-year disease-free survival (DFS) and 6-year overall survival (OS) benefit of adjuvant oxaliplatin in stage II to III resected colon cancer. This update presents 10-year OS and OS and DFS by mismatch repair (MMR) status and BRAF mutation.

Methods: Survival actualization after 10-year follow-up was performed in 2,246 patients with resected stage II to III colon cancer. We assessed MMR status and BRAF mutation in 1,008 formalin-fixed paraffin-embedded specimens.

Results: After a median follow-up of 9.5 years, 10-year OS rates in the bolus/infusional fluorouracil plus leucovorin (LV5FU2) and LV5FU2 plus oxaliplatin (FOLFOX4) arms were 67.1 versus 71.7% (hazard ratio [HR]: 0.85; $P = 0.043$) in the whole population, 79.5 versus 78.4% for stage II (HR: 1.00; $P = 0.980$), and 59.0 versus 67.1% for stage III (HR: 0.80; $P = 0.016$) disease. Ninety-five patients (9.4%) had MMR-deficient (dMMR) tumors, and 94 (10.4%) had BRAF mutation. BRAF mutation was not prognostic for OS ($P = 0.965$), but dMMR was an independent prognostic factor (HR: 2.02; 95% CI: 1.15 to 3.55; $P = 0.014$). HRs for DFS and OS benefit in the FOLFOX4 arm were 0.48 (95% CI: 0.20 to 1.12) and 0.41 (95% CI: 0.16 to 1.07), respectively, in patients with stage II to III dMMR and 0.50 (95% CI: 0.25 to 1.00) and 0.66 (95% CI: 0.31 to 1.42), respectively, in those with BRAF mutation.

Conclusion: The OS benefit of oxaliplatin-based adjuvant chemotherapy, increasing over time and with the disease severity, was confirmed at 10 years in patients with stage II to III colon cancer. These updated results support the use of FOLFOX in patients with stage III disease, including those with dMMR or BRAF mutation.

Commentaires : *Cette nouvelle publication concernant l'essai MOSAIC confirme à long terme (à dix ans) le bénéfice en survie globale et en survie sans progression du FOLFOX par rapport au LV5FU2 après résection d'un cancer colique de stade III (en particulier pour les stades III N2). Le bénéfice n'est pas observé pour les tumeurs de stade II qui reste toujours un sujet de controverse quant à l'intérêt d'une chimiothérapie adjuvante de façon globale et du type de chimiothérapie (5-FU avec ou sans oxaliplatine) à proposer.*

L'analyse moléculaire confirme ici le bon pronostic déjà connu des tumeurs MSI. En revanche, la valeur pronostique du statut mutationnel de BRAF en situation adjuvante reste controversée, car la présence de cette mutation n'avait pas d'impact dans cette étude sur la survie, alors que d'autres études récentes comme l'analyse de l'essai PETACC8 montrent le contraire (Taïeb J et al. JAMA Oncol 2016 Jan 14 [Epub ahead of print]).

Enfin, point important, l'étude suggère le maintien du bénéfice du FOLFOX en cas de tumeur MSI ou de tumeur BRAF muté, mais la différence était toutefois non significative, potentiellement liée à un manque de puissance, car

l'effectif des sous-groupes MSI ou BRAF muté restait faible puisque l'analyse moléculaire n'a concerné qu'à peine 45 % des patients initialement inclus dans l'essai.

Cotation : ☺☺

A. Lièvre

The Anal Fistula Plug in Crohn's Disease Patients with Fistula-in-Ano: a Systematic Review

Nasseri Y, Cassella L, Berns M, et al (2016)
Colorectal Dis doi: 10.1111/codi.13268 [Epub ahead of print]

Aim: The study aimed to review, consolidate, and analyze the findings of studies investigating the efficacy of anal fistula plugs (AFPs) in treating fistula-in-ano in Crohn's patients.

