Title: Pathological complete response in young patients with MSI rectal cancer

Running title: Microsatellite status in early age onset rectal cancer

Authors: REACCT Collaborative

Corresponding Author: Alexandra Zaborowski
Address: Centre for Colorectal Disease
St. Vincent's University Hospital
Elm Park
Dublin 4
Ireland
Email: zaborowa@tcd.ie
Contact number: +353877783672

Financial support: None
Disclosures: The authors have no relevant financial disclosures or conflicts of interest
Publication type: Rapid research communication
This paper is not based on a previous communication to a society or meeting.

Introduction

A major research focus of the past few decades in colorectal cancer (CRC) has been deciphering the underpinning biomolecular processes in order to guide therapeutic decision making and optimise outcomes. Several forms of genetic instability have been described in CRC. Chromosomal instability (CIN) is the hallmark of 85% of cases, whilst microsatellite instability (MSI) is identified in approximately 15%[1].

MSI, a well-defined feature of defective DNA mismatch repair (MMR), may be due to sporadic epigenetic silencing of the MLH1 gene or constitutive mutations in one of the MMR genes (i.e. Lynch Syndrome)[2]. Immunohistochemistry is used to classify tumours as MMR-deficient or MMR-proficient, whilst PCR is used to identify MSI. Dichotomisation of CRC on the basis of MMR or MSI status is now routinely recommended for all patients regardless of age at diagnosis or family history.

Apart from representing an important screening tool for Lynch Syndrome, MSI status may also provide valuable prognostic and therapeutic information. MSI is associated with improved disease-specific survival[3,4]. Controversy exists as to whether MSI confers a relative resistance to 5-fluorouracil (5-FU) chemotherapy, and the impact of MSI status on response to neoadjuvant chemoradiotherapy is unclear[5,6].

One of the biggest epidemiological crises facing the world of surgical oncology, is the rapidly rising incidence of early onset rectal cancer (EORC), defined as diagnosis before 50 years[7,8]. The reasons for this increase are unclear. Whilst overlapping key drivers are implicated in both early and late-onset disease, a number of notable biomolecular differences have been observed[9-11]. Although EORC is more likely to occur in the context of a hereditary cancer syndrome, the majority of cases are sporadic and microsatellite stable[12,13]. As young patients have historically represented a small proportion of cases, the impact of microsatellite status on disease-specific outcomes in this patient group is unknown. Individual institutional data in isolation are too small for meaningful analyses. The REACCT Collaborative was established to aggregate large volume real-world data from specialist centres across the world. The objective of this study was to evaluate the impact of microsatellite status on oncological outcomes in patients diagnosed with rectal cancer aged less than 50 years.

Methods

A complete description of the study methodology is available in *Appendix S1.* In brief, a retrospective international multicentre observational cohort study to assess the clinicopathological features, molecular characteristics and disease specific outcomes of patients diagnosed with early age onset rectal cancer over a 20-year period (2000 to 2020) was performed. Inclusion criteria were adults aged between 18 and 49 years with a histologically confirmed diagnosis of non-metastatic rectal cancer undergoing surgery with curative intent and known MSI status. Data was provided by members of the REACCT Collaborative. Patients who fulfilled the inclusion criteria of the study were selected from the REACCT Collaborative database. Collected data included baseline patient demographics, clinical stage, surgical, and treatment data, histopathological and molecular features, and cancer-specific as well as overall survival information. Microsatellite instability was determined by PCR or immunohistochemistry (IHC). Loss of mismatch repair (MMR) proteins *MLH1*, *PMS2*, *MSH2* or *MSH6* on IHC was classified as MSI. A hereditary cancer syndrome was defined as diagnosis of a constitutive pathogenic variant on germline testing.

Results

Baseline demographics

A total of 400 patients diagnosed with rectal cancer under the age of 50 over a 20-year interval were included in the study. Of those, 50 had tumours with defined MSI. The remaining 350 had MSS tumours. This represents 9.1% of the total number of patients with EOCRC in the REACCT Collaborative database. The median (range) age was 43 (23-49) years and 204 (58.3%) were male. MSI was associated with a first degree relative with CRC. Females accounted for 58% of the MSI group. There was no difference in clinical stage between the two groups.

