Original article

How accurate are medical oncologists' impressions of the management of patients with metastatic colorectal cancer (mCRC) in Australia?

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Running title: impressions of mCRC management

Abstract: **249** words *(250 allowed)*

Aim: Current efforts to understand patient management in clinical practice are largely based on clinician surveys with uncertain reliability. The TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) database is a multi-site registry collecting comprehensive treatment and outcome data on consecutive metastatic colorectal cancer (mCRC) patients at multiple sites across Australia. This study aims to determine the accuracy of oncologists' impressions of real-word practice by comparing clinicians' estimates to data captured by TRACC.

Methods: 19 medical oncologists from 9 hospitals contributing data to TRACC completed a 34-question survey regarding their impression of the management and outcomes of mCRC at their own practice and other hospitals contributing to the database. Responses were then compared with TRACC data to determine how closely their impressions reflected actual practice.

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Results: Data on 1300 patients with mCRC was available. Median clinician estimated frequency of KRAS testing within 6 months of diagnosis was 80% (range:20-100%); the TRACC documented rate was 43%. Clinicians generally overestimated the rates of first-line treatment, particularly in patients over 75 years. Estimate for bevacizumab in first-line was 60% (35-80%) versus 49% in TRACC. Estimated rate for liver resection varied substantially (5-35%), and the estimated median (27%) was inconsistent with the TRACC rate (12%). Oncologists generally felt their practice was similar to other hospitals.

Conclusions: Oncologists' estimates of current clinical practice varied and were discordant with the TRACC database, often with a tendency to overestimate interventions. We would conclude that clinician surveys alone do not reliably capture contemporary clinical practices in mCRC.

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Keywords: Accuracy, clinician, colorectal cancer, data collection, surveys.

Manuscript: 3419 words *(3500 allowed)*

Introduction

Colorectal cancer is the third most common malignancy worldwide,[1] with 40 – 50% of patients either being diagnosed with de novo or later developing metastatic disease. The landscape in the management of metastatic colorectal cancer (mCRC) is constantly changing. The addition of irinotecan and oxaliplatin to fluropyrimidine-based palliative chemotherapy improved survival outcomes,[2,3] with further gains following the introduction of biological agents including bevacizumab[4]

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and the epidermal growth factor (EGFR) inhibitors.[5] These improved survival outcomes have been shown to have translated to survival gains in routine clinical practice.[6] Furthermore, liver resections – and somewhat more controversially – use of adjuvant chemotherapy in this setting, has also been incorporated into the treatment paradigm of mCRC.

The TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) registry[7] is a multi-site effort to collect comprehensive data on consecutive mCRC cases at participating sites. It was initiated at major Victoria hospitals, with subsequent expansion to an ever increasing number of interstate and regional sites. Most recently international sites have been engaged. Established with support from Roche Products Pty Limited (Australia) the goals of TRACC include supporting clinical and translational research projects, with data collection commencing in July 2009. Clinician-entered point of care data prospectively captures patient and disease characteristics, treatment strategies and outcomes for consecutive patients.

To date, an understanding of patient management in routine clinical practice – predominantly for the purposes of the pharmaceutical industry in unpublished datasets – has frequently been based on clinician surveys[8]. Current data on clinician impressions of real world practices lies more commonly in the arenas of supportive care and survivorship[9.10,11]. Less frequently conducted and published are practice surveys on real-world treatment delivery, biomarker assessments, and cancer outcomes. An up-to-date, accurate understand of how clinical trial results translate to real-world practices has been recognized as an evidence gap in advanced cancer care[12]. Importantly, to our knowledge, survey results regarding clinical practice have not been compared to contemporary, prospectively collected datasets in validating the accuracies of their results. As such, the reliability of individual clinicians' responses to surveys regarding their own and other oncologists practice is unknown.

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In our study, clinician responses to a list of questions pertaining to management and clinical outcomes for patients with mCRC were contrasted with data from their own and other institutions which had been recorded in the TRACC registry. The aim of this study is to determine the accuracy of oncologists' impressions of real-word practice by comparing clinicians' estimates to data captured by TRACC. Our hypothesis was that clinician impressions obtained via questionnaires would not accurately reflect real-world practice as documented in TRACC.