Method: A literature review was conducted via Pubmed, Embase, Medline, Scopus and Cochrane Library for the period 1995–2015. Articles were selected and reviewed based on specific inclusion and exclusion criteria.

Results: A total of 16 studies were extracted, of which 12 were included in the systematic review. In total, 84 patients (N = 1–20 per study), with a median age of 45 (18–72) years, and a median follow-up time of 9 (3–24) months were analyzed. The total success rate, defined as closure of the fistula track, was 49/84 (58.3%, 95% CI: [47–69]). Success in patients with recurrent anal fistulas was 2/5 (40%, 95% CI: [5–85]). Overall, the success rates of Surgisis® and GORE® BIO-A® brand plugs were 48/80 (60%, 95% CI: [48–71]) and 1/4 (25%, 95% CI: [1–81]). The recurrence rate of fistula-in-ano in the five studies that reported recurrence was 3/22 (13.6%). In two comparative studies, inferior overall success rates were found in patients who received preoperative immunomodulators versus those who did not (3/11 [27.3%] vs 17/23 [73.9%]).

Conclusion: The studies suggest that the use of an AFP in Crohn's disease patients is a safe procedure with reasonable success, little morbidity and a low risk of incontinence. The current literature is limited by a number of factors including small study cohorts, grouping of fistulas in Crohn's disease with other types of anal fistula, short and highly variable follow-up times, and multiple confounding factors such as number of fistula tracts, use of pre-operative steroids or immunosuppressants, previous use of setons and variation in surgical technique.

Commentaires : *De l'intérêt parfois limité des revues systématiques. Les auteurs de cet article ont cherché à rassembler les données existantes sur l'insertion d'un plug dans les fistules anales de maladies de Crohn. Mais alors que cette méthodologie cherche à augmenter la quantité de données analysables en une seule fois pour en faire émerger des preuves de meilleure qualité, la cible semble ici avoir été manquée. L'énumération des différentes études recrutées met en lumière leur faiblesse plus qu'elle ne donne l'impression de renforcer l'évidence. Les effectifs sont minuscules, les études sont non contrôlées, etc. Au total, cela n'enlève rien au mérite des auteurs princeps et secondaires, mais il est clair qu'aucune conclusion probante ne se dégage de ce travail. Le taux de « succès » du plug se situe dans la moyenne de ce qui a pu être rapporté, ce qui est logique, mais il est impossible d'en déduire que le plug a eu un intérêt indiscutable pour les différents patients soumis à ce traitement. Non par chauvinisme mais par réalisme, on invitera le lecteur à se reporter à la conclusion décevante mais crédible de l'essai du GETAID récemment publié [Senéjoux et al, J Crohns Colitis 2015] : l'insertion d'un plug ne semble pas faire mieux que le retrait simple du séton.*

Cotation : ☺

J.D. Zeitoun

Doppler-Guided Haemorrhoidal Artery Ligation with Suture Mucopexy Compared with Suture Mucopexy Alone for the Treatment of Grade 3 haemorrhoids: a Prospective-Randomised Controlled Trial

Aigner F, Kronberger I, Oberwalder M, et al (2016)
Colorectal Dis doi: 10.1111/codi.13280.
[Epub ahead of print]

Aim: Novel minimally invasive techniques aimed to reposition the haemorrhoidal zone have been established for prolapsing haemorrhoids. We present a prospective randomised controlled trial to evaluate the efficacy of additional Doppler-guided ligation of submucosal haemorrhoidal arteries in patients with symptomatic grade 3 haemorrhoids. The trial was registered as ClinicalTrials. gov Identifier: NCT02372981.

Method: All consecutive patients with symptomatic grade 3 haemorrhoids were randomly allocated to one of the two study arms: (Group A) DG-HAL with mucopexy or (Group B) mucopexy alone. End points were postoperative pain, faecal incontinence, bleeding, residual prolapse and alterations of vascularisation of the anorectal vascular plexus. Vascularisation of the anorectal vascular plexus was assessed by transperineal contrast enhanced ultrasound. Patients recorded their symptoms in a diary maintained for a month.

