Received: 15 July 2020 | Revised: 29 August 2020 | Accepted: 8 September 2020

DOI: 10.1002/cnr2.1297

ORIGINAL ARTICLE

Cancer Reports | WILEY

Current status on microsatellite instability, prognosis and adjuvant therapy in colon cancer: A nationwide survey of medical oncologists, colorectal surgeons and gastrointestinal pathologists

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Abstract

Background: There is significant variation in attitude both towards the role of microsatellite instability (MSI) in predicting prognosis, and towards its role in guiding which Stage II colon cancer patients may benefit from adjuvant chemotherapy.

Aim: To examine the current status of specialist attitudes towards MSI in guiding prognosis and adjuvant therapy in stage II colon cancer.

Methods: The Pathology in Colon Cancer, Prognosis and Uptake of Adjuvant Therapy (PiCC UP) Australia and New Zealand questionnaire was distributed to colorectal surgeons, medical oncologists and pathologists after institutional board approval. A 5-scale Likert score was used to assess attitudes towards 23 pathological features for prognosis and 18 features for adjuvant therapy. Data were analysed using a rating scale and graded response model in item response theory (IRT) on STATA (Stata MP, version 15; StataCorp LP).

Results: 164 specialists (45 oncologists, 86 surgeons and 33 pathologists) participated. 80.5% regularly attended colorectal multidisciplinary team (MDT) meetings. 89.63% and 59.26% of specialists reported that MSI status was likely or definitely to influence prognosis in colon cancer and recommendations for adjuvant therapy in Stage II colon cancer respectively.

IRT modelling was achieved in 17 pathological features for prognosis. MSI IRT score was 4.47 (95% CI: 4.05-4.68). IRT modelling was achieved in 10 pathological features for adjuvant therapy. MSI IRT score was 3.62 (2.89-4.15). MSI ranked 10 (of 17) in order of importance in determining prognosis and ranked three (of 10) in guiding adjuvant therapy.

Conclusion: MSI status is considered an important biomarker when selecting patients for adjuvant therapy in Stage II colon cancer. MSI is also considered useful in prognostication of colon cancer. MSI status was ranked similar to the tumour grade of differentiation and the presence of perineural invasion.

KEYWORDS

adjuvant therapy, colon cancer, microsatellite instability, prognosis

1 | INTRODUCTION

Since its discovery in 1993, microsatellite instability (MSI) in colorectal cancer (CRC) has been linked with patient survival and there has been debate as to its utility in management decisions in the use of adjuvant chemotherapy for patients with Stage II colon cancer. In 31 of 47 non-overlapping studies reported in two meta-analysis on MSI and prognosis in colorectal cancer, there was no statistically significant difference or only marginal significance.[1,2] The benefit associated with chemotherapy in Stage II colon cancer is small, and decision-making in patients with Stage II colon cancer is often individualised to patient's preferences and comorbidities.

In 1999, the College of American Pathologist released a consensus statement on prognostic factors and colorectal cancer.[3] In this consensus statement, prognostic factors were categorised into different subgroups based on the strength of published evidence according to the prognostic value. Category I included factors with proven prognostic value. Category IIa included factors that were biologically or clinically shown to have value but remains to be validated in statistically robust studies. Category IIb included factors which were promising but lacked sufficient data. Category III included factors which were indeterminate for prognostic value. Category IV included factors that have no prognostic significance.

In this consensus, MSI status was not considered a strong prognostic factor in colon cancer.

Category I factors included pT category, regional lymph node (pN) metastases, perineural, vascular or lymphatic vessels invasion, residual tumour following surgery (R classification), preoperative CEA. Category IIa included tumour grade, radial margin status, residual tumour in the resection specimen following neoadjuvant therapy.

Since then, two systematic reviews on MSI by Popat et al[1] and Guastadisegni et al[2] have reported that MSI status was a good marker of CRC prognosis, with MSI high colorectal cancers having a better prognosis compared to those with intact mismatch repair. However, there have been many studies which have reported no difference or worse prognosis.[4-13]

In terms of guiding chemotherapy, the American Society of Clinical Oncology provided recommendations for adjuvant chemotherapy for Stage II colon cancer in 2004. The society concluded that routine use of adjuvant chemotherapy for patients with Stage II colon cancer was not supported by evidence from randomised controlled trials (RCTs).[14]

This practice guideline was supported by the results of the International Multicentre Pooled Analysis of Colon Cancer Trial B2 (IMPACT B2) study which combined data from five randomised controlled trial yet failed to show benefit with adjuvant chemotherapy when compared to patients treated by surgery alone.[15] In this study the 5-year overall survival estimate was not statistically significant (80% for surgery vs 82% for those who received surgery with adjuvant therapy) and the study concluded that chemotherapy was not recommended as standard adjuvant therapy for patients with B2 colon cancer.

Nonetheless, it remains unclear whether some Stage II colon cancers would benefit from adjuvant chemotherapy. The European Society for Medical Oncology (ESMO) guidelines suggest that patients with Stage II colon cancer with high risk adverse features including: lymph node sampling <12, poorly differentiated tumours, the presence of vascular, perineural or lymphatic invasion; tumour presentation with obstruction or tumour perforation and pT4 stage should receive adjuvant fluoropyrimidine ChT, in the absence of MSI.[16,17] With the presence of MSI, there may be limited benefit from chemotherapy in Stage II colon cancer. Several studies have shown that MSI-H CRCs may not benefit from 5-FU based chemotherapy.[18,19] The use of adjuvant therapy for Stage II colon cancer with adverse features has not been shown to improve five-year survival by more than an absolute 5%.[14]

There is significant variation in recommendations for MSI testing between guidelines in Australia, Asia-Pacific, the United States and Europe. With the National Institute for Clinical Excellence (NICE) guidelines recently recommending universal MSI testing to detect Lynch Syndrome,[20] it is important to determine the importance placed on MSI as a biomarker not only in familial CRC, but also in sporadic CRC as testing is universal. This study assesses specialist attitudes towards the utilisation of MSI in guiding prognosis and in decision-making for adjuvant therapy for Stage II colon cancer. This study interrogates the perspectives of key decision-makers of colon cancer MDTs including colorectal surgeons in Australia and New Zealand, and medical oncologist and gastrointestinal pathologists in Australia.