Methods

A 34-question survey (Figure S1 in the Supplementary Appendix) regarding impressions of the management and outcomes of mCRC was distributed via email to 26 medical oncologists who were principal investigators of BioGrid Australia *(BioGrid Australia is an electronic data linkage platform for authorized researchers with collaborations with major Australian Hospitals)* [13] and further distributed to clinicians within their institutions. 19/26 medical oncologists (response rate of 73%) contributing data to TRACC at 9 hospitals (6 public hospitals, 3 private hospitals) in Australia completed the questionnaire.

The questions pertained to the clinician's individual practices at the hospital at which they work and at all other Australian hospitals contributing TRACC data. Areas covered included molecular testing (KRAS mutation analysis), systemic chemotherapy use, choice and duration of agents, and rate of liver resection, a potentially curative intervention. The questionnaire also examined clinical practice in a subgroup of elderly patients. Clinicians responded with their estimates in free text corresponding to the questions, and the survey was conducted over 8 weeks during March and April of 2014. The TRACC data, collected from July 2009 onwards, was extracted at the end of the survey collection for analysis. Only data from Australian hospitals was used, and only Australian oncologists were surveyed in our study. Responses were compared with TRACC data for the individual clinician's

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hospital, and then for all hospitals combined to explore the accuracy of clinician estimates. For this study, the median responses are expressed as the median estimate in ‘percentage’ or ‘months’ as appropriate for the survey question, and are reported as a direct comparison to the corresponding TRACC median data. For this study, comparison between median clinician estimates and the TRACC data with differences of <10% absolute percentage points will be regarded as a consistent result. For example, for a TRACC rate of 50%, a concordant median estimate is between 40 and 60%. A difference >50% absolute percentage points from TRACC rate will be regarded as an outlier in response. Given the small sample size we did not collect demographic data as we felt any subset analyses would not be adequately powered.

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Results

Estimates of overall chemotherapy and bevacizumab use

Median clinician estimates of chemotherapy use in their own practice (80%; range: 65-95%) were largely reflective of the 75% rate captured in the TRACC database. This is also comparable to the median estimate of chemotherapy use at other Australian sites (75%; range 65-95%) (Figure 1A). The median estimate for clinicians prescribing bevacizumab in the first-line setting was higher at their own institution compared to other hospitals (75% vs. 65%; range 60-90% for own hospital and 50-90% for other hospitals) (Figure 2B). TRACC data indicated that bevacizumab was used in 67%. Medians for own hospital and other hospitals (8 and 10 months) were both above the real data (5 months), with a broad range of estimates was seen for duration of bevacizumab therapy (4-16 months at own hospital and 4-14 months at other hospitals) (Table 1B). Clinicians tended to estimate longer bevacizumab duration at other hospitals compared with their own.

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Estimates of chemotherapy and bevacizumab use in the elderly (≥ 75y.o.)

Median clinician estimates of chemotherapy use in the elderly at their own hospital was 79% and varied widely (range: 50-90%). Clinicians tended to over-estimate their own practice compared to the TRACC database rate of 57%. There was a estimated 10% greater use at clinicians' own vs other hospitals (median 60%; range 50-90%) (Figure 1B). With regards to bevacizumab use in the elderly, there was a similar tendency to over-estimate use at the clinician's own hospital (median 60%; range 35-85%) compared to the TRACC median of 49%. A 10% over-estimate of bevacizumab use was reported in this elderly subgroup for the clinician's own practices compared to elsewhere (median: 60% vs 50%; range 30-85%) (Figure 1C).

Estimates of first-line irinotecan-based treatment

Whilst the median estimated use of irinotecan-based treatment in the first-line setting (10%) was close to TRACC captured data (7%), a wide range was seen (range: 2-75%) (Figure 2A). Generally clinicians estimated that other hospitals were twice as likely to use first-line irinotecan as their own hospital (median 10% vs 20%). The range of 5-40% was seen for estimates of first-line irinotecan based chemotherapy use at other hospitals. The estimated median duration of first-line irinotecan was 6 months for both clinician's own practice and at other hospitals (Table 1A). However a very wide range of estimates was seen, from 3 to14 months. The TRACC database shows a median of 5 months.

Estimates of KRAS testing

Clinicians estimated they were doing more testing than other hospitals (median 80% vs. 60%). Estimates of KRAS testing within 6 months of diagnosis varied widely (range: 20-100%) (Figure 3). In comparison, TRACC database analysis revealed only 43% of patients had been tested within 6 months of diagnosis.