Pathological features

There were no significant differences in differentiation, or lymphovascular, extramural venous or perineural invasion between the two groups. A complete pathologic response (pCR) was more common among the MSI group (32.3% vs 15.7%, p = 0.044). Patients with MSI were less likely to pathological node positive disease (22.0% vs 41.7%, p = 0.008).

Molecular characteristics

MSI tumours were more likely to occur in the context of genetic predisposition. A hereditary

cancer syndrome was diagnosed in 30.0% of patients (n=15) with MSI tumours compared to 3.1% of patients (n=11) with MSS tumours (HR 13.21, 95% CI 5.63-30.97, p = <0.0001). Only 72.0% (n=36) of the MSI group and 65.7% (n=230) of the MSS group had undergone genetic testing at the time of data collection.

Survival

Survival data was available for 392 patients (98%). Overall median follow-up was 35 months (1-197). Among the MSI group median overall survival was 58 months (1-197), with 1-, 3- and 5-year overall survival rates of 100%, 95% and 89% respectively. Equivalent values in the MSS group were 32 months (1-158) and 96%, 90% and 84%. Median disease-free survival was 57 months in the MSI group (1-197) and 23 months (1-158) in the MSS group. In patients with MSI, the disease-free survival rate at 1, 3 and 5 years was 98%, 90% and 87%, compared with 89%, 72% and 66% among those with MSS tumours (*Figure 1*). On sub-analysis based on pathological stage, survival was better in the MSI group for stage I, II and III disease, however the differences were not statistically significant.

Disease recurrence

In the MSI group, no patient developed locoregional disease recurrence compared with 24 patients (6.9%) in the MSS group (p = 0.159). Five patients (10%) with MSI developed metastatic disease compared with 72 (20.6%) in the MSS group (p = 0.084).

Factors predictive of disease-specific outcomes

On univariable analysis, in the MSI group, no variable was significantly associated with disease recurrence. In the MSS group, lymphovascular, extramural, and perineural invasion, TRG 3, and node positivity were significantly associated with worse DFS on univariable analysis. On multivariable analysis, only lymphovascular invasion (HR 2.831, 95% CI 1.09, 7.31, p = 0.032) and adjuvant chemotherapy (HR 4.893, 95% CI 1.29, 18.63, p = 0.02) were significantly associated with disease recurrence.

Discussion

Increased understanding of the biomolecular processes that underpin tumour development has enabled the molecular stratification of patients with CRC. The most commonly used molecular classification system in clinical practice dichostomises CRC into tumours with MSI and tumours that are MSS. Unsurprisingly, tumours that arise from different oncogenic pathways differ clinically. In this study of 400 patients with early age onset rectal cancer, 12.5% of patients demonstrated MSI. MSI was associated with reduced likelihood of nodal positivity, increased rate of pCR and improved disease-specific survial. MSI tumours were also more likely (but not exclusively) to occur in the context of a hereditary cancer syndrome.

Epidemiological and registry-based studies have demonstrated an alarming increase in EOCRC worldwide over the past four decades[7,15,16]. This increase is predominantly driven by a rise in the rate of distal tumours[8]. Historically, males have accounted for a greater proportion of patients with rectal cancer than females. A recent nationwide Swedish registry-based study however, reported a male-to-female incidence rate ratio of 1.07 in adults aged 18-49, compared to 1.71 among those aged greater than 49[17]. MSI has been shown to have a female preponderance, in particular among patients with proximal colon tumours[18]. In the present study, although there were more males overall, females accounted for the majority (58%) of patients in the MSI group. This is in contrast to a large North American nationwide study of all age rectal cancer where the majority of patients in both the MSI and MSS groups were male (60.8% and 61% respectively)[19]. The impact of female sex on risk of early age rectal cancer or presence of MSI remains to be defined.