2 | METHODS

The Pathology in Colon Cancer, Prognosis and Uptake of Adjuvant Therapy (PiCC UP) Australia and New Zealand questionnaire was distributed to colorectal surgeons, medical oncologists and pathologists.

A 5-scale Likert score was used to assess attitudes towards 23 pathological features for prognosis and 18 features for recommending the use of adjuvant therapy. The questionnaire received institutional board approval (5270) AU RED LNR/17/WMEAD/343. The questionnaire was distributed to members of the Medical Oncology Group of Australia (MOGA), the Colorectal Surgical Society Australia and New Zealand (CSSANZ) and the Australasian Gastrointestinal Pathology Society (AGPS).

The relationship between MSI status and prognosis was evaluated for the following clinicopathological features: Right vs left colon cancer; size of tumour; tumour rupture (pT4); tumour grade (degree of differentiation); tumour infiltrating lymphocytes (TILs); tumour budding; microsatellite instability (MSI) status; KRAS status; EGFR status; BRAF status; CDX2; invasion beyond the muscularis propria; circumferential resection margin (CRM); perineural invasion (PNI); lymphovascular invasion (LVI); involved surgical margin; involved radial margin; lymph node yield (LNY); involved lymph nodes; lymph node ratio (LNR); apical node status; distant metastases—liver only; distant metastases—extrahepatic.

The relationship between MSI status and recommendation for adjuvant chemotherapy for Stage II colon cancer was evaluated for the following clinicopathological features: Right vs left colon cancer; maximum diameter (size of tumour); tumour rupture (pT4); tumour grade (differentiation); tumour infiltrating lymphocytes (TILs); tumour budding; microsatellite instability (MSI); KRAS status; EGFR status; BRAF status; invasion beyond the muscularis propria; circumferential resection margin (CRM); perineural invasion (PNI); lymphovascular invasion (LVI); involved surgical margin; involved radial margin; lymph node yield (LNY).

Summary statistics and weighted averages were calculated for all pathological features. Data were then analysed using a rating scale and graded response model in item response theory (IRT) on STATA (Stata MP, version 15; StataCorp LP). Item response theory is useful in scoring of tests and questionnaires and is based on the theory that there is a relationship between the individual's performance on a questionnaire or test item and the individual's level of performance overall and this is incorporated into scaling the item. Using the American College of Pathologists classification system, we correlated an IRT score of ≥4.50 as Category I; between 4.00 and 4.49 as Category IIa; 3.50 and 3.99 as Category IIb; 2.50 and 3.49 as Category III; <2.50 as Category IV for prognostication. After IRT modelling, the pathological features were ranked in importance according to IRT score. For guiding adjuvant chemotherapy in Stage II colon cancer, importance was ranked according to the IRT score and a score of ≥4.50 (rounded to 5) was considered to definitely influence decision-making for adjuvant chemotherapy for Stage II colon cancer; 3.50-4.49 (rounded to 4) likely; 2.50-3.49 (rounded to 3) neutral; < 2.5 (rounded to 1-2) not likely to be useful in guiding adjuvant therapy. Differences in the importance placed on MSI status between medical oncologist, surgeons and pathologists was also evaluated in a subset analysis and both an IRT score and the mean score were recorded. A Kruskal-Wallis test was used to test the difference between the three groups.

3 | RESULTS

164 specialists (45 oncologists, 86 surgeons and 33 pathologists) participated in the survey. Some 80.5% regularly participated in colorectal MDTs. Six advanced trainees (non-specialists) responded to the questionnaire. These were excluded from analysis.

89.63% of specialists reported that MSI status was *likely* or *definitely* to influence prognosis in colon cancer. MSI was ranked 11 (of 23) pathological features in importance in influencing prognosis. Not unexpectedly, the highest ranked features included distant metastases (98.53%), tumour rupture (98.53%), involved lymph nodes (97.80%), distant metastases—liver (97.06%) and involved surgical margin (97.04%). The other pathological features that ranked ahead of MSI status in influencing prognosis included CRM, involved radial margin, lymphovascular invasion, invasion beyond muscularis and grade (degree of differentiation). MSI status was ranked similar in importance to degree of differentiation and perineural invasion. CDX2 status, EGFR status, size of tumour, lymph node ratio (LNR) and sidedness were ranked of lowest importance in determining prognosis in colon cancer by percentage of specialists who responded *likely* or *definitely* to influence prognosis in colon cancer (refer to Figures 1-3 and eTable 1).

