GASTROINTESTINAL (COLORECTAL) CANCER

Biologic Agents in the Treatment of Colorectal Cancer: The Reality of Where We Are and Where We Need to Go

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“Right Drug for the Right Patient”: Hurdles and the Path Forward in Colorectal Cancer

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OVERVIEW

Predictive biomarkers have been heralded as the way to develop the “right drug for the right patient.” However, despite many studies incorporating novel biomarkers with targeted therapies, there has been little progress over the 5 years since the identification of KRAS mutations’ ability to predict resistance to epidermal growth factor receptor (EGFR) monoclonal antibodies. Recently approved therapeutics (regorafenib, aflibercept) or label extensions for existing therapies (bevacizumab) lack companion biomarkers. The current model of biomarker development, “target-based biomarker” design, attempts to identify individual biomarkers that are closely tied to the activity of a particular treatment. There are several limitations to prospective utilization of predictive biomarkers in novel therapy development, including technical validation of the assay and the logistics of timely biomarker determination with available material that limit the options. Tumor heterogeneity, both between different regions in the tumor and as a result of changes induced over time and under the selective pressure of chemotherapy, can reduce the precision of biomarker determination. Biomarkers present in low frequencies are increasingly common in drug development and will require efficient screening infrastructure to be feasible. Although development efforts will continue in the current target-based biomarker model for the near future, it is increasingly apparent that a new model is needed. A “taxonomy-based biomarker” model has been proposed, which is less tied to novel drug development and instead attempts to classify individual tumors based on their intrinsic biology. This requires integrating multiple characteristics of the tumors, including gene mutations, amplifications, methylation, as well as RNA and protein expression. Identification of the taxonomy of colorectal cancer will then allow more efficient development of targeted agents that can leverage the distinct molecular vulnerabilities of the resulting subsets. A transition to a taxonomy-based biomarker model would provide the classification structure and biologic insights needed to advance the ultimate goal of the right drug for the right patient.

Five years ago at the ASCO Annual Meeting, the oncology community was presented with considerable evidence that codon 12 and 13 KRAS mutations were associated with resistance to EGFR monoclonal antibodies. These datasets, and their subsequent publications, provided clear evidence that KRAS was a predictive biomarker and led the way for rapid adoption and clinical implementation of this test. This was appropriately hailed as a great opportunity to optimize treatment for patients and minimize exposure to inactive agents for a subset of the patients. The discovery of the predictive ability of KRAS was upheld as a critical example of personalized medicine (or, as it is now commonly referred, precision medicine). It demonstrated the potential clinical benefit of a strong and discrete predictive biomarker, and accelerated interest in biomarker discovery in colorectal cancer (CRC). However, over the past 5 years, predictive biomarkers for biologic therapy of CRC have been slow to appear. Indeed, the latest wave of positive phase III studies (bevacizumab, ziv-aflibercept, regorafenib) have been performed in all patients without regard for the molecular or pathologic features of the patients’ tumors.

Meanwhile, the interest in defining these predictive markers has exceeded our ability as an oncology community to deliver high-quality and validated biomarkers. The promise and concept of personalized or precision medicine is easily appreciated: selection of the most active therapy with avoidance of ineffective potentially toxic therapies, through the application of biomarkers derived from the molecular biology of the tumor. Patients with refractory, metastatic disease and their oncologists look for such tests with considerable zeal, and the diagnostic biomarker market has provided opportunities for such proprietary testing that has outpaced our ability to provide the necessary technical and clinical validation. Other marketed tests, although based on sound scientific hypotheses, have lacked access to samples from randomized clinical trials that would be required to provide a true validation cohort for such predictive biomarkers. Premature application of these tests to clinical care has resulted in an appropriate degree of skepticism by oncologists and patients.
as the clinical benefits promised by these marketed tests are not realized.

In other settings, a rush to adopt predictive biomarkers based on retrospective studies led to incorrect conclusions. The presence of a BRAF mutation is one such example, where early studies demonstrated a lack of radiographic response and short progress-free survival in patients with BRAF-mutant tumors after treatment with an EGFR-monoclonal antibody. Clinical practices in many settings were changed based on this data, with clarity coming from subsequent studies demonstrating that the BRAF mutation is a marker of very poor prognosis irrespective of treatment and its presence does not exclude the potential for relative benefit from EGFR inhibition. Ultimately, the utilization of technically and clinically unvalidated assays harms the field and is counterproductive to the goals of personalized or precision medicine. The continued efforts to develop the right drug for the right patient and the complexities behind this apparently simple concept will be reviewed.

TARGET-BASED BIOMARKERS: THE CURRENT MODEL

There are two general approaches that have been proposed for linking prospective biomarkers to biologic therapy (Fig. 1). The first approach, which we term the “target-based biomarker model,” starts with an understanding of the mechanism of action of a novel targeted therapy and derives potential predictive biomarkers for this therapy. In many settings, these are related to mutations related to the agents’ mechanism of action (e.g., PIK3CA mutations for inhibitors of PI3K/MTOR pathway) or expression levels of receptors or ligands relevant to the target (e.g., HER2 expression or amplification for HER2 inhibitors). Typically, panels of cell lines with or without the molecular alteration of interest are interrogated to determine the relative sensitivity to the targeted agent, with validation in a small and selected number of xenograft models, although more sophisticated bioinformatics efforts are increasingly being utilized to support biomarker identification and development. If not previously developed, in vitro diagnostic development plans are initiated to support a potential regulatory filing of a companion diagnostic for the novel agent. Although there are an increasing number of successful agents and biomarkers that have followed this path in other tumor types, there are risks that exist in relying solely on this model. Codevelopment of a biomarker and novel therapeutic is increasingly difficult, as both have to navigate separate complex regulatory hurdles, where delays in either can hold up timely drug development. More importantly, this biomarker work is focused on a specific molecular target and does not fully recapitulate the molecular biology of the tumors. As a result, in the event of the failure of the drug, the biomarker is of less enduring benefit to the field.

Current Hurdles

Technical validation. Despite these limitations, this approach has been utilized for the vast majority of integral biomarker studies to date and will likely remain the approach for the near future. There are several additional hurdles to the target-based biomarker model that have become evident. These involve the design and application of biomarkers, and practical considerations for implementation of the tests in clinical research. The extent of technical validation required for biomarkers has appropriately become more rigorous for biomarkers used to affect the care of the patient. For research studies performed with these integral biomarkers, performance of these tests in a clinical laboratory (Clinical Laboratory Improvement Amendments [CLIA]-compliant laboratory) remains necessary but is no longer sufficient, with increased requirements from the U.S. Food and Drug Administration for biomarker technical validation including potential requirement to file an investigational device exemption (IDE), as recently outlined for a National Institutes of Health cooperative group study.7 For some continuous biomarkers (such as protein or RNA expression or copy number), this includes detailed justification of thresholds defining high and low biomarker levels, while for mutation-based biomarkers, delineation and justification of specific codons considered to be biologically relevant may be required. These concepts also apply to biomarker signatures which combine various individual components, where these requirements are increasingly rigorous.