An emerging focus of modern management of rectal cancer, is the role of molecular profile in therapeutic decision making. Neoadjuvant chemoradiotherapy is the standard of care for locally advanced disease, however pathological response varies considerably. Achieving a pCR is a positive prognostic indicator, associated with excellent locoregional control[20]. A startling result from these data is the enhanced pCR event rate in young patients with MSI rectal cancer. This opens the possibility of organ preservation in this specific group. It is known that disease-free survival with pCR is excellent, therefore it may be possible to consider avoiding operation in some of these patients[21]. It should be remembered that these are otherwise healthy individuals in whom socioeconomic, psychosocial and quality of life factors are arguably more important than at advanced stages of life. Where that is the case it will be important to build on the knowledge base being acquired from discrete choice

experimental data in patients with pCR due to chemoradiotherapy for oesophageal cancer. In those studies, it was found that patients were prepared to give up life years in order to avoid the potentially disabling symptoms due to the anatomical, physiological and social impact of major surgical extirpation[22]. In particular the negative impact on genitourinary function that may arise as a result of major pelvic surgery and the established risk of poor lower gastrointestinal function (low anterior resection syndrome) may be avoided with an organ preserving approach[23,24]. The socioeconomic advantages to eliminating major surgery in this youthful population group is intuitively better. However, there are negative consequences to neoadjuvant chemoradiotherapy which include (but are not limited to) diminished fertility, pelvic fractures, and neuropathy[25-27]. Clearly, research to determine discrete choice experimental information from patients in this distinct patient group is needed to inform patient-doctor decision-making.

Despite receiving more treatment, young patients with rectal cancer demonstrate similar disease-specific survival to their older counterparts[12]. Oncological outcomes according to MSI status however are limited. In the present study, patients with MSI demonstrated better disease-specific survival. Statistical differences were purposely not assessed because this data represents real-world data which can be relatively crude. Where that is the case, the use of statistics could be misleading. Nonetheless, the absolute difference of 15% between 5-year disease-free survival (MSI vs MSS; 87% vs 66%) is certainly clinically significant. As expected, overall survival did not differ with between groups.

MSI status is an important screening tool for genetic cancer predisposition e.g. Lynch Syndrome. Constitutive pathogenic mutations in the MMR genes lead to defective MMR, of which MSI is a well-defined feature[2]. In the present study, 6.5% of patients overall were diagnosed with a genetic predisposition. These data, in keeping with other series, suggest that rectal cancer in young adults is infrequently due to a hereditary cancer syndrome (albeit more frequently than their older counterparts)[12]. For MSI tumours however, almost 1 in 3 patients had a genetic predisposition (MSI vs MSS; 30.0% vs 3.1%) highlighting the important of genetic testing in this group. Despite young age at disease onset being a hallmark of genetic predisposition, the majority of cases of EOCRC are sporadic with MSS tumours[11,28]. As the full spectrum of genes implicated is unknown however, it is possible that a proportion of patients with sporadic disease actually harbour mutations not yet identified[13,29]. Advances in next-generation sequencing with multigene panel testing will unveil this spectrum.

This study has limitations including the retrospective nature, lack of complete dataset for the entire study group, and heterogeneity in treatment across the collaborative group. The study period spanned 20 years, and chemotherapy and radiotherapy strategies have evolved over that time. Nonetheless, this study represents real-world data and provides a useful platform for future planning. Evidently, neoadjuvant therapy should be a focus of modern trials in this patient group. Total neoadjuvant therapy, which is associated with favourable short-term outcomes including improved chemotherapy compliance and superior pCR rates, may represent an attractive strategy[30]. Furthermore, there is potential for immunotherapy to be integrated into the neoadjuvant treatment paradigm. Checkpoint inhibitors may offer a great therapeutic advantage in select patients. The NICHE study demonstrated remarkable response to checkpoint blockade among patients with non-metastatic colon cancer[31]. Importantly, collaboration undoubtedly represents an ideal approach to answer these key questions.

Figure legend

Figure 1. Kaplan-Meier curve of disease free survival for patients with Stage I-III disease comparing MSI and MSS.