MSI status was ranked 8 (of 18) in importance in decision-making for the use of adjuvant chemotherapy in Stage II colon cancer. 59.26% of specialists believed that MSI status was *likely* or *definitely* to influence recommendations for adjuvant therapy in Stage II colon cancer. Within the literature, features considered high risk features in Stage II colon cancer include pT4, tumour rupture, presence of lymphovascular invasion, poor differentiation and bowel perforation or bowel obstruction [21]. MSI status for stratification for adjuvant treatment in Stage II colon cancer has been increasingly utilised, with recent publications suggesting that MSI-H CRCs do not benefit from 5-FU based chemotherapy [18]. However, there is still ongoing debate as to the role of MSI in guiding adjuvant therapy, and it is without a clear consensus. Compared to MSI status (59.26%), more specialists recorded pT4 (94.86%) and lymphovascular invasion (86.67%) as important in guiding adjuvant therapy. Grade of differentiation was ranked similar to MSI status (62.22%) (refer to Figures 4-6 and eTable 2).

IRT modelling was used to statistically analyse the results of this survey. Weighted means of a Likert scale does not provide the best representation of results based on an ordinal scale consisting of “not at all” (1), “not really” (2), “neutral” (3), “likely” (4) and “definitely” (5). IRT modelling is commonly used to analyse Likert-type surveys, particularly in psychometric assessments. IRT modelling scales each item based on the responses to each item, and the ability of the respondents on the same metric. Thus, IRT corrects for the responses to the item as well as the ability of respondents answering the questionnaire. The relationship between a respondent's answer on an item and the respondent's overall response is incorporated into scaling each individual item. eFigure 1 displays the Category Characteristic Curves after IRT modelling and shows the probability of each of the answers to the question asked. Where the curves cross Theta = 0, this is a good point estimate of the probability of each response.

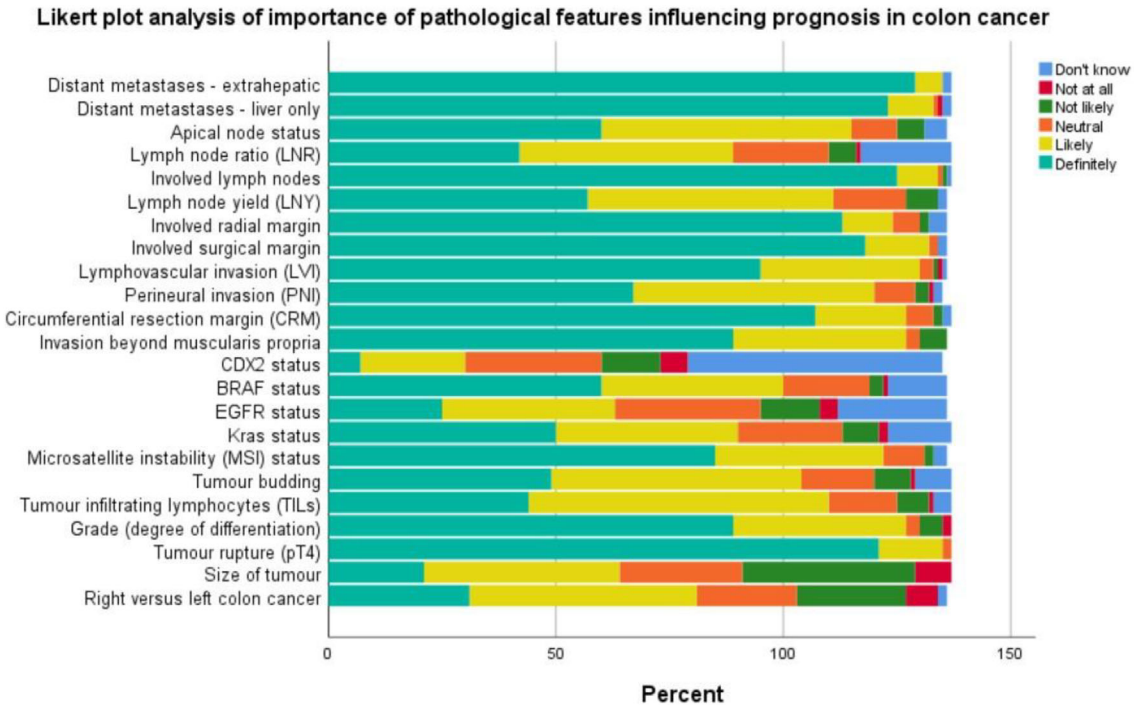

FIGURE 1 Likert plot analysis of the importance of pathological features influencing prognosis in colon cancer