Low frequency of many of the biomarkers of interest. Mutations are currently the most widely utilized integral biomarker for metastatic colorectal cancer. Aside from mutations in KRAS and APC, which are present in approximately 40% and 80% of patients, respectively, many other
mutations of interest are less common and require extensive screening efforts to identify trial candidate (Fig. 2). For example, BRAF mutations are associated with a unique biology and represent a tumor type of considerable interest for study development, but are present in only 5% of the population with metastatic CRC. Full enrollment into a 20-patient proof-of-principle study for such a population requires screening of 400 patients (Fig. 2). For prospective screening studies, this requires consenting and discussing the potential study with a large number of patients who will not ultimately be eligible for treatment. This fact has led to efforts at many institutions and through the cooperative groups to initiate screening “bucket” studies that will provide screening in parallel for several potential studies. As agents are tested against the more common “actionable” activating mutations, and attention turns to mutation subsets of less than 5% (such as

FIG 1. The current and proposed biomarker development models.
AKT mutations or microsatellite instability in metastatic CRC, these large trial infrastructures will be critical to study feasibility.

Logistics of biomarker testing. The logistics of biomarker testing can have disproportionate effects on successful study completion. In our experience, patient satisfaction and willingness to participate is dependent on the turnaround time for biomarker testing and the likelihood that they will have a study in which to participate after completion of the screening. Asking 100 patients to defer treatment for 4 weeks while biomarker testing is performed (for a study that will only enroll two to five of the patients) is not appropriate in the absence of a critical mass of potential clinical trials. This necessary delay and low screening success is compounded by intermittent biomarker assay failure due to inadequate quantity or quality of tumor tissue. For patients with metastatic CRC who are increasingly being treated without palliative resection of the primary tumor, the tissue samples available may be limited to core biopsies, fine-needle aspiration, and endoscopic biopsies, any of which may be insufficient for the increasingly broad biomarker panels proposed. Biomarker optimization for small tissue samples and rapid turnaround time will be critical for meeting the needs of the refractory colorectal cancer population.

Tumor heterogeneity. Given the practical limitations of tissue availability, biomarker testing has primarily been performed using entire sections of slides from formalin-fixed paraffin embedded tissue from the time of diagnosis, which may have been collected several months to years before a patient is being evaluated for a biologic therapy. Tumor heterogeneity occurs in a variety of forms and has the potential for inducing a considerable amount of noise or bias in predictive biomarker studies. Sampling error for a given biomarker can occur when there are regional variations in the biomarker of interest between clones in the assayed site of disease (intratumoral heterogeneity). Intertumoral heterogeneity, or variations between the primary and sites of metastases, can also occur with varying frequency that is dependent on the biomarker of interest. For some “founder” mutations, such as KRAS and APC, this intratumoral heterogeneity appears to be low in the absence of selective pressure from chemotherapy, but for biomarkers based on copy number or protein expression, these variations can be substantial. Temporal heterogeneity is also present, either through acquisition or loss of biomarker expression (e.g., acquired EGFR and KRAS mutations after EGFR monoclonal antibodies8-10) or through clonal drift over time. Indeed, data obtained through interrogation of circulating-free DNA in plasma of patients progressing on EGFR monoclonal antibodies suggest that different regions of the tumor can acquire separate escape mutations, resulting in an overall increase in tumor heterogeneity. This increased spatial heterogeneity has induced a cautionary pause in efforts to rebiopsy patients with metastatic disease for biomarker assessment. At a minimum, the degree of intratumoral, intertumoral, temporal, and treatment-induced heterogeneity should be determined for each biomarker with as much clarity as possible before embarking on efforts to utilize this biomarker for patient selection.

TAXONOMY-CENTRIC BIOMARKER: FUTURE EMPHASIS

Although the target-based biomarker model will continue to predominate drug development over the next several years, we and others have instead called on the colorectal cancer field to increase development of “taxonomy-centric biomarker models.” As shown in Fig. 1, this effort relies on an initial classification based on the intrinsic biology of the tumor. This approach is independent from considerations of the specific therapies. Although breast cancer and lymphoma have been successful in classifying tumor subtypes based on
gene expression patterns, the results in colorectal cancer have been mixed, without clear subtypes emerging, with some notable recent exceptions.\textsuperscript{11,12} Instead, it is increasingly apparent that multi-"omic" approaches will be needed that can incorporate several critical features of colorectal cancer, including the diversity of mutation frequency, hypermethylation, microsatellite instability, and chromosomal instability. These molecular subtypes, which remain to be defined, would provide molecularly homogeneous subsets amenable to therapeutic interventions with biologic therapy appropriate for the critical pathway activation. There remain limits to this approach, however, not the least of which is the regulatory hurdle to using multidimensional signatures that may span platforms to define appropriate patients for therapeutic interventions. We propose that a concurrent effort be undertaken to identify surrogate biomarkers that define these taxonomy groupings. Such a surrogate biomarker could be readily applied for patient selection for a novel targeted therapy and codeveloped as an integral biomarker. Although the taxonomy approach would not address all of the biomarker hurdles identified previously, it would have the advantage of providing an enduring scientific advance even in the event of a failure of individual experimental therapeutics. As an example, the epithelial-mesenchymal transition (EMT) phenotype has been identified by several groups as a key molecular subtype in colorectal cancer. Gene and protein signature have been correlated with this phenotype, but we have shown that MET protein expression may be a reasonable surrogate biomarker for this, with the advantage of being readily implemented into prospective enrichment studies of agents that may target this subset.

This taxonomy-centric biomarker model is consistent with recent calls for a "new taxonomy" of disease, which has been advocated by a National Academies/Institute of Medicine working group.\textsuperscript{13} Several points raised in their report are applicable to this effort. First, this taxonomy-centric biomarker model would heavily rely on molecular biology to define the intrinsic biology, but also incorporate traditional pathologic and clinical characteristics. This represents a substantial need in the field of colorectal cancer, where hundreds of papers have reported on the prognostic implication of isolated genomic, proteomic, pathologic, or clinical attributes without a full understanding of how the subsets defined by these biomarkers overlap. For example, the good prognosis of lymphocytic infiltrates in the primary tumor has a strong overlap with good-prognosis microsatellite instability seen by molecular testing, but many of the early papers failed to appreciate this correlation. Many other such overlapping biomarkers likely remain to be uncovered, and would provide useful orthogonal approaches to taxonomy classification. Second, the working group encourages the use of this taxonomy as a mechanism to understand unique routes of pathogenesis and critical molecular drivers for each subtype. This would have the direct effect of providing potential therapeutic targets that may be relevant for each subtype and opportunities for more intelligently designed biomarker-driven clinical trials. Finally, the working group encourages these taxonomies to be dynamic and evolving—ready to shift the definitions as needed to incorporate new knowledge. As a corollary, datasets used to derive and refine these taxonomies should continue to be deposited in openly available databases. Although this provides challenges in the realm of clinical drug development, this approach also allows the field to move forward before a community consensus forms around the exact definitions of each of the subtypes of the new taxonomy.

In summary, biomarker development for biologic therapy in colorectal cancer is currently utilizing a target-based strategy, which has inherent limitations and inefficiencies. A transition to a taxonomy-based biomarker model would provide the classification structure and biologic insights needed to advance the ultimate goal of the right drug for the right patient.

### Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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### References

4. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer...
The start of the new millennium brought with it the promise of solving the human genome and the capacity to design new drugs and antibodies. As a result, it also brought with it the expectations that the progress in treating disease, cancer included, would be rapid and substantial. Indeed, by the year 2000 several new “biologic” or “targeted” agents promised to be effective in cancer treatment. Imatinib turned an untreatable sarcoma, gastrointestinal stromal tumor (GIST), into one that could be managed in many patients with twice daily oral medication. And, although not as dramatic in their effect, antibodies against the EGFR and VEGF pathways had cleared the regulatory hurdles and were becoming available by early 2004 for the routine treatment of metastatic colorectal cancer.

The U.S. cooperative groups were poised to take advantage of the wealth of new biologic agents and less novel but different chemotherapeutics; the challenge was how bold to be and what magnitude of improvement to expect. As two of the cooperative groups worked on proposals with different combinations and designs, the hope for efficiency ultimately led to the single joint effort that became the Intergroup advanced colorectal cancer study: CALGB/SWOG #80405.

As designed, this three-armed study built first on a chemotherapy backbone of the treating physician’s choice: FOLFOX or FOLFIRI since data then, as now, suggested that these two regimens represented the best of our combinations of the cytotoxic agents developed in the previous decades, that they were of similar efficacy, and had toxicity profiles which were of similar intensity but different character. The study then tested the value of adding bevacizumab alone, cetuximab alone, or both antibodies to the chemotherapy. A paraffin bloc was required for EGFR staining, although patients would be enrolled without the knowledge of the result. A total of 2,289 patients would be accrued to power the study to demonstrate a Hazard Ratio of 1.25 in favor of the dual biologics (27.5 vs. 22 months) with expected accrual taking 30 months.

The study closed to accrual in March 2012, 96 months after it had opened. The final accrual was as about as planned, although just 1,177 patients with KRAS wild type tumors would be analyzed in the two-arm study comparing chemotherapy with either bevacizumab or cetuximab. The hazard ratio remained the same for a 2-sided test.

Now, nearly 10 years, seven “Dear Doctor” letters, and numerous amendments later, we await the results of that study. But rather than having expectations for major clinical advances, we have turned our hopes to the correlative science component, enabled by the mandated collection of biospecimens. It is this aspect of the trial that now holds out the most hope for a paradigm change. The primary hypothesis of the study, that dual antibody therapy would represent a safe and more efficacious therapy for patients with metastatic colorectal cancer, has already all but been refuted.

Could we have known that the questions would change, the assumptions would be wrong, and that it would take us ten years to find out? Looking back, what mistakes can we now identify that we, as a cancer community, made? More importantly, what can we learn from a critical and constructive look at our mistakes, our thought processes, our efforts, and our results that might inform our current and future projects and accelerate progress in the fight to develop better treatments for patients with colorectal cancer?

5-fluorouracil (5FU) was patented in August of 1957 and had the field to itself for almost four decades. The fact that no other drug demonstrated meaningful activity in colorectal cancer during that time, no doubt, accounts for the therapeutic nihilism and the perception that colorectal cancer, like all GI malignancies, was a “chemo-refractory” disease. This misconception was reinforced by the limitations of screening and surveillance techniques with the result that many patients treated in the latter third of the twentieth century had advanced bulky disease and a marginal performance status by the time that chemotherapy was first considered or initiated. Treatment with first line therapy was regarded as being of debatable benefit; second line therapy was essentially non-existent.

This changed with the work initially reported by Shimada and colleagues, in which an investigational agent from the Yakult Honsha company, the 11th compound in an
exploratory series of water-soluble derivatives of the natural plant product camptothecin (designated “CPT-11”), showed activity in patients with 5FU-refractory colorectal cancer. Studies repeated in the United States confirmed efficacy, leading to accelerated approval by the U.S. Food and Drug Administration (FDA) in June of 1996. Confirmatory studies subsequently showed that this agent conferred a small but statistically significant survival benefit.3

The “golden age” of colorectal cancer drug development had begun. From 1996 to 2003, oxaliplatin, capecitabine, cetuximab, and bevacizumab also became available, creating the sense that the dam had been breached, and that a veritable flood of new and more effective agents would flow from the now unfettered pipelines of pharmaceutical and biotechnology companies, and that major, dramatic progress would soon follow in the treatment of colorectal cancer. A closer look at the data, however, sheds some light on why, perhaps, those expectations were greater than they should have been.

GREAT EXPECTATIONS
Every drug that has entered development since 5FU has been initially designed to replace it. In that respect, every drug, including those we use today, has been a failure, and a failure that we frankly have failed to adequately acknowledge. No drug thus far has shown greater single agent activity than 5FU, and the fallback position of drug development has essential been the “if you can’t beat ‘em, join ‘em” approach: add that failed drug to 5FU, thereby creating a combination, and show that the combination is better than single agent 5FU alone. It is worth looking at the relatively modest amounts of improvement that set us on this path of combination therapy. The addition of irinotecan to 5FU added 2.2 months of survival in the two first line randomized trials, each of which did not plan for a cross-over to sequential second-line irinotecan in the control arm. Although the results were statistically significant, there was little public debate as to whether or not they were “clinically significant” or “substantial,” and that discussion was trumped with the “proof of principle” argument: that any drug that showed activity by a new mechanism was “proving the principle” of a valid approach to the problem. With that came the tacit assumption that refinements and advances would soon follow that would bring the level of activity offered by that principle to a higher and higher level. As we have seen, however, this assumption has often not been supported by follow-up data, and, in fact, the first data have all too often been found to be the best.

THE LAST STUDY OF CYTOTOXICS
The last U.S. Cooperative Group colorectal trial of the twentieth century, and of the cytotoxic era, was the pivotal N9741 trial. Initially a four-arm study looking at three different schedules of irinotecan plus 5FU with a Mayo Clinic 5FU/leucovorin control arm, this trial underwent multiple closures, additions, subtractions, and refinements before its final iteration as a three-arm trial with weekly bolus irinotecan/fluorouracil/leucovorin (IFL) as the control arm, and infusional 5FU/leucovorin plus oxaliplatin (FOLFOX) and irinotecan/oxaliplatin (IROX) as the investigational arms. This study established that FOLFOX was the superior of these three final regimens. Thus, as we stood poised to enter the era of biologic therapy, the FOLFOX regimen was established as our preferred cytotoxic front-line treatment. To their credit, the French investigators who developed FOLFOX continued to tweak the regimen, using less oxaliplatin and less chemotherapy to achieve the same result with less toxicity, but no new cytotoxic agents have been developed in colorectal cancer.