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Estimates of liver resection and adjuvant chemotherapy use

The median estimate of clinicians' own practice was more than twice the TRACC rate (27% vs 12%) (Figure 4). Median estimates of own vs other hospitals were the same at 15%. A broad range of estimates was seen (range: 5-35%) for the proportion of patients who undergo liver resection. Oncologists underestimated the use of adjuvant chemotherapy in this setting, where TRACC data indicates that 88% of patients received treatment, compared with the median clinician estimate of 70% (range: 40-90%). There was only a 5% estimated difference in medians of clinicians' own practice compared to others (75% vs 70%).

Discussion

An accurate impression of what is happening in routine clinical care is critical to ensuring that patients are benefiting from ongoing advances in management and that variation across sites that may compromise outcomes is minimised. Clinician surveys is one way of garnering information regarding routine clinical practice, however, the reliability of the data gathered in these clinician surveys have never before been tested. This study seeks to explore the accuracy of oncologists' impressions of treatment of mCRC by comparing individual estimates to data captured by TRACC; a prospectively clinician entered registry at the point of clinical contact. Overall, this study demonstrates a clinician tendency to overestimate rates of interventions, and an impression of own clinical practices differing from others. Whilst in some instances the median responses were close to rates captured in a prospective registry for real world practices, individual estimates could be substantially different. A wide range of answers was given when clinicians were questioned about molecular testing, systemic therapy use and liver resection data in patients with mCRC.

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Overestimating rates of intervention

Overall the estimates of interventions of the clinician’s own practice tended to be higher than what was observed in the TRACC database, the exception being the use of adjuvant chemotherapy in the context of liver resection. Reasons for this could only be postulated; potentially TRACC data rates are an aggregate of multiple sites which could include centres where perhaps real intervention rates are lower, thus diluting the intervention rates contributed by centres where the clinicians surveyed practices. In saying so, when clinicians were questioned on their thoughts on practices at other hospitals as well, generally the answers for own versus other hospital were also different, although there was no clear pattern with the estimates of the intervention at other hospital sometimes being lower and sometimes being higher.

An impression of own practices differing from other hospitals

We had thought that generally the answers for own institution and elsewhere would have been reasonably similar, indicating that clinicians thought there was a consistency in practice across Australian sites; however, this was not observed across all domains. A potential reason for this observation could be that in answering questions about other hospital practices, clinicians may be influenced by an impression that – wrongly or rightly – a summation of institutions across Australia may practice differently due to differences in demographics, resources available, public versus private, or other factors that may influence other institutional routine practices compared to their own. Notably, the most prominent discrepancies in estimates of own versus other hospital practices this was seen for the rates of liver resection, with results varying widely and with no clear trends. This can perhaps be explained by the fact that liver resection would be highly hospital dependent relating to local surgical expertise and resources or access. Those at a tertiary referral centre would estimate their rates of resection to be higher than other hospitals, and conversely oncologists at regional centres may provide lower estimates. This may explain the wide spread of estimates.

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Understanding how clinicians derive their responses

It is of interest to consider how clinicians are deriving their responses, and the factors that may have influenced their answers. We anticipate that in some instances they will be working from a reference point, whereas in others there will be no available data to suggest what the answer could or should be. A reference point could be data from a clinical trial, frequently reported data in the literature, or a previous discussion with colleagues. For example, many clinicians will be familiar with data from clinical trials that report the duration of first-line chemotherapy or of first-line bevacizumab, and then might derive from that what a reasonable answer might be for routine clinical care, using their own personal experience to modify the trial data to what they expect is happening in routine practice. The median time to progression in the pivotal phase III study by Colluci et al[14] looking at first-line FOLFIRI versus FOLFOX4 were 7 months in both arms; where clinicians estimated 6 or 7 months in our study (Table 1B). The seminal trial for use of combination chemotherapy with bevacizumab by Hurwitz et al[4] showed a clinically significant survival difference in the first line setting (20.3 vs 15.6m; HR0.66, p<0.001) with a median duration of combination treatment of 40.4 weeks. Clinician estimates for own site and other hospitals – whilst queried regarding combination with oxaliplatin – was 8 and 10 months respectively, where TRACC-captured practice data showed a much lower duration of 5 months. Whilst it can only be postulated that certain high-impact clinical trials can conceivably become a factor in an oncologists' impressions of patterns of care, this observation is of interest, especially in the context that TRACC captured contemporary data were not unexpectedly lower. By the same token, even for data points where detail is reported in studies there was a wide variation in estimates, in some instances responses far exceeded what was seen in clinical trial populations. In addition, other potential factors that may inform an individual clinician's answer may include formal and informal departmental discussions, results of unit audits, and the depth of experiences perhaps relating to years in practice. In any case, the message is that clinician's estimates cannot be relied upon, alone or combined, to give an accurate reflection of real world practice.