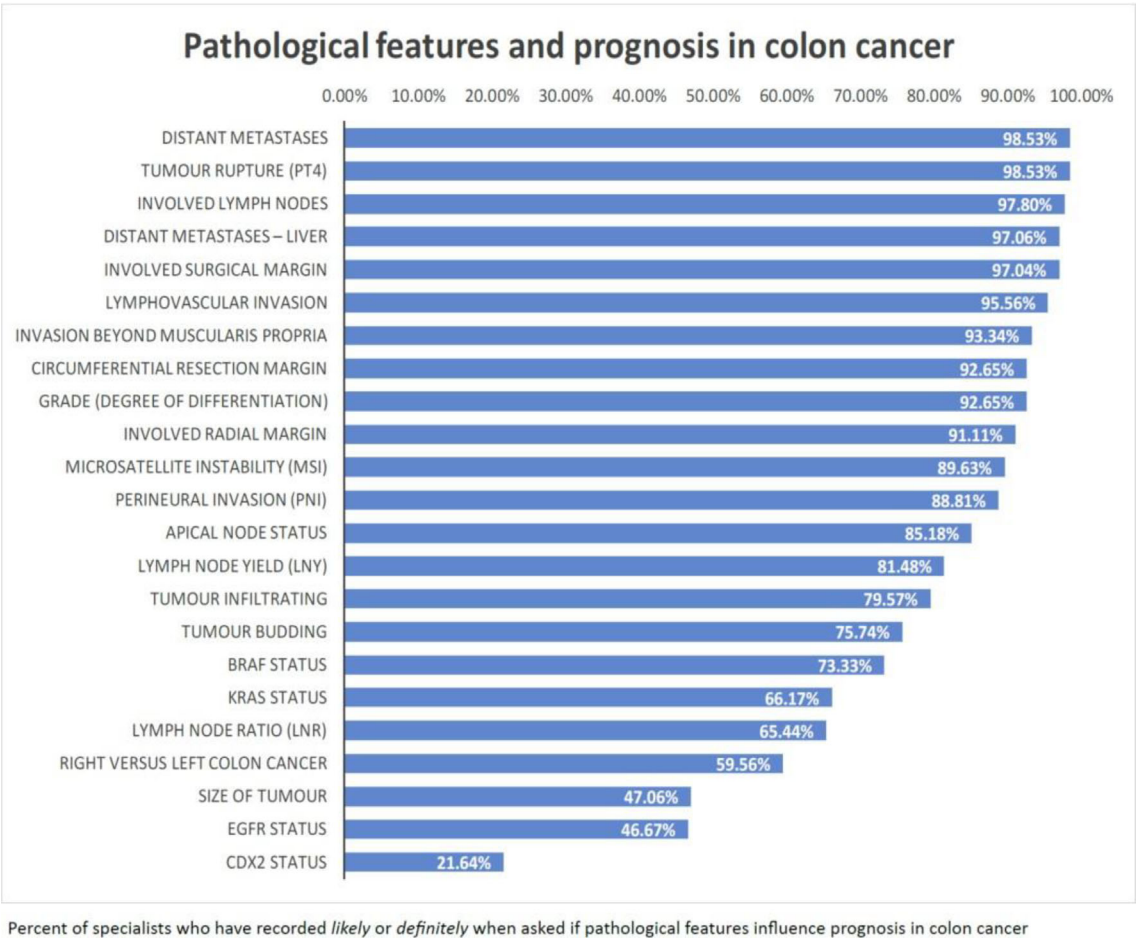

FIGURE 2 Bar chart analysis of the importance of pathological features influencing prognosis in colon cancer

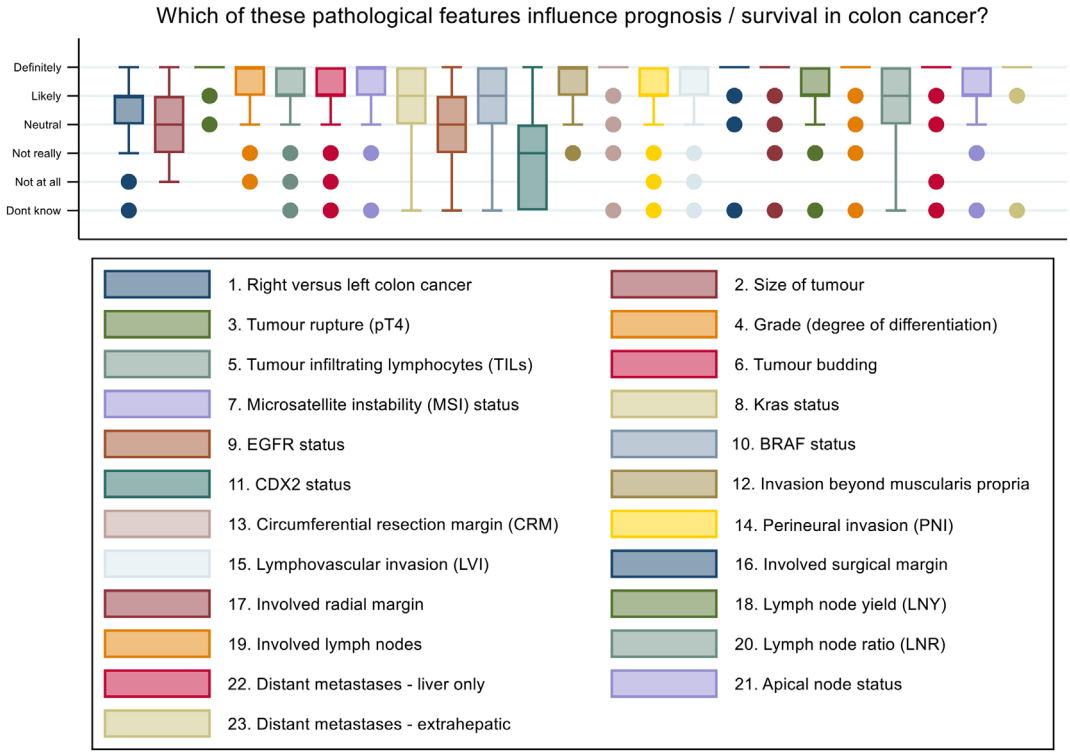

FIGURE 3 Box plot analysis of the importance of pathological features influencing prognosis in colon cancer