ENTER THE BIOLOGICS
Bevacizumab, like all early “targeted” or “biologic” therapies, was envisioned to be a step beyond current cancer chemotherapy, and to replace it as a stand-alone treatment. Drugs that caused nausea, vomiting, neutropenia, diarrhea, and alopecia would go the way of bloodletting, leaches, and mercurials. However, it was apparent early on that the expected single agent activity of bevacizumab was lacking, and the development strategy reverted to combination therapy. The talking points remained, however, as a lack of cytotoxic side effects of bevacizumab in colorectal cancer (a relatively non-vascular tumor) became the mantra, ignoring that it was now being joined to the same cytotoxic regimens we used to use. Bevacizumab debuted at the 2003 ASCO Annual Meeting, when the AVF2107 study was presented by Hurwitz and colleagues. In this trial, bevacizumab when added to the IFL regimen, conferred a 4.4 month PFS advantage and a 4.7 month overall survival benefit, both highly statistically significant. At the same session in Chicago, Cunningham and colleagues presented the “BOND” trial (so-called because it was Merck KgA trial #007), confirming earlier smaller U.S. trials that showed a 23% response rate when cetuximab was added to irinotecan after irinotecan failure, and an 11% response rate when used alone after irinotecan failure. And so the

KEY POINTS

- After almost 40 years of minimal progress, the period from 1996 to 2003 saw a flurry of new drugs become available.
- Progress since 2003 has been minimal.
- Most new agents with activity in the metastatic setting (irinotecan, bevacizumab, cetuximab) do not have activity in the adjuvant setting and so have not increased the cure rate.
- Combinations of biologics have been disappointing.
- Progress to date is less than we would have expected.
- Therapy individualized according to molecular characterization of each tumor appears to be the way forward.
stage was set for the decade we are now completing, from ASCO 2003 to ASCO 2013. What have we learned in this decade, what have we accomplished, and where are we headed from here?

THE LOST DECADE?

It is hard to admit, but the progress that seemed so promising in the “golden age” discussed above has been unfulfilled since 2003. (Technically, both cetuximab and bevacizumab received regulatory approval in early 2004, but the data were first presented in 2003.) First, no new mechanisms of action have been brought to bear on colorectal cancer since then; panitumumab and ziv-afibercept appear to be variations on the existing theme, and it is debatable whether they offer any meaningful therapeutic advantage over existing agents. Regorafenib, also most likely working predominantly through VEGF but perhaps through other mechanisms as well, offers a modest survival benefit but is hardly at the level of advancement we would have predicted in 2003 that we would reach by now. In fact, what many of our trials have shown us is that many of our assumptions were wrong.

First, we assumed that adding bevacizumab to any chemotherapy backbone would represent an advance. By the time that the IFL/bev data became available, the N9741 trial had shown us that FOLFOX was a superior regimen to IFL. Having no desire to resurrect IFL, which, as a result of the use of bolus 5FU and weekly irinotecan has greater toxicity than FOLFOX, regulatory authorities wisely approved bevacizumab for use in conjunction with a “5FU-containing regimen.” This, of course, translated into a de facto approval of FOLFOX plus bevacizumab which, without first line efficacy data, became the most widely used front line regimen in the United States as well as the basis of two large adjuvant trials (both of which failed).10,11

At the ASCO 2003 Annual Meeting, discussions were initiated that led to formally studying this regimen. The then recently activated N016966 trial, an industry-sponsored trial comparing FOLFOX to CapeOx, was redesigned as a 2x2 trial of CapeOx vs. FOLFOX with the appending of a second randomization between bevacizumab and placebo. The results were disappointing. First, CapeOx was found to be no worse, but also no better than, FOLFOX, in terms of both efficacy and safety.12,13 In terms of bevacizumab, this would technically be considered a positive trial, in that the progression-free survival was improved with a p value less than 0.05. However, the actual improvement of 1.4 months (8 months vs. 9.4 months) in progression free survival paled in comparison to the 4.4 month improvement seen in the IFL trial, whereas the overall survival improvement (also 1.4 months) fell just short of statistical significance at p = 0.078, but far short of the 4.7 month survival benefit seen with IFL.14 Because investigators often incorrectly discontinued patients from bevacizumab when they stopped oxaliplatin for neurotoxicity, the full effect of bevacizumab may have been blunted, but even modeling for this does not project an outcome that approached that seen with IFL. Thus, the hope that adding bevacizumab to FOLFOX would bring us to the much-anticipated benchmark of a median PFS of over one year was not achieved, and that lofty goal still remains elusive.

The next assumption was that moving an agent active in the late-line setting into first line would greatly increase the activity of that agent. Cetuximab showed activity after failure of other available chemotherapies, and it was hoped that combining it with front line therapy would lead to greater efficacy. The first indication that this was not likely to be the case was the truncated C80203 trial, which was interrupted by the availability of bevacizumab, and which failed to show a dramatic benefit in the cetuximab-containing arm.15 The first full trial to evaluate the addition of cetuximab to front line FOLFIRI, the 1,200 + patient CRYSTAL trial, showed a statistically significant median PFS advantage, albeit of only 0.8 months, or about 24 days.16

Somewhere in this process but years later than we should have, we focused our attention on KRAS. Khambata-Ford and colleagues published evidence that exon-2 mutations in the KRAS gene conferred refractoriness to cetuximab,16 and Amado and colleagues showed the same in an even more striking manner in a large prospectively accrued trial of patients treated with panitumumab.17 In the hype about targeted therapy, we had forgotten to ask whether or not the tumor had the target. A reanalysis of the CRYSTAL data showed that patients with KRAS wild-type tumors achieved a 3 month survival benefit with front line cetuximab, whereas those with KRAS-mutated tumors not only had no benefit but trended toward an inferior outcome.18 The first vestiges of “personalized medicine” had entered the world of colorectal cancer. Although this was a good finding, it was not the advance we had hoped for several reasons. First, evidence did not suggest that early or first line use of cetuximab was better than last line use; a similar, perhaps even better survival benefit was shown in the KRAS wild type subgroup that was treated with cetuximab in the salvage setting in the NCIC C017 trial.19 More importantly, KRAS was an exclusionary marker, a marker that told us who not to treat. What we all really want from personalized medicine, an inclusionary marker that tells us who to treat with an agent that otherwise would not be anticipated to work in this disease, is still lacking to this day.

The next assumption was that an empiric combination of biologic agents would be beneficial. In the so-called BOND-2 trial, a small NCI-sponsored pilot trial to assess the safety of dual antibody therapy, cetuximab plus bevacizumab, was given alone or in conjunction with irinotecan in patients with irinotecan-refractory colorectal cancer who were naïve to both antibodies. The toxicities were as would have been expected from the individual agents, and the efficacy was encouraging compared with historic controls.20 Excitement was building for the assumed improvements that bringing this dual antibody combination into front line therapy might bring, and from this, the intergroup C80405 trial (described in the introduction) was born. It is an interesting comment on the progression of scientific thinking that nowhere in the
original 120-page correlative science protocol for C80405 is KRA5 mentioned.

Two other trials occurred in parallel, however, that addressed the hypothesis that dual anti-EGFR and VEGF inhibition would result in a superior outcome. One was the so-called CAIRO-2 study. The CAIRO-2 trial essentially ignored the findings of the CAIRO-1 trial (as have most of us, because it is an inconvenient finding) and used capcitabine/oxaliplatin/bevacizumab as a control arm and added cetuximab to this regimen in the experimental arm. Not only was there no benefit to this dual antibody maneuver, but the cetuximab-containing arm had inferior progression-free survival, no benefit in overall survival, and increased toxicity. Those patients with KRA5-mutated tumors who received cetuximab did statistically significantly worse than those who did not, whereas the KRA5 wild type tumors simply showed no benefit.

A similar finding was reported in the PACCE trial, which was doing a very similar study using pantitumumab. Again, the addition of the anti-EGFR inhibitor, in this case panitumumab, to bevacizumab plus chemotherapy (in this case, FOLFOX) not only failed to result in improved outcome, but actually led to inferior progression-free and overall survival.