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For each question asked there was a broad range of responses given, with the tightest data being for chemotherapy use (estimated range of 65-95%; TRACC median of 80%) and the widest spread of answers being seen for KRAS testing (estimated range of 20-100%; TRACC median of 43%). In addition to the median response, it is also of interest to consider the broad range of responses given. The tightest data was for chemotherapy use (estimated range of 65-95%; TRACC median of 80%) and the widest spread of answers was seen for KRAS testing (estimated range of 20-100%; TRACC median of 43%). Clearly there was no individual question where the clinician responses were tightly clustered, if we were to apply the same parameter in considering median estimate concordance of <10% variation from TRACC-captured data to the range of responses as an exploratory exercise. Generally individual clinician answers were spread across a wide spectrum. Whilst true outlying (>50%) median response did not occur, it is of interest in considering individual clinician answers that substantially differed from the TRACC median. For example, estimated use of irinotecan-based treatment in the first-line setting included a 40% and a 75% response, where TRACC data showed 7%. Perhaps the clinicians who gave those responses preferentially give irinotecan as first-line treatment, and that these estimates do reflect their own practices, however the TRACC rate is diluted by the practice of other clinicians contributing to the database. Another possibility is that the clinician misread the question. Ensuring questions are as explicit as possible is important in all surveys. In this instance the question asked was “what percentage of all patients receive irinotecan based treatment as first-line treatment?”, and it is not clear how this wording could have been altered to make the question more precise.

The role of adjuvant chemotherapy following hepatic resection remains unclear, with no individual study showing a survival advantage[15,16]. This contrasts with the other questions asked in the survey, where there is an accepted role for the intervention. Of interest this was the one intervention where the data from TRACC indicated that more patients were undergoing the intervention than was estimated by the clinicians. It is possible that at the time of the survey the rate of chemotherapy administration was declining, following data published in 2013 that showed no overall survival impact

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of adjuvant FOLFOX chemotherapy,[17] whereas the query of the TRACC data was for patients treated from mid 2009. For RAS testing the opposite might be true, with the intervention increasing over time, so that may be one explanation for clinician estimates of RAS testing being higher than the TRACC data over the time period going back to 2009.

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Limitations, potential confounder, and the use TRACC registry as a comparator

Limitations of our data include the small sample size of 19 oncologists. However, as all clinicians who took part in the survey are also contributors to the TRACC database, we would expect their answers to have been more consistent. Another limitation is that the data collection is ongoing, and may be incomplete for some patients. For the patients in the registry that were early in follow-up they may have yet not undergone an intervention that ultimately would have occurred, however the questions asked (of oncologists' estimates of all patients) and the way that data is captured (prospective data on consecutive patients) should minimise this. Liver resection is typically done early, in the few months after diagnosis, so it is likely almost all liver resection data would have been captured. KRAS testing may not yet have been performed for some patients, as it may have been clinically appropriate to do this after first-line or even second-line therapy. This is why we specifically asked about testing in the first 6 months. It is also possible testing may have occurred and the data has not been entered. An informal audit at several sites found only a small number of un-entered cases, indicating reasonably complete data at these sites but this may not be the case at other TRACC sites, therefore, the real rate of testing is potentially higher.

Also affecting KRAS testing rates is the evolving treatment landscape in Australia for mCRC since 2009 when TRACC data set commenced. Cetuximab and panitumumab became available in 2011 and 2013 respectively on the Pharmaceutical Benefit Scheme (PBS), and henceforth became part of the algorithm for standard of care treatment necessitating KRAS testing. First-line use for cetuximab was only approved on the PBS in 2015. In comparison to KRAS testing, first-line chemotherapy data

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is a mandatory field in TRACC database collection, and if first-line treatment is not proceeding due to age, frailty or poor performance status then that is prospectively recorded in the database for all patients.

A potential confounder is that the results were not taken into context of whether clinicians practiced privately or in the public sector. Of interest are data in a study by Field *et al.* showing higher rates of treatment delivery in the private sector, which was associated with better survival outcomes.[18] In our results, clinician estimates of practice at other sites were in reference to practice overall regardless of public or private status, and the spread of results were generally comparable in inaccuracies when it came to estimating their own practice. It would be conceivable that individual clinicians had varying levels of accuracy in estimating the practice at their own institution, however this would not account for the spread of estimates of practices at other Australian sites overall.