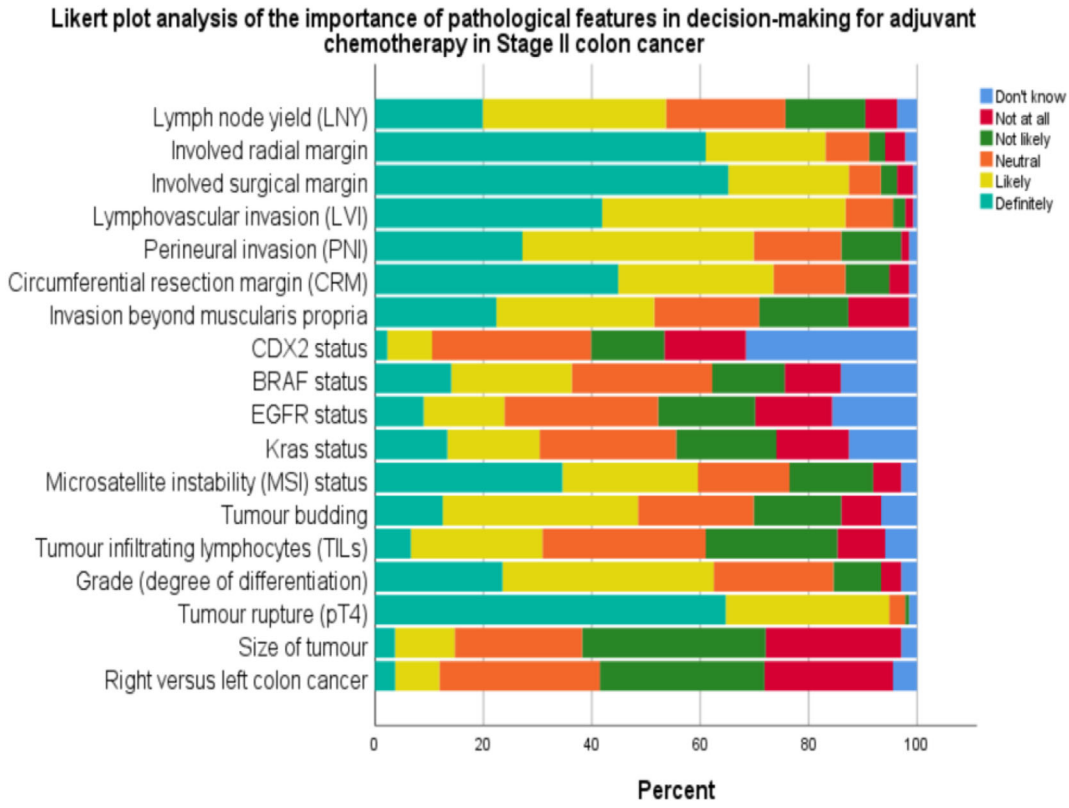

FIGURE 4 Likert plot analysis of the importance of pathological features influencing decision-making for adjuvant chemotherapy in Stage II colon cancer

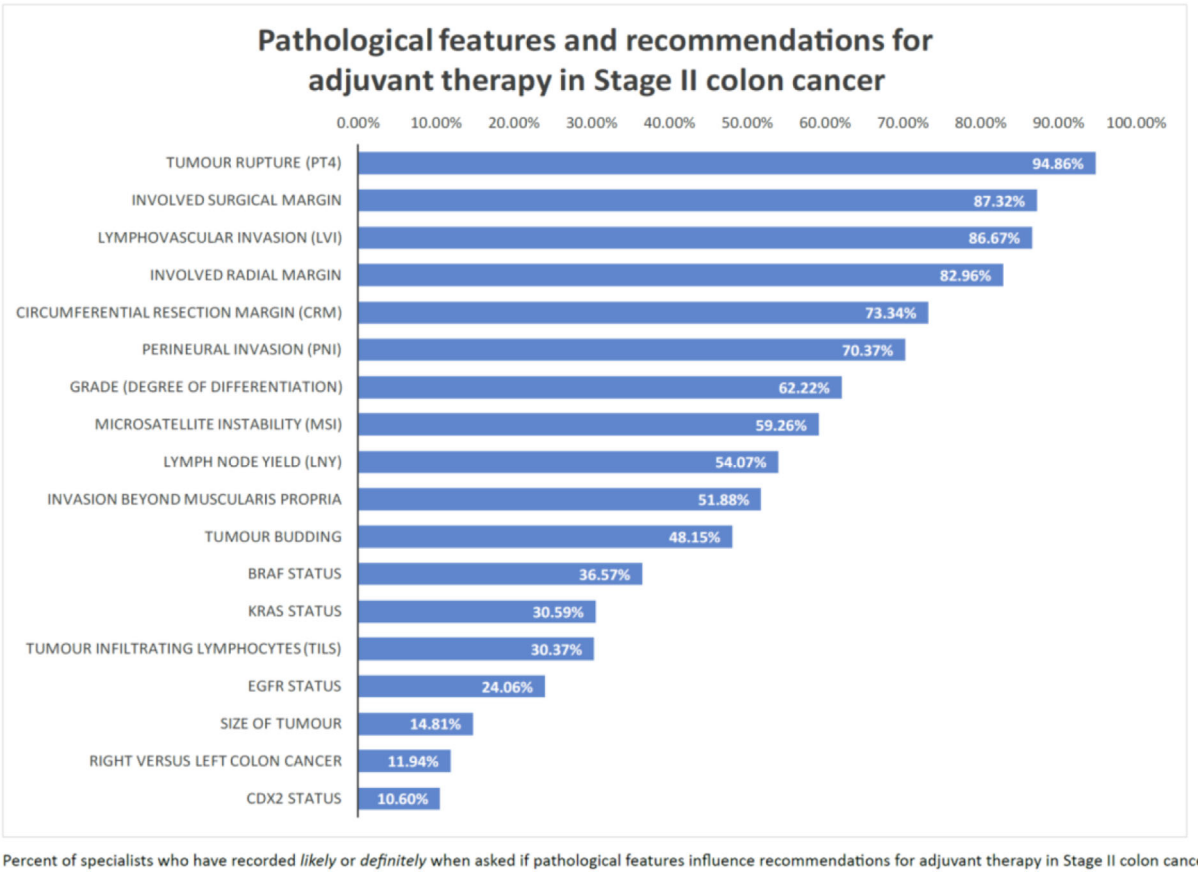

FIGURE 5 Bar chart analysis of the importance of pathological features influencing recommendations for adjuvant therapy in Stage II colon cancer

