Essay

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The Patient Journey and Guideline Concordant Care in Colorectal Cancer – Is Current Practice Enough?

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Abstract

Colorectal cancer is a major healthcare burden, and modern management of non-metastatic disease relies heavily on guideline concordant care with a basis in histopathologic staging and empiric systemic therapy. While multidisciplinary care pathways and standardized guidelines have improved outcomes at a population level, they fall short in addressing the inter-patient and intra-tumoral heterogeneity that drives lack of response, recurrence, and unnecessary toxicity. Using a hypothetical patient journey, our commentary highlights how current practice often fails to align with patient needs despite being "guideline concordant". We discuss limitations of current treatment paradigms and the shortcomings of even modern tools like genomic profiling, highlighting the continued need for complementary approaches. We hypothesize that functional precision medicine approaches offer a critical missing link, providing illustrative examples drawn from our recent colorectal cancer clinical correlation study where we demonstrated the ability to predict treatment response and identify drug resistant tumor subclones. Integrating these technologies alongside genomic and minimal residual disease assessments could refine therapy selection and improve existing surveillance strategies. Ultimately, we suggest that while guideline concordant care remains necessary, it is no longer sufficient. It is time for colorectal cancer management to move toward a personalized framework that maximally benefits patient outcomes.

Keywords: colorectal cancer; guideline concordant care; functional precision medicine; metastasis; tumor heterogeneity; minimal residual disease; new approach methodologies; resistant subclones

1. Introduction

Colorectal cancer represents a considerable health burden worldwide, being the third most common cancer type and the second-leading cause of cancer related death [1]. The standard of care for patients with non-metastatic colorectal cancer is surgical resection with clinical and histopathologic staging informing the recommendation for adjuvant systemic therapy [2,3]. Currently, there are no validated markers that can reliably guide chemotherapy selection in patients for whom histopathologic staging indicates systemic therapy may be beneficial [4,5]. Further, toxicity of systemic therapy is of great concern to clinicians and patients alike [6]. Despite recent enthusiasm for a small number of patients that are candidates for immunotherapy [7,8] treatment is largely empiric, with "guideline concordant care" driving clinical recommendations and being considered the gold standard [9]. While guideline concordant care can include precision/personalized medicine, a one-size-fits all approach of empiric guidelines leaves a lot to be desired in terms of individual patient benefit and patient expectations [10–12]. As physicians and researchers, we need to ask ourselves - is standard of care enough?

In this commentary we describe a hypothetical patient journey for a patient with colon cancer manifesting with common difficulties that hinder the ability to provide personalized medicine.

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2. The Patient Journey

We describe a clinically grounded hypothetical journey of a patient with colorectal cancer. Our hypothetical patient is a 55-year-old female who has just undergone her first screening colonoscopy. She has no family history of colon cancer but unfortunately has a 3 cm polyp in her right colon biopsied that appears to be cancerous. She is called 5 business days later and informed that she has invasive colonic adenocarcinoma [13,14]. She is also informed that she has been referred to her local university hospital colon cancer multidisciplinary clinic (MDC) [15]. She is extremely concerned but somewhat comforted by the reputed academic prowess of the university and the rapid referral for her problem [16]. She arrives for an early morning appointment at which time she has a full medical history taken and physical examination performed by a mid-level provider or a junior level surgery or medicine resident (doctor in training). Following her history and physical exam she is quickly shuttled to the lab for a full panel of electrolytes and "tumor markers". From there she is transferred for a CT examination of her chest, abdomen and pelvis. Rapidly, she has completed what is currently considered an appropriate patient intake [15,17,18] . At this point she will return for an afternoon appointment to discuss her case. Our patient is considering a litany of questions regarding her cancer stage [19], her surgery and whether or not she will require chemotherapy and radiation [20]. Her questions have been gleaned from Google searches [21] and well-meaning advice from family, friends and acquaintances who have had experience with colon cancer or at least hold personal opinions on medical procedures [22].