Results: Forty patients were recruited and randomised to the two study groups. Patients in Group A had less pain in the first two postoperative weeks. At the 12-month

follow-up, two patients in Group A (10%) and one in Group B (5%) showed recurrent grade 3 haemorrhoids ($P = 0.274$). No significant morphological changes were observed in the transperineal ultrasound findings between the preoperative assessment and the assessment at 1 and 6 months in either group ($P > 0.05$).

Conclusion: Mucopexy techniques for treating prolapsing haemorrhoids are effective, but Doppler-guided HAL does not add significantly to the results achieved by mucopexy Repositioning the haemorrhoidal zone is the key to success, and mucopexy should be placed at the sites of the largest visible prolapse. This article is protected by copyright. All rights reserved.

Commentaires : *Un essai décevant d'une équipe qui nous a habitués à mieux. On se souvient en effet des descriptions brillantes de la vascularisation anopérinéale après hémorroïdopexie [Aigner et al,* Colorectal Dis *2010], lesquelles avaient amené les auteurs à observer que la technique de Longo n'était pas associée à une réduction significative du débit artériel et à formuler que c'est via le retour veineux que cette chirurgie était efficace. Ce nouvel article nous frustre, non que la question posée ne soit pas pertinente (évaluation de l'intérêt spécifique des ligatures sous doppler dans la mucopexie). Mais c'est la petitesse de l'effectif qui rend l'essai à notre sens non conclusif. Bien que les auteurs n'aient observé aucune différence d'efficacité entre les deux bras (avec ou sans ligatures sous doppler), il semble déraisonnable de condamner sur ce seul résultat les ligatures sous doppler. Depuis la première étude qui avait semé le doute sur l'intérêt réel des ligatures guidées, aucun essai solide n'a pu apporter une suite de réponse à cette question médicale et économique. On a du mal à imaginer que ces ligatures ciblées n'aient d'intérêt chez aucun malade tant elles semblent directement s'adresser à l'un des mécanismes de la maladie hémorroïdaire, mais comment identifier ces patients justement bénéficiaires ? C'est peut-être la principale question sans réponse sur le sujet.*

Cotation : ☺

J.D. Zeitoun

Determining the Optimal Timing for Initiation of Adjuvant Chemotherapy after Resection for Stage II and III Colon Cancer

Sun Z, Adam MA, Kim J, et al (2016)
Dis Colon Rectum 59:87–93. doi: 10.1097/DCR

Background: Several reports suggest that the efficacy of adjuvant chemotherapy on survival diminishes over time for colon cancer; however, precise timing of its loss of benefit has not been established.

Objective: This study aimed to determine the relationship between time to adjuvant chemotherapy and survival and to identify a threshold for increased risk of mortality.

Design: This was a retrospective study. Multivariable Cox proportional hazard modeling with restricted cubic splines was used to evaluate the adjusted association between time to adjuvant chemotherapy and overall survival and to establish an optimal threshold for the initiation of therapy.

Settings: Data were collected from the National Cancer Data Base.

Patients: Adults who received adjuvant chemotherapy following resection of stage II to III colon cancers were selected.

Main outcome measures: The primary outcome measured was overall survival.

Results: A total of 7,794 patients were included. After adjusting for clinical, tumor, and treatment characteristics, our model determined a critical threshold of chemotherapy initiation at 44 days from surgery, after which there was an increase in the overall mortality. At a median follow-up of 61 months, the risk of mortality was increased in those who received adjuvant chemotherapy after 44 days from surgery (adjusted HR: 1.14; 95% CI: [1.05–1.24]; $P = 0.002$), but not in those who received chemotherapy before 44 days from surgery ($P = 0.11$). Each additional week of delay was associated with a 7% decrease in survival (HR: 1.07; 95% CI: [1.04–1.10]; $P < 0.001$).