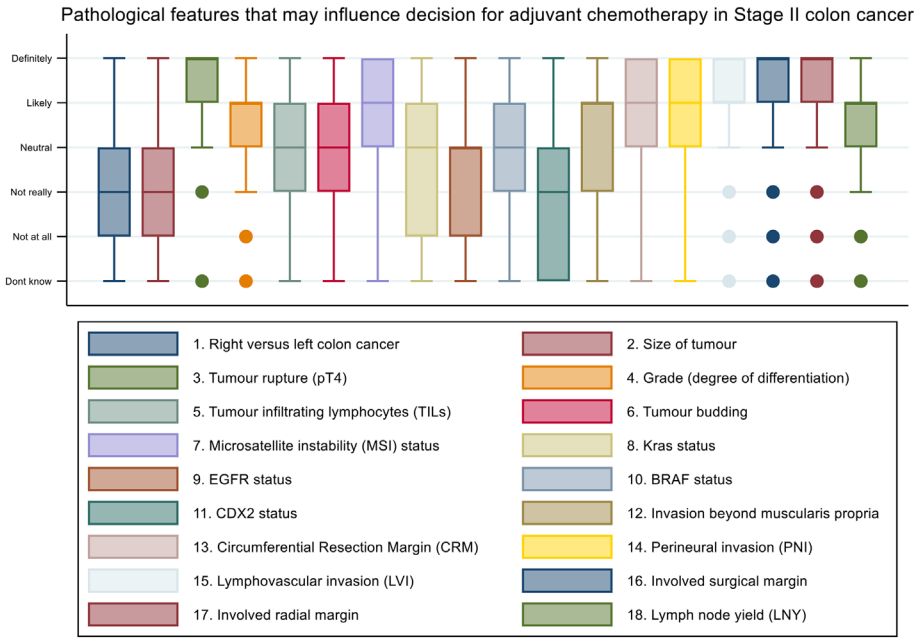

FIGURE 6 Box plot analysis of the importance of pathological features influencing recommendations for adjuvant therapy in Stage II colon cancer

eFigure 1 (left) confirmed that most respondents believed that MSI impacts on prognosis in colon cancer. The responses were more varied when assessing MSI status and recommendation for adjuvant therapy in Stage II colon cancer as seen in eFigure 1 (right).

IRT modelling was achieved in 17 pathological features for prognosis. MSI IRT score was 4.47 (95% CI: 4.05-4.68) (rounded to 4) (grade IIa). MSI status ranked 10 (of 17) in order of importance in determining prognosis (refer to Table 1). Six pathological features

TABLE 1 Item Response Theory (IRT) score for pathological features in colon cancer influencing prognosis

Pathological features	Grade	Prognosis IRT score	Lower limit 95% C.I.	Upper limit 95% C.I.
Distant Metastases	Grade I	4.88	4.85	4.91
Lymph Node Metastases		4.88	4.56	4.96
Tumour Rupture		4.87	4.78	4.93
Liver Metastases		4.85	4.45	4.95
Involved Margin		4.83	4.46	4.93
Radial Margin		4.69	4.13	4.87
Circumferential Resection Margin		4.65	4.63	4.67
Lymphovascular Invasion		4.64	4.28	4.78
Grade of Differentiation		4.52	4.35	4.63
Microsatellite Instability	Grade IIa	***4.47***	***4.05***	***4.68***
Perineural Invasion		4.35	3.77	4.59
BRAF Status		4.3	0.211	4.95
Lymph Node Yield		4.14	4.11	4.17
Lymph Node Ratio	Grade IIb	3.96	0.161	4.83
Location—Right vs Left		3.54	2.63	4.15
Size of Tumour	Grade III	3.23	2.93	3.52
EGFR Status		2.97	2.58	3.31

Note: Bold italicised: Pathological feature MSI.

TABLE 2 Item Response Theory (IRT) score for pathological features in colon cancer influencing decision-making for adjuvant chemotherapy in Stage II colon cancer

Pathological features	Adjuvant chemotherapy IRT score	Lower limit 95% C.I.	Upper limit 95% C.I.	Adjuvant recommendations
Tumour Rupture	4.55	4.49	4.59	Definitely
Lymphovascular Invasion	4.25	3.72	4.51	Likely
Microsatellite Instability	***3.62***	***2.89***	***4.15***	
Lymph Node Yield	3.36	3.14	3.56	
Invasion beyond Muscularis Propria	3.34	2.36	4.07	Neutral
Tumour Budding	3.18	1.85	3.97	
Tumour Infiltrating Lymphocytes	2.81	1.78	3.62	Neutral
BRAF Status	2.78	1.52	3.76	
Size of Tumour	2.25	1.77	2.81	Not really
Location—Right vs Left Side	2.24	2.14	2.36	

Note: Bold italicised: Pathological feature MSI.

were not computable due to discontinuous regions. These included tumour infiltrating lymphocytes, tumour budding, KRAS status, CDX2, invasion beyond muscularis propria and apical node status.

IRT modelling was achieved in 10 pathological features for adjuvant therapy. MSI IRT score was 3.62 (2.89-4.15) (rounded to 4) (likely). MSI ranked 3 (of 10) in guiding adjuvant therapy in Stage II colon cancer (see Table 2).