No. at risk	**0m**	**12m**	**24m**	**36m**	**48m**	**60m**
MSI	50	42	37	31	29	22
MSS	342	247	166	128	87	66

References

1. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. *Nat Med*. Nov 2015;21(11):1350-6. doi:10.1038/nm.3967
2. Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of Lynch syndrome: 1895-2015. *Nat Rev Cancer*. 03 2015;15(3):181-94. doi:10.1038/nrc3878
3. Benatti P, Gafà R, Barana D, et al. Microsatellite instability and colorectal cancer prognosis. *Clin Cancer Res*. Dec 2005;11(23):8332-40. doi:10.1158/1078-0432.CCR-05-1030
4. Kim CG, Ahn JB, Jung M, et al. Effects of microsatellite instability on recurrence patterns and outcomes in colorectal cancers. *Br J Cancer*. 06 28 2016;115(1):25-33. doi:10.1038/bjc.2016.161
5. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol*. Jul 2010;28(20):3219-26. doi:10.1200/JCO.2009.27.1825
6. Des Guetz G, Schischmanoff O, Nicolas P, Perret GY, Morere JF, Uzzan B. Does microsatellite instability predict the efficacy of adjuvant chemotherapy in colorectal cancer? A systematic review with meta-analysis. *Eur J Cancer*. Jul 2009;45(10):1890-6. doi:10.1016/j.ejca.2009.04.018
7. Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. *JAMA Surg*. Jan 2015;150(1):17-22. doi:10.1001/jamasurg.2014.1756
8. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut*. May 2019;doi:10.1136/gutjnl-2018-317592
9. Willauer AN, Liu Y, Pereira AAL, et al. Clinical and molecular characterization of early-onset colorectal cancer. *Cancer*. 06 2019;125(12):2002-2010. doi:10.1002/cncr.31994
10. Lieu CH, Golemis EA, Serebriiskii IG, et al. Comprehensive Genomic Landscapes in Early and Later Onset Colorectal Cancer. *Clin Cancer Res*. 10 2019;25(19):5852-5858. doi:10.1158/1078-0432.CCR-19-0899
11. Antelo M, Balaguer F, Shia J, et al. A high degree of LINE-1 hypomethylation is a unique feature of early-onset colorectal cancer. *PLoS One*. 2012;7(9):e45357. doi:10.1371/journal.pone.0045357
12. Zaborowski AM, Murphy B, Creavin B, et al. Clinicopathological features and oncological outcomes of patients with young-onset rectal cancer. *Br J Surg*. Apr 2020;107(5):606-612. doi:10.1002/bjs.11526
13. Pearlman R, Frankel WL, Swanson B, et al. Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer. *JAMA Oncol*. Apr 2017;3(4):464-471. doi:10.1001/jamaoncol.2016.5194
14. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. Mar 2017;67(2):93-99. doi:10.3322/caac.21388
15. Chambers AC, Dixon SW, White P, Williams AC, Thomas MG, Messenger DE. Demographic trends in the incidence of young-onset colorectal cancer: a population-based study. *Br J Surg*. Apr 2020;107(5):595-605. doi:10.1002/bjs.11486
16. Lui RN, Tsoi KKF, Ho JMW, et al. Global Increasing Incidence of Young-Onset Colorectal Cancer Across 5 Continents: A Joinpoint Regression Analysis of 1,922,167 Cases. *Cancer Epidemiol Biomarkers Prev*. 08 2019;28(8):1275-1282. doi:10.1158/1055-9965.EPI-18-1111