Limitations: This study was limited by selection bias and the inability to compare specific chemotherapy regimens.

Conclusions: This study objectively determines the optimal timing of adjuvant chemotherapy for patients with resected colon cancer. Delay beyond 6 weeks is associated with compromised survival. These findings emphasize the importance of the timely initiation of therapy, and suggest that efforts to enhance recovery following surgery have the potential to improve survival by decreasing delay to adjuvant chemotherapy.

Commentaires : *Il s'agit d'une cohorte nationale de 7 794 patients avec cancer du côlon stades II–III nécessitant une chimiothérapie adjuvante. Les auteurs rapportent qu'au-delà de six semaines après la chirurgie, la survie du patient est altérée et que chaque semaine supplémentaire est associée à une perte de 7 % de survie globale. Cela signifie donc, contrairement à ce qui est souvent rapporté, qu'au-delà de six semaines, il y aurait encore un intérêt à débuter une chimiothérapie adjudante, même s'il existe une perte de chance pour le patient. De plus, l'importance de la réhabilitation précoce, versant oncologie, est soulignée de façon intéressante par les auteurs.*

Cotation : ☺ ☺

Q. Denost

The Outcomes and Patterns of Treatment Failure after Surgery for Locally Recurrent Rectal Cancer

Harris CA, Solomon MJ, Heriot AG, et al (2015)
Ann Surg Dec 16 [Epub ahead of print]

Objective: To assess the outcomes and patterns of treatment failure of patients who underwent pelvic exenteration surgery for recurrent rectal cancer.

Background: Despite advances in the management of rectal cancer, local recurrence still occurs. For appropriately selected patients, pelvic exenteration surgery can achieve long-term disease control.

Methods: Prospectively maintained databases of 5 high volume institutions for pelvic exenteration surgery were reviewed and data combined. We assessed the combined endpoints of overall 5-year survival, cancer-specific 5-year mortality, local recurrence, and the development of metastatic disease.

Results: Five hundred thirty-three patients who had undergone surgery for locally recurrent rectal cancer were identified. Five-year cancer-specific survival for patients with a complete (R0) resection is 44%, which was achieved in 59% of patients. For those with R1 and R2 resections, the 5-year survival was 26% and 10%, respectively. Radical resection required sacrectomy in 170 patients (32%), and total cystectomy in 105 patients (20%). Treatment failure included local recurrence alone in 75 patients (14%) and systemic metastases with or without local recurrence in 226 patients (42%). Chemoradiotherapy before exenteration was associated with a significant ($P < 0.05$) improvement in overall 5-year cancer-specific survival for those patients with an R0 resection. Postoperative chemotherapy did not alter outcomes.

Conclusions: R0 resection of the pelvic recurrence is the most significant factor affecting overall and disease-free survival. The surgery is complex and often highly morbid, and where possible patients should be given perioperative chemoradiotherapy. Further investigations are required to determine the role of adjuvant chemotherapy.

Commentaires : *Il est intéressant de voir dans cet article regroupant les données de cinq grands centres internationaux de prise en charge des récidives pelviennes de cancer du rectum que le taux de R0 est le même que dans les séries nationales avec des centres non experts. Les localisations des récidives et les chirurgies réalisées sont bien entendu différentes que dans les séries nationales ou les méta-analyses. L'impact du statut R0 sur la survie globale et sans récidive est déjà bien connu et est rappelé dans cet article. Il est intéressant de voir que les auteurs soulignent le meilleur pronostic des patients avec traitement néoadjuvant dans ces indications. Cela permet de glisser que le groupe Greccar travaille sur un projet en ce sens…*

Cotation : ☺ ☺

Q. Denost

Watch-and-wait Approach versus Surgical Resection after Chemoradiotherapy for Patients with Rectal Cancer (the OnCoRe project): a Propensity-score Matched Cohort Analysis

Renehan AG, Malcomson L, Emsley R, et al (2015)
Lancet Oncol Dec 16 pii: S1470-2045(15)00467-2.
doi:10.1016/S1470-2045(15)00467-2 [Epub ahead of print]

Background: Induction of a clinical complete response with chemoradiotherapy, followed by observation via a watch-and-wait approach, has emerged as a management option for patients with rectal cancer. We aimed to address the shortage of evidence regarding the safety of the watch-and-wait approach by comparing oncological outcomes between patients managed by watch and wait who achieved a clinical complete response and those who had surgical resection (standard care).