The responses of surgeons, medical oncologists and pathologists showed the varied attitudes between specialist groups (refer to Table 3 and eFigure 2 (left and right)). The weighted average for MSI status influencing prognosis was 4.44, after IRT modelling 4.47 (4.05-4.68) (medical oncologist 4.78 (4.48-4.93); pathologist 4.47 (4.05-4.68)). Unfortunately, the IRT score for colorectal surgeons was not computable due to discontinuous regions. The weighted average for MSI status and decision-making for adjuvant therapy for Stage II colon cancer was 3.59. After IRT modelling 3.62 (2.89-4.15) (medical oncologist 4.44 (3.56-4.84); colorectal surgeon 3.41 (2.47-4.23). The IRT model showed a difference between the groups, particularly medical oncologists placing greater importance of MSI status in guiding adjuvant therapy in Stage II colon cancer.

The IRT scores were generated from the Test Characteristic Curves (TCC) generated after IRT modelling and fit. Where the curve crosses Theta = 0 represents the IRT score +/− 1.96 SD making up the upper and lower limits of the 95% confidence intervals. The TCC for MSI status in represented in eFigure 3 (left) prognosis; eFigure 3 (right) adjuvant chemotherapy.

The importance of MSI status when compared to other biomarkers requiring immunohistochemical (IHC) is shown in Table 4. MSI status is ranked more important than BRAF, KRAS, CDX2 and EGFR status. While surgeons, medical oncologists and pathologists agreed that MSI status influenced prognosis, a Kruskal-Wallis H test showed that there was a statistically significant difference in importance placed on MSI status between the three groups in recommending adjuvant chemotherapy for Stage II colon cancer ($\chi^2(2) = 14.86$; $P = .001$).

Overall most surgeons, medical oncologists and pathologists were knowledgeable about MSI status with only 2.21% and 2.94% responding "do not know" about its importance in guiding prognosis and adjuvant therapy respectively. In comparison, a significant number of respondents did not know about the importance of other IHC markers—CDX2, EGFR, KRAS and BRAF status (refer to eFigure 4).

TABLE 3 MSI status, prognosis and recommendation for adjuvant chemotherapy in Stage II colon cancer IRT scores stratified by Surgeon, Medical Oncologist and Pathologist

Respondent	MSI status and Prognosis IRT Score	Classification
Colorectal / General Surgeon	not computable, discontinuous regions	n/a
Medical Oncologist	4.78 (4.48–4.93)	Grade I
Pathologist	4.33 (3.33-4.82)	Grade IIa
Overall	4.47 (4.05–4.68)	Grade IIa
Respondent	MSI status and Adjuvant Chemotherapy IRT Score	Recommendation
Colorectal / General Surgeon	3.41 (2.47–4.23)	Neutral
Medical Oncologist	4.44 (3.56–4.84)	Likely
Pathologist	not computable, discontinuous regions	n/a
Overall	3.62 (2.89–4.15)	Likely

4 | DISCUSSION

There has been ongoing debate on the utility of MSI status in guiding prognosis and in recommendations for adjuvant chemotherapy in Stage II colon cancer over the past two decades. While several meta-analysis have reported better prognosis associated with MSI,[1,2] many studies have reported no difference or worse prognosis.[4-13] While the current ESMO guidelines for early colon cancer treatment places importance on MSI status in guiding adjuvant therapy,[17] international guidelines have not reached a consensus.

The 2016 Japanese Society for Cancer of the Colon and Rectum Guidelines only approved MSI testing for patients suspected of having Lynch syndrome.[22] Internationally, many studies reporting outcomes based on clinico-pathologic factors for colon cancer do not include MSI status as it is not routinely collected.[23]

While the 2016 NICE guidelines (UK), the 2017 American Society of Colon and Rectal Surgeons (ASCRS) and the 2017 Australian guidelines recommend all newly diagnosed patients with colorectal cancer should have MSI/MMR deficiency testing,[20,24,25] the calls for universal MMRD testing has been to identify Lynch syndrome rather than to use MSI status to guide prognosis or in decision-making for adjuvant therapy.

The current Australian stance on adjuvant therapy in Stage II colon cancer is that the "optimal approach is uncertain and should be considered only in high risk patients on a case-by-case basis."[26] Factors that have been identified as increasing the risk of recurrence include T4 tumours, perforation and inadequate node sampling. MSI status was not reported in the overview of evidence as an adverse feature in Stage II colon cancer.

In this study, a survey of colorectal surgeons, medical oncologists and pathologists in Australia and New Zealand, majority responded that MSI status was likely to influence prognosis in colon cancer and likely to guide a recommendation for the use of adjuvant therapy for Stage II colon cancer.

Importantly, 89.63% of respondents believed that MSI was "likely" or "definitely" to influence prognosis and 59.26% believed that MSI should "likely" or "definitely" guide adjuvant therapy in Stage II colon cancer.