The TRACC database, used as the benchmark comparator for the clinicians' estimates in this study, has strengths and weaknesses of its own as a registry of contemporary routine clinical care. Prospective, clinician-entered, multidisciplinary treatment and outcome data on consecutive patients at the point of clinical care provides the most complete and accurate method of data collection. Limitations are that any treatment related differences observed in patient outcomes may reflect the confounding effect of many factors that impact both treatment selection and outcome. For the purposes of this study a large patient sample size would have allowed more precision in our understanding of contemporary practice.

While it has been hoped for quite some time that the increased use of electronic health records would translate into more real world data becoming readily available this has yet to happen, suggesting at least for the near future registry based data will be the most reliable source of information regarding what is happening in clinical practice. It is also worth noting that prospectively collected clinical data

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has multiple uses other than informing our direct understanding of interventions being used in routine practice. For example, using TRACC data a novel set of quality indicators for metastatic colorectal management have been described by Turner *et al*.[19]

Regardless of the intended use of the responses, our survey indicates that relying on clinicians' estimates of their own and others practice will lead to a wide spectrum of answers. Even looking at the median result may produce an answer substantially different to what is actually happening in routine practice. Given this we would conclude that clinical surveys alone are an inaccurate way of describing contemporary clinical practice in mCRC, are inconsistent with results from a prospectively collected database, and can be potentially misleading.

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Figure legends

Table 1 **Estimates of duration of therapies**

A - Clinician estimates of chemotherapy use in first-line setting (duration in months)

B - Clinician estimates of bevacizumab use in first-line setting (duration in months)

Figure 1A. **Estimates of patients treated with chemotherapy**

Clinician estimates of chemotherapy use (range of 65-95%) were reflective of real-life data where 75% of patients with mCRC are treated with chemotherapy according to TRACC data.

Figure 1B. **Estimates of elderly patients (≥ 75 years) treated with chemotherapy**

Clinician estimates of chemotherapy use in the elderly varied widely (50-90%), tending to over-estimate use and estimating a 10% greater use at clinicians' own vs. other hospitals. TRACC data indicates 57%.

Figure 1C. **Estimates of elderly patients (≥ 75 years) treated with chemotherapy and bevacizumab**

There was a wider range of estimates of bevacizumab use, a tendency to over-estimate use at the clinician's own hospital, and to estimate that bevacizumab use was greater at their hospital than elsewhere.

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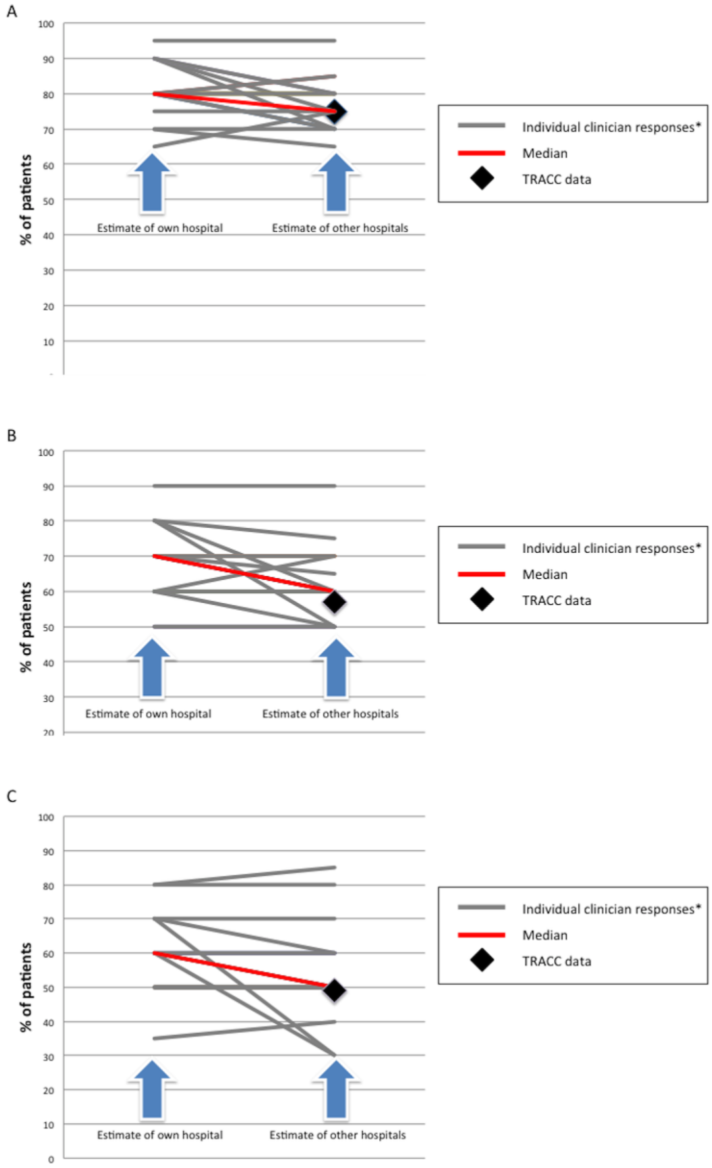