17. Sun M, Wang Y, Sundquist J, Sundquist K, Ji J. Temporal Trends of Sex Disparity in Incidence and Survival of Colorectal Cancer: Variations by Anatomical Site and Age at Diagnosis. *Clin Epidemiol*. 2020;12:73-81. doi:10.2147/CLEP.S240006
18. Merok MA, Ahlquist T, Røyrvik EC, et al. Microsatellite instability has a positive prognostic impact on stage II colorectal cancer after complete resection: results from a large, consecutive Norwegian series. *Ann Oncol*. May 2013;24(5):1274-82. doi:10.1093/annonc/mds614
19. Hasan S, Renz P, Wegner RE, et al. Microsatellite Instability (MSI) as an Independent Predictor of Pathologic Complete Response (PCR) in Locally Advanced Rectal Cancer: A National Cancer Database (NCDB) Analysis. *Ann Surg*. 04 2020;271(4):716-723. doi:10.1097/SLA.0000000000003051
20. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br J Surg*. Jul 2012;99(7):918-28. doi:10.1002/bjs.8702
21. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet*. 06 2018;391(10139):2537-2545. doi:10.1016/S0140-6736(18)31078-X
22. Noordman BJ, de Bekker-Grob EW, Coene PPLO, et al. Patients' preferences for treatment after neoadjuvant chemoradiotherapy for oesophageal cancer. *Br J Surg*. 11 2018;105(12):1630-1638. doi:10.1002/bjs.10897
23. Bryant CL, Lunniss PJ, Knowles CH, Thaha MA, Chan CL. Anterior resection syndrome. *Lancet Oncol*. Sep 2012;13(9):e403-8. doi:10.1016/S1470-2045(12)70236-X
24. Pieniowski EHA, Palmer GJ, Juul T, et al. Low Anterior Resection Syndrome and Quality of Life After Sphincter-Sparing Rectal Cancer Surgery: A Long-term Longitudinal Follow-up. *Dis Colon Rectum*. 01 2019;62(1):14-20. doi:10.1097/DCR.0000000000001228
25. Segelman J, Buchli C, Svanström Röjvall A, et al. Effect of radiotherapy for rectal cancer on ovarian androgen production. *Br J Surg*. 02 2019;106(3):267-275. doi:10.1002/bjs.10980
26. Kang YM, Chao TF, Wang TH, Hu YW. Increased risk of pelvic fracture after radiotherapy in rectal cancer survivors: A propensity matched study. *Cancer Med*. 07 2019;8(8):3639-3647. doi:10.1002/cam4.2030
27. Mols F, Beijers T, Lemmens V, van den Hurk CJ, Vreugdenhil G, van de Poll-Franse LV. Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. *J Clin Oncol*. Jul 20 2013;31(21):2699-707. doi:10.1200/JCO.2013.49.1514
28. Stoffel EM, Koeppe E, Everett J, et al. Germline Genetic Features of Young Individuals With Colorectal Cancer. *Gastroenterology*. 03 2018;154(4):897-905.e1. doi:10.1053/j.gastro.2017.11.004
29. Mork ME, You YN, Ying J, et al. High Prevalence of Hereditary Cancer Syndromes in Adolescents and Young Adults With Colorectal Cancer. *J Clin Oncol*. Nov 2015;33(31):3544-9. doi:10.1200/JCO.2015.61.4503
30. Zaborowski A, Stakelum A, Winter DC. Systematic review of outcomes after total neoadjuvant therapy for locally advanced rectal cancer. *Br J Surg*. Jul 2019;106(8):979-987. doi:10.1002/bjs.11171
31. Chalabi M, Fanchi LF, Dijkstra KK, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med*. Apr 2020;doi:10.1038/s41591-020-0805-8