Methods: Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) was a propensity-score matched cohort analysis study, that included patients of all ages diagnosed with rectal adenocarcinoma without distant metastases who had received preoperative chemoradiotherapy (45 Gy in 25 daily fractions with concurrent fluoropyrimidine-based chemotherapy) at a tertiary cancer centre in Manchester, UK, between Jan 14, 2011, and April 15, 2013. Patients who had a clinical complete response were offered management with the watch-and-wait approach, and patients who did not have a complete clinical response were offered surgical resection if eligible. We also included patients with a clinical complete response managed by watch and wait between March 10, 2005, and Jan 21, 2015, across three neighbouring UK regional cancer centres, whose details were obtained through a registry. For comparative analyses, we derived one-to-one paired cohorts of watch and wait versus surgical resection using propensity-score matching (including T stage, age, and performance status). The primary endpoint was non-regrowth disease-free survival from the date that chemoradiotherapy was started, and secondary endpoints were overall survival, and colostomy-free survival. We used a conservative *P*-value of less than 0.01 to indicate statistical significance in the comparative analyses.

Findings: Two hundred and fifty-nine patients were included in our Manchester tertiary cancer centre cohort, 228 of whom underwent surgical resection at referring hospitals and 31 of whom had a clinical complete response, managed

by watch and wait. A further 98 patients were added to the watch-and-wait group via the registry. Of the 129 patients managed by watch and wait (median follow-up 33 months [IQR 19–43]), 44 (34%) had local regrowths (3-year actuarial rate 38% [95% CI 30–48]); 36 (88%) of 41 patients with non-metastatic local regrowths were salvaged. In the matched analyses (109 patients in each treatment group), no differences in 3-year non-regrowth disease-free survival were noted between watch and wait and surgical resection (88% [95% CI 75–94] with watch and wait vs 78% [63–87] with surgical resection; time-varying $P = 0.043$). Similarly, no difference in 3-year overall survival was noted (96% [88–98] vs 87% [77–93]; time-varying $P = 0.024$). By contrast, patients managed by watch and wait had significantly better 3-year colostomy-free survival than did those who had surgical resection (74% [95% CI 64–82] vs 47% [37–57]; hazard ratio 0.445 [95% CI 0.31–0.63; $P < 0.0001$), with a 26% (95% CI 13–39) absolute difference in patients who avoided permanent colostomy at 3 years between treatment groups.

Interpretation: A substantial proportion of patients with rectal cancer managed by watch and wait avoided major surgery and averted permanent colostomy without loss of oncological safety at 3 years. These findings should inform decision making at the outset of chemoradiotherapy.

Commentaires : *Voici une nouvelle étude évaluant les possibilités de conservation rectale par la stratégie* Watch-and-Wait (WaW). *Il s'agit d'une étude rétrospective utilisant un score de propension pour comparer cette stratégie avec la stratégie classique associant radiochimiothérapie puis proctectomie avec exérèse totale du mésorectum. Les auteurs de cette étude publiée dans une revue prestigieuse concluent que cette approche permet à environ 25 % des patients d'éviter une colostomie définitive, et ce sans surrisque oncologique. Bien que méthodologiquement satisfaisante, cette étude suggère plusieurs remarques :*