The dual antibody arm of the C80405 protocol has been closed by the data safety monitoring board, and with CAIRO-2 and PACCE trials being negative, we know that dual antibody therapy with first line chemotherapy is a failed concept. Although C80405 will illuminate the relative benefits of anti-EGFR compared with anti-VEGF strategies in the front line setting, the greatest potential for pivotal information lies in the enormous tissue and serum bank that has been established with this trial. We have reason for optimism that this large data set will permit useful scientific inquiry that will inform our understanding of the biology of the genotypic subsets that make up the phenotype that is colorectal cancer.

In summary, following a flurry of positive studies leading to small but hopeful steps forward, the past 10 years have been a sobering period of consolidation of our knowledge and a humbling reminder that our victories have been fragile and modest, at best, and that we do not know what we think we know. The CAIRO-1 and FOCUS studies call into question the benefits of combination therapy. The N016966 trial showed us that the contribution of bevacizumab may be smaller than we cared to think, and that the interaction of this biologic with oxaliplatin-based therapy may offer less benefit than was seen with irinotecan-based treatments. The CAIRO-2 and PACCE trials show us that front line dual anti-EGFR, anti-VEGF antibodies are not beneficial, and in fact, may be harmful. In addition, the COIN and NORDIC 7 trials fail to show benefit of the addition of cetuximab to front line oxaliplatin-based chemotherapy.

Meanwhile in the adjuvant setting, we have discovered that neither irinotecan, bevacizumab, nor cetuximab contribute to the cure rate in stage III colon cancer, whereas adding oxaliplatin to concurrent radiation fails to increase the complete response rate or the cure rate in rectal cancer. Thus, how these agents, active in the macro-metastatic setting, kill tumors in the micro metastatic (adjuvant setting) is different in ways we do not currently understand.

The way forward is undoubtedly through better scientific understanding of the biology of the disease, and through individualization of therapy based on that biology. A trial looking for a treatment for all, or even most, of the patients with colorectal cancer is unlikely to show us large advances. Only though targeting specific genotypes with specific therapies might we hope to accomplish that progress. As we start the next decade in colorectal cancer treatment investigations, we must learn from our past mistakes, or we are destined to repeat them.

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References


The Economics of New Drugs: Can We Afford to Make Progress in a Common Disease?

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OVERVIEW

The concept of personalized medicine is beginning to come to fruition, but the cost of drug development is untenable today. To identify new initiatives that would support a more sustainable business model, the economics of drug development are analyzed, including the cost of drug development, cost of capital, target market size, returns to innovators at the product and firm levels, and, finally, product pricing. We argue that a quick fix is not available. Instead, a rethinking of the entire pharmaceutical development process is needed from the way that clinical trials are conducted, to the role of biomarkers in segmenting markets, to the use of grant support, and conditional approval to decrease the cost of capital. In aggregate, the opportunities abound.

The concept of personalized medicine is beginning to come to fruition with new therapies tailored to specific populations of oncology patients. Unfortunately, these new products are being brought to market at prices of tens to hundreds of thousands of dollars per patient. Rather than just a pricing anomaly, we believe these prices reflect an unsustainable business model for this technology.1 In this article, we argue that it is essential that we re-envision the entire business model for personalized health care if we are to have a pathway forward that will sustain innovation.

The current business model supporting pharmaceutical development is based on traditional drug development in which small molecules are broadly marketed. This general framework was extended to the development of biologic products as they were introduced to the market. However, we believe it cannot be extended to personalized medicine without significant reconsideration of some of the core concepts and practices in oncology because of the increasingly prohibitive costs and the dynamics of the personalized-medicine market. We will examine the economics of each step along the development pathway and suggest policies to control costs across the product lifecycle.

This analysis encompasses all aspects of clinical development and product marketing. Specifically, we will examine the cost of drug development in personalized medicine, cost of capital for product development, target market size, marketing costs, returns to innovators at a product level, returns to innovators at a firm level, and, finally, product pricing. This examination will identify new initiatives that would support a more sustainable business model to encourage continued innovation in oncology.

COSTS OF CLINICAL DEVELOPMENT

The out-of-pocket costs of drug development are significant. In the seminal paper on the topic by DiMasi et al. from 2003, direct costs were estimated to account for $130 million of the $802 million (2000 U.S. dollars) that it would cost to develop and approve a new therapy.2 When this analysis was repeated for biopharmaceuticals in 2007, the costs estimate rose to $166 million and $1.2 billion (2005 U.S. dollars), respectively.3 This price tag is likely far higher today, driven by the complexities of developing and implementing clinical trials, including the central costs for the sponsor, the costs of data collection and analysis, the payments required to site investigators, the site expenses (e.g., laboratory, genomic and imaging studies), and the cost of trial committees such as those for adjudication and data safety monitoring.

Clinical trials are a resource-intense endeavor.4 There are many steps devoted to the identification of trial participants, to the screening of patients to identify those eligible to participate, to the fixed overhead required to recreate each trial from the ground up, to the development and monitoring of data collection, and to the hidden non-value–added costs within institutions such as overhead. At the Duke Clinical Research Institute, we are working to devise a new approach to the cost-prohibitive aspects of clinical research, leveraging mobile health and informatics technologies in the process. The goal is to streamline drug development, and reimagine the roles and responsibilities of both the patients and clinicians.

Patients with rare diseases such as chordoma are often engaged by patient advocacy organizations and enrolled in disease-specific registries of varying sophistication.
The registries can be used to identify and approach potential participants for clinical trials, but this function is vastly underutilized. In conjunction with advocacy groups, a registry framework is being built wherein trial start-up, recruitment, monitoring, genetic analyses, support of randomization in routine practice, and other needs, could be automated and monitored in aggregate. Novel technologies should play a larger role in the conduct of clinical research, including the aggregation of data about the patient experience across demographics and populations, the collection of symptoms and quality-of-life data, the documentation of adverse events, and the capture of robust treatment information in real-time directly from the patient and clinicians. In this process, the traditional medical establishment can be circumvented, going directly to patients and streamlining the process.

Critical pieces of the clinical trial process can be augmented or replaced. Start-up times can be drastically reduced because a national cohort of patients interested in participating has been identified before approval of the study. Recruitment goals will be far easier to attain, as enrollment will no longer be dependent on site-based patient identification during clinical visits. Aspects of follow-up can be automated, not requiring the patient to be seen. The data provided can be supplemented with informatics-enabled conduits from electronic health records to automatically populate aspects of the registry systems. Biobanks can be clinically annotated using the registry system, providing ready access to tissue. In the end, our hope is that the direct cost of drug development could be drastically reduced.

**COST OF CAPITAL**

The costs of drug development include the cost of financing the out-of-pocket cash outlays for the development program (clinical trials) and the time costs of development programs that can span a decade or more. These costs are referred to as the cost of capital. The longer the delay between cash being expended and revenues being generated, the more the expended cash would be worth in today’s dollars and, by extension, the higher the cost of capital. In the original Grabowski model, the cost of capital increased the cost of preclinical and clinical development from $169 million to $375 million.\(^3\)

These are real costs to firms, both in supporting the capital allocation as well as in “opportunity costs” that come from not pursuing other investment opportunities. The cost of drug development can be reduced by envisioning new ways to decrease the time required for clinical trials to be completed and to decrease the cash outlays required of sponsors.