Both on weighted average (MSI 4.44; LVI 4.61; PNI 4.31) and IRT modelling (MSI 4.47; LVI 4.64; PNI 4.35), MSI status was ranked close

TABLE 4 The importance of biomarkers in colon cancer according to Surgeon, Medical Oncologist and Pathologist (presented as mean values, Kruskal-Wallis test used to compare between groups)

Prognosis	MSI	p	BRAF	p	KRAS	p	CDX2	p	EGFR	p
Surgeon	4.37		3.77		3.51		1.83		1.43	
Medical Oncologist	4.75	0.121	4.45	0.025	4.1	0.086	1.67	0.407	0.99	0.128
Pathologist	4.29		3.42		3.37		1.58		2.02	
Recommendations for adjuvant therapy in Stage II Colon Cancer	MSI	p	BRAF	p	KRAS	p	CDX2	p	EGFR	p
Surgeon	3.39		2.89		2.8		1.77		2.63	
Medical Oncologist	4.37	0.001	2.48	0.481	1.93	0.022	1.89	0.748	1.89	0.047
Pathologist	3.31		2.65		2.69		1.54		2.15	

to LVI and PNI as a marker of prognosis. MSI status ranked 8 (of 18) in order of importance for guiding adjuvant therapy on weighted average and 3 (of 10) after IRT modelling. Interestingly, a recent study by Skancke et al (2019) retrospectively reviewing the National Cancer Database for Colon Cancer from 2010 to 2014 conclude that both LVI and PNI have a detrimental effect on survival after diagnosis of Stage II colon cancer and showed that chemotherapy was protective when LVI and PNI were present.

The 2016 Canadian guidelines recommend that patients with Stage II colon cancer without high risk features do not benefit adjuvant chemotherapy. In the presence of high risk features, the presence of MSI high provides a protective effect and it would be reasonable to treat either with observation or with FOLFOX, keeping in mind that in Stage II patients whose tumours are MSI high, adjuvant chemotherapy may have caused a detrimental effect to overall survival.[27]

In 2016, the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer collected data for patients with Stage II colon cancer and created a nomogram for factors which potentially influence recurrence. In this study, gender, CEA, side of tumour, tumour depth, presence of lymphatic invasion, venous invasion and the number of lymph nodes harvested were identified as prognostic factors that affected recurrence.[28] The study did not include MSI status as MMRD/MSI testing is not routinely performed in Japan. While the nomogram did not include MSI, a recent meta-analysis by Bockelman et al for Stage II/III colon cancer reported a statistically significant lower risk of recurrence for MSI-H colon cancer (HR 0.54 [0.41-0.68]),[29] similar to the findings of Popat et al[1] and Guastadisegni et al.[2]

There is increasing awareness of MSI status as a molecular biomarker in colon cancer. Most surgeons, medical oncologists and pathologists in this study reported that they were aware of the importance of MSI status (see Figure 4). Much fewer knew about the importance of CDX2, KRAS, EGFR and BRAF. Medical oncologists were more likely to use MSI status to guide the use of adjuvant therapy for Stage II colon cancer, but surgeons, oncologists and pathologists were aware of its association with prognosis.

This study has its limitations. It is a survey of attitudes of specialist clinicians towards MSI as a molecular biomarker in colon cancer. Specialist opinions do not provide the same level of evidence as clinical data from cohort studies or randomised controlled trials. The survey was distributed to colorectal surgeons in Australia and New Zealand, but was only distributed to medical oncologists and gastrointestinal pathologists in Australia. While this is a limitation, this survey, to date, was the largest survey of specialists in Asia Pacific on the importance of MSI in guiding prognosis and adjuvant treatment in colon cancer. Another limitation of this study was that the use of item response theory requires complex modelling and was not computable for six and eight pathological features associated with prognosis and adjuvant therapy respectively. However, the advantage of IRT was that it allowed scaling of results based on difficulty of items and the ability of respondents on the same metric. It is commonly used to assess Likert-type surveys especially in psychometric surveys, and the IRT results provided good correlation with both the weighted mean as well as Likert plot analysis reported in this study.

5 | CONCLUSION

In a nationwide survey of colorectal surgeons, medical oncologists and gastrointestinal pathologists, MSI status was ranked more important than other molecular biomarkers including BRAF, KRAS, CDX2 and EGFR status. MSI was ranked similar to LVI or PNI in prognostication and similar to grade of differentiation for guidance for adjuvant therapy in Stage II colon cancer. Surgeons, medical oncologists and gastrointestinal pathologists involved in the management of patients with colon cancer in Australia and New Zealand consider MSI as an important biomarker that is useful in prognostication of colon cancer and should be used to guide adjuvant therapy in Stage II colon cancer. Further large-scale level 1 research evidence evaluating the association between MSI with adjuvant therapy in stage II colon cancer patients and prognosis respectively needs to be examined carefully and translated into a consensus in guidelines not only between countries internationally but also with a general agreement between the specialty groups (colorectal surgeons, medical oncologists and gastrointestinal pathologists) involved in the management of colon cancer.

ACKNOWLEDGEMENTS

The authors would like to thank all of the specialist colorectal surgeons, medical oncologists and gastrointestinal pathologists who participated in the survey.

ETHICS STATEMENT

This study received institutional board approval (5270) AU RED LNR/17/WMEAD/343. Completion of the survey was regarded as informed consent for participation.

CONFLICT OF INTEREST

The authors declare no conflicts of interests and no financial disclosures.

This paper was presented at the 17th Asia Pacific Federation of Coloproctology (APFCP) in Kuala Lumpur, Malaysia in 2019 and won Best Research Presentation at the APFCP.

AUTHOR CONTRIBUTIONS

James Toh: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; validation; visualization; writing-original draft; writing-review and editing. Hema Mahajan: Methodology; validation; writing-review and editing. Pierre Chapuis: Conceptualization; methodology; supervision; writing-review and editing. Kevin Spring: Conceptualization; methodology; supervision; writing-review and editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Toh JWT, Mahajan H, Chapuis P, Spring K. Current status on microsatellite instability, prognosis and adjuvant therapy in colon cancer: A nationwide survey of medical oncologists, colorectal surgeons and gastrointestinal pathologists. *Cancer Reports*. 2021;4:e1297. https://doi.org/10.1002/cnr2.1297