At a planned lunch, a large group of physicians, mid-level providers, residents, interns, medical students and other assorted ancillary personnel are reviewing and discussing the cases to be seen in clinic that afternoon. From her intake it is has been discovered that our patient has no evidence of metastatic or regional disease on her axial imaging, no family history, no mitigating medical issues, she is eligible for no study protocols and has no abnormal tumor markers detected in her pathology review to suggest she is a candidate for immunotherapy. It is therefore recommended that she have upfront surgery via a minimally invasive technique that promises limited pain and a rapid discharge from the hospital [23,24]. Having returned to the clinic she is greeted by the provider she met that morning along with a more senior physician who will be her surgeon. The surgeon engages in a brief introduction, explains the plan of care and asks if our patient has any questions. The patient begins by asking, "what stage cancer do I have?" [19]. This is a common question and, in many ways, demonstrates the lack of pre-clinic preparation patients receive as they go through the initial intake process." [16,25,26]. In the best of circumstances, her stage question leads into a discussion of the tumor, lymph nodes and metastatic disease (TNM) staging system and the need for surgery to remove and further evaluate her tumor. The risks and benefits of the surgery along with brief mention of the complications will be followed by signing of a surgical consent and she will be placed on the surgery schedule. At some point in this process the patient will likely hear that she will be receiving "guideline concordant care" [15,17,18].

It is not clear if most patients have knowledge of what this means [27]. This phrase has undoubtedly been mentioned at the physician lunch while reviewing pathology slides and CT scans. Within a few days to weeks from this visit our patient will return to the hospital to undergo surgical segmental resection of a portion of her colon. Presumably the surgery goes well and is also guideline concordant [28]. At this point our patient has her clinical staging completed [29]. For the sake of this commentary, we will assume that she has had no unexpected metastases seen during her operative intervention, nor visible evidence of T4 disease (cancer penetrating the wall of the colon) detected. Based on her preoperative testing, she has stage 1-3 colon cancer pending her formal pathology evaluation. As previously mentioned, she has no family history or other contributory factors that would be considered "high risk" for systemic recurrence. At this point she is again told that she will be recommended to undergo guideline concordant care once her pathology is known that might include chemotherapy. Our patient does well from a surgical standpoint and is told that within 72 hours she will be discharged to complete her recovery at home [30].

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In this hypothetical scenario, our patient will have her case reviewed at a multidisciplinary tumor board and a discussion of her next steps in care will take place. Once again, her plan of care should be guideline concordant. For the purposes of this hypothetical case- our patient's pathology has returned as a T2, N0, MX moderately differentiated adenocarcinoma. Based on the existing guidelines [15] for early-stage disease she will be recommended to have surveillance, whereas more advanced disease would elicit a recommendation for adjuvant therapy [31,32]. In this scenario the patient will be informed that her chance of survival with surgery alone is quite high (around 90%) [33]. Unfortunately, there is a small, but real chance her cancer can recur and therefore ongoing surveillance is important.