In a recently published illustration of this concept, Valverde et al.\(^5\) outlined a new approach to drug development for rare diseases that they called the “Grant-and-Access” program. Despite the Orphan Drug Act of 1983, many rare diseases have few treatment options and those treatments that have been developed are exceedingly expensive. The authors proposed an approach in which federal grants are used to subsidize the direct cost of clinical drug development. In return for this financial assistance, sponsors for the agent being developed would agree to a cap on the price that is ultimately charged on the basis of a rate of return model in which a presupposed return on their investment would be guaranteed if the agent is approved. The concept of accelerating development by reducing the cost of capital has already expanded well beyond this initial example. Organizations like the Gates Foundation provide grants for promising research ventures to decrease the cost of development and ensure that innovation moves forward in an accessible fashion. One could foresee a path in which the patient advocacy groups who are reimagining the research enterprise would also help fund promising product development to decrease the capital costs for sponsors.

Another approach to addressing the cost of capital issue would be to envision a system based on conditional approval as a core construct. Accelerated approval has been common in oncology in which agents are preliminary approved for marketing on the basis of surrogate markers such as progression-free survival for particularly serious diseases with few alternative treatments. Final approval is contingent on confirmation of the efficacy of the drug on further study. Conditional approval shares the same premise; however, it differs from accelerated approval in that it allows for a development strategy consisting of smaller phase III trial programs with significant postmarket requirements on safety and efficacy. An agent is withdrawn from the market if safety or efficacy end points are not met at any point in the development pathway. This approach directly addresses concerns about the cost of capital in two ways: (1) it decreases the direct costs of clinical trials, and thus the capital required for the initial development by decreasing the size of preapproval trials; and (2) it decreases the time from trial initiation to approval and allows the generation of revenues earlier in the process, decreasing the time costs of drug development.
TARGET MARKET SIZE
As personalized medicine gains traction and biomarkers are developed alongside novel agents, the market size for targeted therapies may be smaller because of market segmentation. Market segmentation occurs when, instead of broadly marketing an agent, its use is limited only to those patients with a given biomarker that predicts a high likelihood of response and/or a low likelihood of adverse events. As examples, testing for KRAS mutations before the use of cetuximab (Erbitux, Bristol Myers Squibb, Princeton, New Jersey, USA) in patients with colorectal cancer or HER2/neu testing before the use of trastuzumab (Herceptin, Genentech/Roche; San Francisco, CA, USA) in patients with breast cancer, targets the agents only to those patients most likely to benefit. To date, sponsors have compensated for this decrease in market size through higher pricing.

Biomarkers may decrease the potential market size for an agent, however patients who are positive for the biomarker are more likely to receive the agent and to respond to it. The economic balance of these competing factors is largely dependent on the nature of the available treatments for a given cancer type. If there are numerous previously approved options, a companion diagnostic may carve out a niche and increase revenues. In those with few available options, it might limit the market beyond what would otherwise be achieved.

Regardless of the situation, there are ways in which biomarkers could be beneficial. Their use will further decrease the out-of-pocket costs by decreasing trial size and duration, thereby decreasing the cost of development. The identification of biomarkers in preclinical and early-phase trials enables the efficacy of an agent to become more pronounced and for a targeted patient population to be enrolled. A prior review by Ginsburg et al. further highlighted ways in which genomic signatures may increase productivity of drug development such as by guiding dose adjustments. A separate analysis estimated that the integration of genomics into preclinical testing may result in a decrease by “20% in the number of new compounds in phase II trials, by 10% in the number of patients in phase III trials, and by 20% in the length of phase III trials.” The overall result could be to decrease the number of failures and further streamline clinical development.

A smaller market size could also provide a benefit in marketing the agent, thereby lowering costs while maintaining higher market penetration. Marketing expenses, especially to support pharmaceutical representatives, account for a significant percentage of overall pharmaceutical industry costs. As a result of rising concerns about expenditures and legislative changes regarding the role of pharmaceutical representatives, the ability to market novel agents is changing quickly.

As market segmentation increases, the target patient population shrinks and new approaches to the marketing of agents, relying on social media and patient advocacy groups, will be powerful. In oncology, imagine if instead of trying to use current advertising and representative-based means to reach the entire colorectal cancer population, one can target, through social media and advocates, those with particular demographics and clinical characteristics known to predict the presence of a biomarker of interest, making the marketing campaign more efficient and far less expensive.

RETURNS TO INNOVATORS AT A FIRM LEVEL
In the previously referenced paper by DiMasi et al., a large portion of the $1.2 billion price tag for each approved molecule is related to the rate of failure of agents. Only 30% of all biotechnology products that are brought into development, and 19% of monoclonal antibodies, are ultimately approved by the United States Food and Drug Administration. The costs of agents that fail are ultimately borne by sponsors. Increasing the likelihood of success would thereby decrease the overall cost of drug development.

To address the rate of failure and the productivity of drug development, the overall approach of the pharmaceutical industry must be reconsidered. At present, profits are driven by a few blockbuster agents, which generate outsized returns for sponsors. In the current model, the required return on investment is dependent on only a few agents. If the development process and cost of capital are reformed as outlined, the same research and development budget could support more clinical development efforts and ultimately lead to more products that are approved and marketed. This increase in productivity could reduce the pricing pressure for each new product since overall returns at the firm level would be based on sales of more products in their portfolio. As Bernard Munos explained to Forbes in 2011, “instead of chasing improvements to blockbuster drugs that help lots of people a little bit we should focus on true breakthroughs that help patients a lot…companies should close their labs and outsource the work to tiny, nimble startups that can explore bigger crazier ideas.” These comments were based on his findings that the share of new drugs (new molecular entities) that came from large pharmaceutical companies dropped from 75% in the 1980s to 35% by 2004 while those of small biotechnology and pharmaceutical companies increased from 23% to 70%.

Having a robust portfolio of products will distribute the costs of development, making all more affordable. As described previously, a first step would be to use genomic signatures to target drugs to high-risk populations in which it might be easier to assess efficacy and decrease the number of compounds that fail in phase II and III testing.

RETURNS TO INNOVATORS AT A PRODUCT LEVEL AND PRODUCT PRICING
In the end, this all leads back to the topic of pharmaceutical pricing for new products, focusing particularly on personalized medicine products. The financial considerations impacting the development of pricing strategies for pharmaceutical companies should not be oversimplified. There are many costs to drug development that complicate pricing decisions and each must be considered and addressed. We propose...
that there are emerging paradigms that could transform the pharmaceutical development framework that need to be further explored.

Consideration must also be given to broader policy issues in the United States regarding market efficiency for personalized medicine products. Even if significant savings are achieved in areas such as out-of-pocket costs and the cost of capital, they would not necessarily be passed on to the consumer through pricing changes. One recent paper suggests that the lack of price elasticity in the U.S. market is a unique feature of the insurance market in the United States. If this is the case, we might need to develop better frameworks to allow insurance companies to have more leverage in reimbursement negotiations with sponsors.