- *on note 34 % de patients en réévolution locale dans le groupe WaW qui ont été exclus de l'analyse de survie sans récidive pour créer un critère appelé* non-regrowth disease-free survival *qui, du coup, est même en faveur de la stratégie conservatrice ;*
- *le suivi est seulement à trois ans et manque sûrement de recul pour analyser les réévolutions locales ;*
- *on est un peu surpris d'un taux de 74 % de colostomie définitive dans le groupe chirurgie !*
- *bien que normalement comparable puisque l'on utilise un test de propension, les patients dans le groupe WaW avaient par définition une réponse complète et ceux du groupe chirurgie une réponse incomplète après radiochimiothérapie, ce qui est en soi un facteur de bon pronostic qui gomme peut-être de moins bons résultats dans le groupe WaW. On peut donc se demander si les groupes sont finalement réellement comparables. Il faudrait dans le groupe chirurgie aussi des tumeurs en réponse complète ;*
- *enfin, parmi les patients en réévolution locale dans le groupe WaW, 30 sur 41 ont pu bénéficier d'une chirurgie de sauvetage avec 54 % de colostomie d'emblée. On aurait aimé en savoir un peu plus sur ce groupe : taux de colostomie définitive à l'issue de la surveillance, morbidité de la chirurgie et résultats oncologiques de ce petit groupe.*

Cette approche séduisante de conservation apparaît possible et efficace pour un groupe de patients, dont il faudrait pouvoir déterminer les caractéristiques en début de stratégie. La chirurgie a quand même encore de beaux jours devant elle. Des études randomisées avec un recul suffisant paraissent nécessaires pour avancer sur le sujet.

Cotation : ☺ ☺

E. Cotte

Non-Steroidal Anti-Inflammatory Drug Use and Risk of Anastomotic Leakage after Anterior Resection: a Protocol-Based Study

Rutegård M, Westermark S, Kverneng-Hultberg D, et al (2016)
Dig Surg 33:129–35

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) have been introduced as opioid-sparing analgesics in colorectal surgery. However, recent research has implicated these drugs as risk factors for anastomotic dehiscence.

Methods: The Swedish Colorectal Cancer Registry was used to identify all patients operated with anterior resection for rectal cancer at centres that performed more than 25 abdominal operations per year, from 2007 to 2012, inclusive. The registry provided individual patient data on demographic variables and symptomatic anastomotic leakage. The patient exposure to NSAIDs was defined according to the protocol of the hospital at which the patient was operated. Logistic regression was employed to estimate ORs and 95% CIs, adjusting for confounders.

Results: The study cohort comprised 2,605 patients operated at 21 centres. In the NSAID group, 102/1,458 (7.0%) suffered an anastomotic leak, as compared to 124/1,023 (10.8%) in the non-NSAID group. With adjustment for confounding, patients treated at NSAID hospitals had a reduced risk of developing anastomotic leakage (OR: 0.68; 95% CI: [0.48-0.96]).

Conclusions: In this retrospective protocol-based study, NSAIDs did not increase the risk of anastomotic leakage

after anterior resection for rectal cancer. The postoperative use of NSAIDs may not be detrimental, but more research is warranted.

Commentaires : *À l'ère de la réhabilitation améliorée après chirurgie (RAAC), l'utilisation des AINS en post-opératoire est une solution pour l'analgésie avec épargne morphinique. Après une période, où tous les protocoles prônaient leur utilisation, certaines études et notamment deux publiées en 2012 (Gorissen et al. Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery. Brit J Surg 2012; 99:721–7 ; et Klein M et al. Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study-based on prospective data. BMJ, 2012 Sep 26;345) ont mis le doute sur le risque de fistule anastomotique associé à l'usage des AINS. Voici une nouvelle étude sur le sujet, cette fois-ci suédoise, avec une large cohorte de 2 605 patients, qui ne retrouve pas d'effet délétère des AINS, voire un effet protecteur sur la survenue de fistule anastomotique. Le débat reste donc toujours ouvert !*

Cotation : ☺ ☺

E. Cotte