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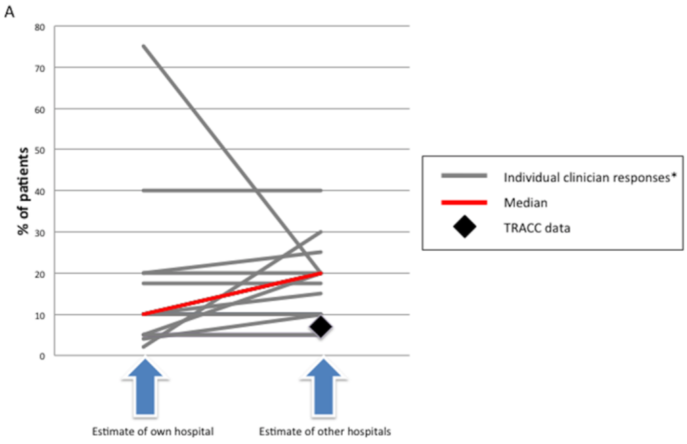
Figure 2A. **Estimates of irinotecan use in the first-line setting**

Whilst the median estimated use of irinotecan-based treatment in the 1st line setting (10%) was close to reality (TRACC data - 7%), a wide range was seen (2-75%). Generally clinicians estimated that other hospitals were twice as likely to use first-line irinotecan as their own hospital.

Figure 2B. **Estimates of bevacizumab use in the first-line setting**

Most clinicians felt their own prescribing of bevacizumab was either similar or higher than other hospitals. Responses had considerable spread ranging from 60 to 90% overall. TRACC data indicated that bevacizumab was used in 67%.



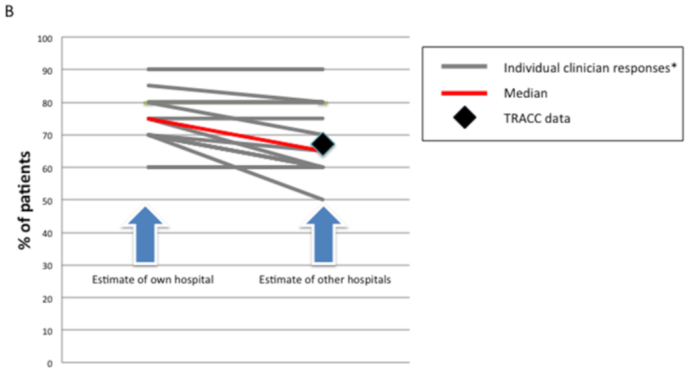


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Figure 3. **Estimates of KRAS testing in patients ≤ 65 years within 6 months of diagnosis**

Estimates of K-RAS testing within 6 months of diagnosis varied widely (20 - 100%, median 65%). Clinicians estimated they were doing more testing than other hospitals (80% vs. 60%).