3. Recurrence, Shortcomings and Potential Paths to Improvement

The above hypothetical patient presentation leaves us to consider whether or not we have done enough? It has clearly been demonstrated that multidisciplinary clinics are very efficient in seeing patients and getting them into treatment [10] and while this appears to cover all the bases, it is certainly not without issues [9,34–36]. In terms of providing personalized care, undoubtedly there is a need for improvements [36]. It is known, even in early stage patients, that a low, but real risk of metastasis exists [38]. The incidence of recurrent disease is higher in stage 3 and 4 colorectal cancer patients and in patients who develop colorectal cancer at a younger age [39–41]. A recent publication from Denmark highlights some difficulties in recommending the best next step in treatment for colon cancer patients with nonmetastatic disease. This study examined a large number of patients with stage 1-3 disease and noted recurrence rates of more than 16% in stage 1 patients at 1 year, decreasing to around 7% at 3 years post-operatively. For stage 2 patients the rates were approximately 22% at 1 year dropping to around 12% at 3 years and finally for stage 3 patients the rates were 35.5% and 24.6% at 1 and 3 years respectively [40]. While lower rates are found in other studies [42,43] there is still a small percentage, but large corresponding number of early stage colon cancer patients who develop metastatic disease that might benefit from systemic therapies. Similarly not all patients with stage 3 disease go on to develop metastases and therefore will not benefit from standard systemic therapies as guidelines recommend [43–45]. When we examine current guidelines as they exist, there is a limited number of options for adjuvant therapy (essentially combinations of standard chemotherapeutic agents: capecitabine; 5 fluorouracil and oxaliplatin) [15,29]. The recommendations are anchored primarily in the MOSAIC Trial [45] In this trial a total of 1123 patients were randomized and the rate of disease-free survival at three years was 78.2 percent (95 percent confidence interval, 75.6 to 80.7) in the group given 5 FU/Leucovorin plus oxaliplatin, and 72.9 percent (95 percent confidence interval, 70.2 to 75.7) in the 5 FU/Leucovorin group (P=0.002). While this is highly significant and the toxicity can generally be managed [6,47] recent work suggests that patients may be more enthusiastic about increased survival from adjuvant chemotherapy than clinicians [48]. More recently it has been shown, amongst more aged patients, the expectation of prolonged survival needs to be higher for them to accept the risks of adjuvant therapy [49]. The real-world benefits of increased survival balanced against long term toxicity (peripheral neuropathy, depression and poor sleep quality) may not be appreciated by patients, particularly as symptoms may commence after treatment is completed [50–52]. Thus, we note that the with use of current guidelines, there is potential to under treat early-stage colon cancer patients and over treat a percentage of more advanced stage patients for whom surgery alone would be sufficient. This again leads us to ask," is current practice enough"? Improvements in selecting patients for receipt of adjuvant therapy as well as candidacy for up front small molecule inhibitors, immunotherapy or even more efficient surveillance definitely need to be addressed in a "guideline concordant" approach, suggesting we need new data.

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4. Colorectal Cancer in the 'Omics Era

Genomic profiling has undeniably had a transformative effect in the field of oncology. The proportion of cancer patients receiving genomically guided treatment and the number benefiting from it has been increasing over the past two decades. One pan-cancer study reported that the percentage of patients benefiting from such treatments increased from 0.7% in 2006 to 4.9% in 2018 [53], while another 2024 study reported 31.6% of tumors carrying a biomarker considered predictive in standard-of-care [54]. A recent CRC-specific study of 575 patients reported a rich landscape of potentially clinically actionable genomic findings, including many well-known driver mutations. Ultimately, they suggested that 51% of patients could theoretically be eligible for clinical actionability based on genomic findings, while 49% could be enrolled in clinical trials of investigational therapies. Nonetheless, this does not represent real-world benefit, due to the current entrenchment of more traditional treatment paradigms. This fact is not without justification, since clinical actionability of a mutation does not guarantee successful treatment. One recent pan-cancer meta-analysis of approximately fifty-five thousand tumors reported that of the 15% of patients who received a genomically guided treatment, the objective response rate was only 25%. While genomically guided treatment has and will continue to be a driver of improved cancer care, it is only one piece of the required treatment armamentarium, and crucial elements are still missing. One such missing element is the transition of functional precision medicine approaches into standard clinical care [55].

5. Clinical Correlation and Resistant Subclone Identification in a Clinical CRC Study

In a recent publication, we demonstrated the ability to predict patient response to treatment in a retrospective clinical study incorporating a cohort of 21 colorectal cancer patients treated with neoadjuvant standard-of-care therapies. Patient response to treatment was predicted using patient-derived tumor organoids (PDTOs) and our proprietary MOSgen™ system and then tested for correlation with actual clinical outcomes. Clinical response was predicted with 83% accuracy using binary patient response categorization and disease-free survival (DFS) also correlated with in-assay measured responses. Furthermore we were able to identify patients whose PDTOs demonstrated higher response to alternative standard-of-care therapies than to the one they received in their clinical treatment, suggesting these patients may have benefited from a non-empiric treatment selection paradigm [56].