CONCLUSION
There are numerous approaches that could fundamentally alter the economics of drug development, thereby allowing for innovation and progress in common diseases. Many of these are ongoing today. Patient advocacy groups and advances in technology are paving the way to address out-of-pocket costs for clinical trials. Grant support and accelerated/conditional approval pathways have the potential to decrease the cost of capital. Biomarkers will segment the market, allowing new approaches to marketing, and will increase the productivity of drug development, decreasing the number of failures among agents in clinical trials. Pharmaceutical companies should reimagine their drug-development pipeline to be more nimble. New policy approaches could replace monopolistic pricing with measured approaches tied to returns on investments. In aggregate, the opportunities abound.

Although many of the concepts we have developed are potentially transformative, they will not address issues with the pricing strategy of the agents currently on the market. Unfortunately, there are few good mechanisms that are immediately available. We seem to have all but abandoned an evaluation strategy that relies on cost-effectiveness. Clinicians and patients have routinely equated any discussions of cost and value to “rationing” and ended discussions abruptly. The widespread use of tiered formularies and cost-sharing efforts focused on the patient are equally problematic. These approaches rely on the theory of moral hazard. Consumers are thought to use greater quantities of a product if they do not directly endure any risk. Through the use of copays and other mechanisms, patients could be forced to have “skin in the game” and thereby encouraged to choose only those treatments that are truly needed. In oncology, we posit that the theory of moral hazard is less relevant. Prospect theory is a behavioral economic theory arguing that people make decisions related to the magnitude of potential losses and gains. Although cost sharing may allow the avoidance of marginal services among the healthy (addressing moral hazard), the potential substantial risk of death related to a cancer diagnosis makes cost sharing less effective and limits the potential role of market forces (prospect theory). If you can imagine someone in good health making a decision about whether to fill a $5 prescription for pain, cost sharing may provide an appropriate influence. On the other hand, a patient with cancer who is told that he or she is likely to die within a few months is willing to risk nearly anything to get their treatment. Unfortunately, the result of prospect is observed in data showing the high rates of bankruptcy in the population of patients with cancer in the United States. For these and other reasons, a quick fix is not available. Instead, a rethinking of the entire pharmaceutical development process is critical.

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References

5. Valverde AM, Reed SD, Schulman KA. Proposed ‘grant-and-access’ program with price caps could stimulate development of drugs for very rare diseases. Health Aff (Millwood). 2012;31:2528-2535.
GASTROINTESTINAL (COLORECTAL) CANCER

Raising the Bar: Can We Diminish the Impact of Race, Age, and Expertise as Factors in Patient Outcome?

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Approach to the Older Patient with Stage II/III Colorectal Cancer: Who Should Get Curative-Intent Therapy?

Erika Ramsdale, MD, Hanna Sanoff, MD, MPH, and Hyman Muss, MD

OVERVIEW
The majority of new colorectal cancer diagnoses occur in adults 65 and older, a rapidly growing segment of the U.S. population. Older adults are a markedly heterogeneous group, and although recent clinical trials in locally advanced colorectal cancer have incorporated limited numbers of older patients, the data cannot be generalized to most older patients. In particular, patients who are not “fit”—those with poor functional reserve, major comorbidities, or who otherwise meet criteria for frailty or “prefrailty”—are poorly represented in published trials. Population-based data demonstrate that older adults are much less likely to be treated in the adjuvant or neoadjuvant settings for stage II/III colorectal cancer, but it is unclear what the basis should be for withholding potentially curative therapy. Age and Eastern Cooperative Oncology Group (ECOG) performance status (PS) are frequently used to determine eligibility for treatment, but data increasingly suggest these are inadequate; the emerging definition of a spectrum of “fit” to “frail” older patients may provide additional guidance. Available data suggest that fit older patients may benefit as much from curative-intent therapy as younger patients. For frail or vulnerable (prefrail) patients, on the other hand, the benefit must be carefully weighed against the risk of toxicity and competing risks from their comorbidities. Life expectancy and patient preferences should always be elucidated. Geriatrician comanagement may be helpful in determining priorities, providing a comprehensive assessment, and modifying competing risk factors. Even many vulnerable or frail patients can successfully complete (and derive benefit from) carefully considered treatment regimens.

Colorectal cancer is the second leading cause of cancer deaths in the United States. In 2012, there were approximately 143,000 new cases of colorectal cancer and nearly 52,000 deaths.1 The majority of these cases occurred in older adults: the average age at diagnosis is 69, with 61% of cases diagnosed in those 65 and older, 37% in people 75 and older, and 12% in people 85 and older.1 Furthermore, 70% of colorectal cancer deaths occur in this older age group. These numbers are projected to increase, with an even greater skew toward older age at diagnosis. By 2030, 20% of the U.S. population will be 65 and older, and more than 71% of incident colorectal cases are projected to occur in this age group.2 It is critical that we determine a method for assessing and treating these older patients, particularly those for whom data are very limited (i.e., the very old, the frail, and those with comorbidities).

CLINICAL TRIALS IN THE ELDERLY
Clinical trials data for older adults with cancer are lacking, compared with that available for younger cohorts. It is well-recognized that older adults are underrepresented in investigational trials, as only about 30% of cancer clinical trial participants are 65 and older.3 In colorectal cancer, approximately 40% of phase II and phase III trial participants are older than 65; using an age cutoff of 70 years, the percentage falls to 15%.3-5 One important barrier to recruitment of older adults is the strict exclusion criteria adopted by most clinical trials, which disqualify patients with significant comorbidities (including prior treatment of malignancies), organ dysfunction, or poor PS, criteria that disproportionately exclude older adults. In fact, in one predictive model, relaxation of the exclusion criteria significantly increased the predicted proportion of older trial participants, almost fully eliminating the observed underrepresentation.3 However, other barriers have been documented and should be considered, including physician hesitancy to recommend clinical trials to older adults, lower health literacy in older populations (and therefore more time required to educate and enroll them), and other social and logistical factors, such as decreased social support and concerns about finances and transportation.6,7

Because of these and other barriers, those older adults who do qualify and get enrolled in clinical trials generally represent only the healthiest and most fit subset of their age cohort. Published clinical trials not only fail to note the heterogeneity of the older population, but they also fail to
capture the details that are most relevant to older patients, such as low grades of toxicity that may have dramatic effects on the function of older patients. Age, performance status (generally the ECOG PS), and a limited comorbidity assessment are generally included in the demographic data, but physicians interpreting the data may be unsure how it maps onto their complex older patients. There is increasing agreement that age alone is a poor index of overall health and functioning, but other factors that are likely to be more prognostic and predictive are only rarely assessed and reported in trials. ECOG PS is a subjective and insufficient measure of functional status in the elderly, and more descriptive data are needed.8

PHYSIOLOGIC RESERVE: FIT VERSUS FRAIL

One concept that seems apt to better stratify older patients than age is the concept of physiologic reserve, or the ability to compensate in response to stressors. Older patients are dispersed on a wide spectrum, with those who are independent and at low risk for functional decline (i.e., “fit”) on one end, those at high risk for functional decline and death (i.e., “frail”) on the other, and those with varying levels of vulnerability along the spectrum. Assessing fitness in older patients with cancer, in addition to providing a more thorough description of this heterogeneous cohort, may help target potential interventions (e.g., development of treatments specifically for frail individuals) and aid in the development of clinical decision-making tools.9