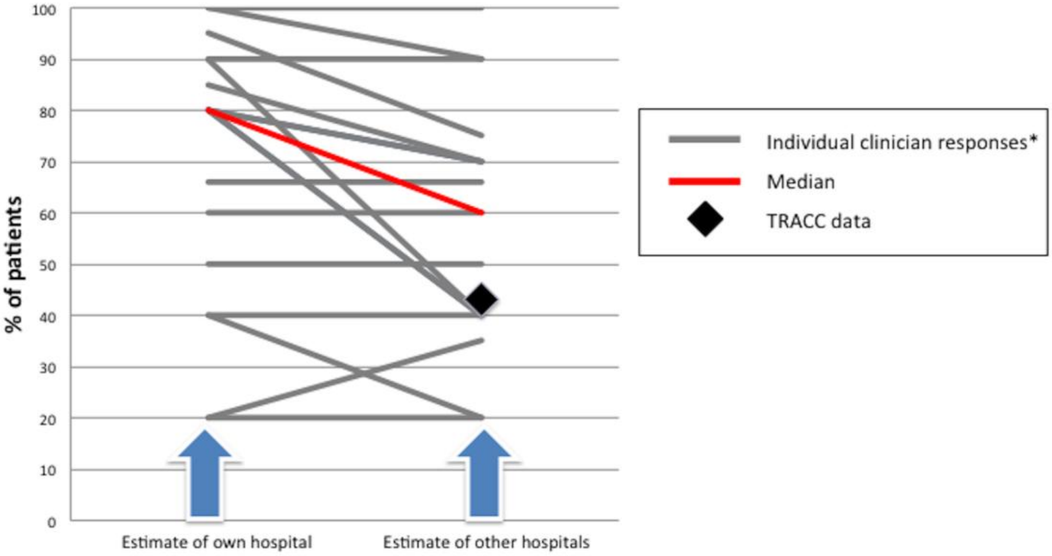

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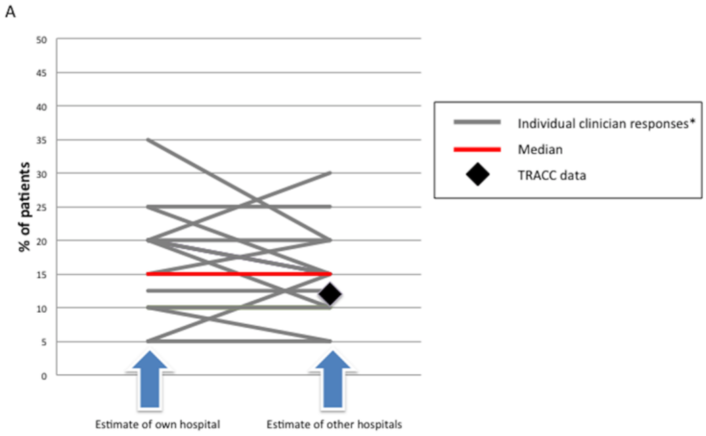
Figure 4A. **Estimates of patients who undergo liver resection with synchronous hepatic metastases**

A broad range of estimates was seen (range 5-35%) for the rate of liver resection. The median estimate was more than twice the real rate (27% vs. 12%). There was no clear trend when clinicians estimated their own hospital data compared with others.

Figure 4B. **Estimates of adjuvant chemotherapy use in the setting of liver resection**

Oncologists underestimated the use of adjuvant chemotherapy in this setting, where TRACC data indicates that 88% of patients received treatment, compared with the median clinician estimate of 70% (range 40-90%).



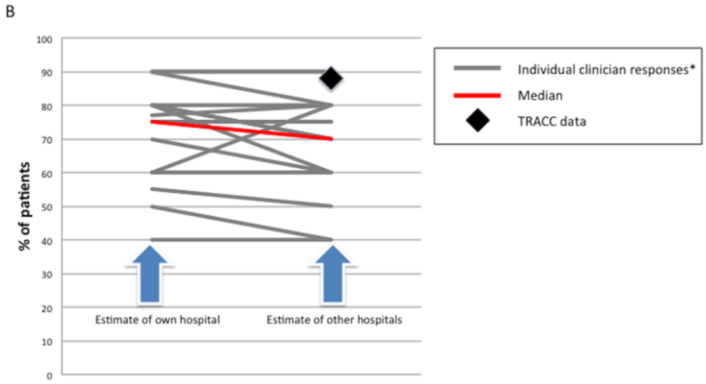


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Table 1 – Estimates of duration of therapies

A.

	Clinician estimates of chemotherapy use in first-line setting (duration in months)		
	Own hospital	Other hospitals	TRACC data
Oxaliplatin based treatment			
Median	7	6	5
Range	3-14	4-14	
Irinotecan based treatment			
Median	6	6	5
Range	3-14	3-14	

B.

	Clinician estimates of bevacizumab use in first-line setting (duration in months)		
	Own hospital	Other hospitals	TRACC data
Oxaliplatin based			

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treatment			
Median	8	10	5
Range	3-16	4-14	

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