The assay used in the aforementioned study utilized brightfield microscopy imaging of approximately 40 individual patient-derived models (MOS® droplets) per well in 384 well plates with wells spanning multiple drugs, and 9-point concentration gradients. Fluorescently labeled epithelial cell adhesion molecule (EpCAM) was used as a marker of tumor cell viability with signal intensity measured longitudinally across a one-week period. While clinical correlation was based upon summation of well-level EpCAM signals, we also utilized machine learning techniques to automatically identify all individual MOS droplets per-well and subsequently generated per-MOS-droplet viability measures. This provided the ability to detect differential growth and response rates for each individual patient MOS model within each well of a plate, corresponding to the well-documented heterogeneity of cancer cells in-vivo (Figure 1a). By combining per-MOS-droplet EpCAM signal measurements with a colored intensity gradient and per-well brightfield microscopy images we were further able to visualize the morphology of MOS models demonstrating heterogeneous responses to drug doses, with some outlier MOS models demonstrating vigorous sustained growth despite high-dose drug treatment while others appeared arrested in growth and condensed in terms of cellular morphology (Figure 1b). EpCAM signal density distributions per-well were also profiled and demonstrated wider distributions corresponding to higher overall levels of growth heterogeneity in vehicle or lower drug dose containing wells, while heterogeneity decreased with high drug doses, and high viability being observed only in isolated outlier MOS models, consistent with a model of rare drug-resistant subclones surviving drug treatment in an in-

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vivo setting, despite the bulk of the cancer being successfully eradicated (Figure 1c). While this analysis was exploratory and the clinical study was retrospective, it suggests the potential for technologies like ours to accurately predict patient treatment sensitivities in a prospective setting and further, to identify sub clonal drug resistance, even determining alternative, accompanying or second-line agents that evoke cell death in initially resistant subpopulations of cells from a single patient assay, early in a patient's clinical journey. Further, identification of these previously unknown subclones opens a new realm of possibilities to improve efficacious treatments in all stages of colorectal cancer. Isolation of these subclones allows focused genetic analysis of problematic cancer populations rather than pan tumor assessment [57,58] Further, our MOSgen platform can be utilized for the development of novel systemic agents and immunotherapies [59,60]. Noting that this platform provides personalized medicine by evaluating problematic subclones that will lead to patient demise with associated side effect but without benefits of adjuvant therapy. Finally we note this platform more than adequately satisfies requirement for a New Approach Methodology (NAM) [61].