Authors: REACCT Collaborative. Members of the REACCT Collaborative are: Alexandra M. Zaborowski, Ahmed Abdile. Michel Adamina, Felix Aigner, Laura d'Allens, Caterina Allmer, Andrea Álvarez, Rocio Anula, Mihailo Andric, Sam Atallah Simon Bach, Miklosh Bala, Marie Barussaud, Augustinas Bausys, Andrew Beggs, Felipe Bellolio, Melissa-Rose Bennett, Anton Berdinskikh, Vicki Bevan, Sebastiano Biondo, Gabriele Bislenghi, Marc Bludau, Nelleke Brouwer, Carl Brown, Christiane Bruns, Daniel D. Buchanan, Pamela Buchwald, Jacobus W.A. Burger, Nikita Burlov, Michela Campanelli, Maylis Capdepont, Michele Carvello, Hwee-Hoon Chew, Dimitri Christoforidis, David Clark, Marta Climent, Rowan Collinson, Kyle G. Cologne, Tomas Contreras, Roland Croner, Ian R. Daniels, Giovanni Dapri, Justin Davies, Paolo Delrio, Quentin Denost, Michael Deutsch, Andre Dias, André D'Hoore, Evgeniy Drozdov, Daniel Duek, Malcolm Dunlop, Adam Dziki, Aleksandra Edmundson, Sergey Efetov, Alaa El-Hussuna, Brodie Elliot, Sameh Emile, Eloy Espin, Martyn Evans, Seraina Faes, Omar Faiz, Nuno Figueiredo, Fergal Fleming, Caterina Foppa, George Fowler, Matteo Frasson, Tim Forgan, Frank Frizelle, Shamil Gadaev, Jose Gellona, Tamara Glyn, Barisic Goran, Emma Greenwood, Marianne G. Guren, Stephanie Guillon, Ida Gutlic, Dieter Hahnloser, Heather Hampel, Ann Hanly, Hirotoshi Hasegawa, Lene Hjerrild Iversen, Andrew Hill, James Hill, Jiri Hoch, Roel Hompes, Luis Hurtado, Fabiano Iaquinandi, Ugne Imbrasaite, Rumana Islam, Mehrenah D Jafari, Andrea Jiménez Salido, Marta Jiménez-Toscano, Yukihide Kanemitsu, Aleksei Karachun, Ahmer A. Karimuddin, Deborah S. Keller, Justin Kelly, Rory Kennelly, Gleb Khrykov, Peter Kocian, Cherry Koh, Neils Kok, Katrina A. Knight, Joep Knol, Christos Kontovounisios, Hartwig Korner, Zoran Krivokapic, Irmgard Kronberger, Hidde Maarten Kroon, Marius Kryzauskas, Said Kural, Miranda Kusters, Zaher Lakkis, Timur Lankov, David Larson, György Lázár, Kai-Yin Lee, Suk Hwan Lee, Jérémie H. Lefèvre, Anna Lepisto, Christopher Lieu, Lynette Loi, Craig Lynch, Helene Maillou-Martinaud, Annalisa Maroli, Sean Martin, Anna Martling, Klaus E. Matzel, Julio Mayol, Frank McDermott, Guillaume Meurette, Monica Millan, Martin Mitteregger, Andrei Moiseenko, John RT. Monson, Stefan Morarasu, Konosuke Moritani, Gabriela Möslein, Martino Munini, Caio Nahas, Sergio Nahas, Ionut Negoi, Anastasia Novikova, Misael Ocares, Koji Okabayashi, Alexandra Olkina, Luis Oñate-Ocaña, Jaime Otero, Cihan Ozen, Ugo Pace, Guilherme Pagin São Julião, Lidiia Panaiotti, Yves Panis, Demetris Papamichael, Swati Patel, Juan Carlos Patrón Uriburu, Sze-Lin Peng, Miguel Pera, Rodrigo O. Perez, Alexei Petrov, Frank Pfeffer, Terry P. Phang, Tomas Poskus, Heather Pringle, David Proud, Ivana Raguz, Nuno Rama, Shahnawaz Rasheed, Manoj J. Raval, Daniela Rega, Christoph Reissfelder, Juan Carlos Reyes Meneses, Frederic Ris, Stefan Riss, Homero Rodriguez-Zentner, Campbell S Roxburgh, Avanish Saklani, Tarik Sammour, Deborah Saraste, Martin Schneider, Ryo Seishima, Aleksandar Sekulic, Toni Seppala, Kieran Sheahan, Alexandra Shlomina, Guiseppe Sigismondo, Tongplaew Singnomklao, Leandro Siragusa, Neil Smart, Alejandro Solis-Peña, Antonino Spinelli, Roxane D. Staiger, Michael J. Stamos, Scott Steele, Ker-Kan Tan, Pieter J Tanis, Paris Tekkis, Biniam Teklay, Sabrina Tengku, Petr Tsarkov, Matthias Turina, Alexis Ulrich, Bruna B. Vailati, Meike van Harten, Cornelis Verhoef, Satish Warrier, Steven Wexner, Hans de Wilt, Benjamin A. Weinberg, Cameron Wells, Albert Wolthuis, Evangelos Xynos, Nancy You, Alexander Zakharenko, Justino Zeballos, Jonathan Zhou, Des C. Winter