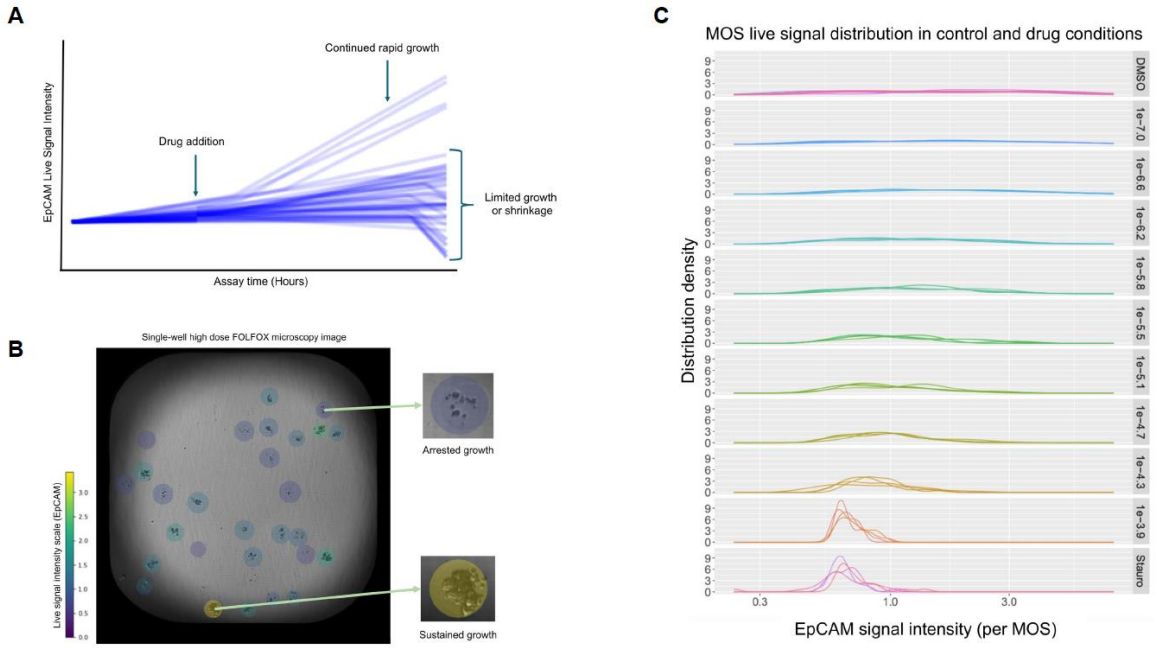

Figure 1. a: Representative example of longitudinal live signal intensity in a drug-treated well for a patient sample. Each line represents a single patient-derived model (MOS droplet). Some natural growth-rate heterogeneity is observed throughout the assay, but post drug addition, distinct populations of MOS droplets are observed including those with limited growth, death, and in select instances continued rapid cell growth. **b. Representative brightfield microscopy image visualizing tumor model heterogeneity.** A single high-dose FOLFOX-treated well containing independent patient-derived CRC models (MOS droplets) overlaid with a color gradient indicating high to low viability measured by EpCAM fluorescence signal intensity. While the majority of MOS droplets demonstrate low viability, an outlier shows continued sustained growth suggesting treatment resistance. **c. Representative single patient (MOS model) EpCAM signal intensity distributions.** Vehicle (top) and kill control (bottom) wells are shown, with increasing doses of a single treatment (rows 2-10). Wider distributions in vehicle and lower drug doses correspond to higher overall levels of growth heterogeneity. Peaks in in higher drug doses correspond to decreased heterogeneity in viability with the majority of MOS models undergoing growth arrest or death and only outlier MOS models retaining high viability, consistent with drug resistance.

6. Conclusions

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There have been advances in the care of colorectal cancer patients, including ERAS (enhanced recovery after surgery) and Minimally Invasive Surgery (MIS) with the promise reduced pain and earlier hospital discharge [62,63]. There have been advances in our ability to measure minimal residual disease MRD in colon cancer [64,65]. More recently, there have been exciting advances in immunotherapy for appropriately selected patients [8]. Unfortunately, guideline concordant therapy for non-metastatic colon cancer revolves around systemic therapy recommendations based on data that is two decades old [15,17,18]. At the same time, the aged, frail population continues to increase [66], and more young patients are presenting with aggressive colon cancers than ever before [67]. The time for incorporation of personalized medicine in colon cancer care is now. The work of Nors et al. [41] has demonstrated that recurrence rates for non-metastatic colorectal cancer, particularly at 1 to 2 years, are much higher than previously quoted. We have demonstrated in MOS models, created from primary colon cancers, that problematic subclones are readily present and do not respond to standard of care systemic therapy (Figure 1b-c). These findings explain unexpected disease recurrence in early-stage disease as well as treatment failure in patients receiving standard of care systemic therapy for more advanced disease. Identification of problematic subclones allow fastidious use of "omics" by focusing investigation on problematic subclones rather than addressing potentially billions of cells in a primary tumor. Further, this work allows improved diagnostics for all cancer patients. MOS models have the potential, particularly as it is amenable to AI and machine learning, [56,68,69] to rapidly advance therapeutic development and finally offers the opportunity for personalized in way that will accommodate both patients and providers [70,71].

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