Given the complex interaction of multiple factors that constitute reserve, the definition and measurement of frailty are still evolving. One tool commonly applied to older patients with cancer (the Balducci frailty criteria) identifies a frail patient as meeting one or more of the following criteria: (1) older than 85, (2) dependence in one or more activities of daily living (ADL), (3) presence of three or more comorbidities, or (4) the presence of one or more geriatric syndromes (e.g., dementia, depression, osteoporosis, falls, incontinence, failure to thrive).10 Another tool validated in older patients with cancer is the Vulnerable Elders Survey-13, a 13-item self-administered questionnaire incorporating overall health status and assessment of the level of difficulty achieving common tasks (e.g., writing, walking a quarter mile, bathing, managing money).11 In community-dwelling older adults, a proposed “frailty phenotype” presents with at least three of the following criteria: unintentional weight loss (>10 pounds in the past year), self-reported exhaustion, weakness (measured by grip strength), slow walking speed, and low physical activity (Fig. 1).12

All three of these assessment tools derive from a more general tool known as the Comprehensive Geriatric Assessment (CGA), a systematic multidisciplinary evaluation of an older adult across multiple domains, including physical functioning, comorbid conditions, cognition, psychological state, social support, and nutritional status.10 This is a powerful tool for describing and stratifying older adults beyond age and ECOG PS, and can be harnessed to help answer several critical questions in older patients with cancer. In addition to classifying patients as fit or frail, it has specifically been used to predict survival outcomes, guide dosing of chemotherapy agents, and predict the risk of chemotherapy toxicity.13-16 The use of a full CGA in routine clinical practice is currently limited by several factors: the time-intensive nature of the assessment, the multiplicity of tools available for each domain of the CGA, and the need for multidisciplinary resources and expertise in interpreting the results. Work is ongoing to produce brief but standardized versions of the CGA for use as clinical decision tools.

### KEY POINTS

- The majority of colorectal cancer occurs in older adults (65 or older).
- Clinical trials have generally only included the most “fit” older adults, yielding data that can not be generalized to a heterogeneous older cohort.
- Physiologic reserve, or the ability of the body to compensate in response to stressors, is a useful concept in older adults; criteria have emerged to characterize whether an older patient is “fit,” “frail,” or somewhere in between.
- Fit older patients may benefit as much as younger patients from curative-intent therapy for locally advanced colorectal cancer.
- For frail or vulnerable (“prefrail”) patients, treatment decisions are complex and individualized, but some general recommendations can be derived from the available data and expert consensus.
DETERMINING APPROPRIATE THERAPY IN OLDER PATIENTS WITH COLORECTAL CANCER

Combining the available knowledge from clinical trials with measures that detect vulnerability (“prefrailty”) or overt frailty in older patients with colorectal cancer may provide better guidance for treatment decisions than using age alone. We review possible implications in the treatment of stage II/III colon cancer in the adjuvant setting, and stage II/III rectal cancer in the neoadjuvant and adjuvant settings.

ADJUVANT THERAPY FOR COLON CANCER

Multiple large clinical trials demonstrate that adjuvant fluoropyrimidine monotherapy (i.e., 5-FU/LV or capecitabine) improves survival in stage II and III, although the absolute benefit in stage II is quite small. A pooled analysis of seven of these adjuvant 5-FU trials (3,351 patients) demonstrated that adults 70 and older (506 patients) derived as much benefit as younger patients for the endpoints of overall survival and time to recurrence, with no excess toxicity. A similar survival benefit from adjuvant 5-FU was confirmed in large population-based cohorts of older patients in the SEER-Medicare program.

The addition of oxaliplatin to adjuvant 5-FU (FOLFOX) offers improved disease-free and overall survival for patients with stage III, and possibly high-risk stage II, colon cancer. In contrast, a subgroup analysis of the XELOXA trial found no suggestion of a survival benefit in patients 70 and older for the addition of oxaliplatin (mortality hazard ratio [HR] for MOSAIC 1.10, 95% CI 0.73–1.65; for C-07 1.32, 95% CI 1.03–1.70). Disease-free survival was also no better in older patients treated with oxaliplatin/5-FU than in older patients treated with 5-FU. In contrast, a subgroup analysis of the XELOXA trial found no interaction between age and disease-free survival in a regimen adding oxaliplatin to a fluoropyrimidine, though the point estimate in the older subgroup was closer to the null. A large population-based analysis showed a small improvement in survival from adjuvant oxaliplatin in patients older than 75, but that benefit was marginal.

Therefore, although the exact role of oxaliplatin in older patients is evolving, there are unequivocal data showing that adjuvant 5-FU improves survival in older patients and is quite well-tolerated. However, despite these data, increasing age is significantly associated with a lower likelihood of receiving any adjuvant chemotherapy. Although 78% of patients younger than age 55 receive adjuvant therapy, only 65% of those 65 to 74, 47% of those 75 to 79, and 24% of those older than 80 are treated. Although these may simply represent the most fit among their cohorts, it is unclear how treatment decisions are being made in these patients. Given the lack of interaction between age and benefit of 5-FU in the trials described above, it is clear that factors other than age should determine who should be treated with adjuvant therapy.

A general approach to therapy decisions in older patients with colon cancer for whom adjuvant therapy is indicated, should begin with an assessment of the patient’s life expectancy; tools are available to assist with this. A healthy, fit 75-year-old man, for example, has a life expectancy of more than 14 years, but a frail 75-year-old man has a life expectancy of only 4.9 years. Most colon cancers will recur within three years, and nearly all patients with recurrences will die within 5 years; in patients with significant competing mortality risks, however, even a 15% improvement in survival may not warrant a six-month course of adjuvant therapy.

In particular, although mortality risk from the chemotherapy itself is generally quite low, it is associated with adverse effects that may potentiate or be potentiated by comorbidities or other vulnerabilities of the older patient, leading to morbidity or worsened quality of life. For example, peripheral neuropathy is the most common adverse effect from oxaliplatin, which may significantly worsen pre-existing sensory symptoms from diabetes or lumbar stenosis and lead to increased falls and disability. In these patients, the small incremental efficacy of oxaliplatin is not worth the risk of debilitating neuropathy.

Attenuated regimens may also be reasonable for older patients who are prefrail or frail. Eliminating the bolus of 5-FU from infusioned regimens may significantly mitigate hematologic toxicity. Moreover, some data indicate that three months of adjuvant therapy may be noninferior to six months. This is currently being further tested in several large phase III trials, but in the meantime it may be reasonable to truncate therapy in older patients who develop significant adverse events during treatment. Oxaliplatin should not be given to frail patients, nor should it be given to patients with preexisting neuropathy. It should be considered on a case-by-case basis for fit patients, as data for efficacy in older patients are not compelling, and oxaliplatin adds significant potential adverse effects even for the healthiest patients. If oxaliplatin is added to a fluoropyrimidine for fit patients, it should be discontinued if significant toxicity emerges. Figure 2 summarizes a general algorithm for older patients, incorporating these recommendations.

NEOADJUVANT AND ADJUVANT THERAPY FOR RECTAL CANCER

Compared with cancers arising in the colon, cancers arising in the rectum have a higher rate of local recurrence. In addition to adjuvant chemotherapy, therefore, perioperative radiation therapy with 5-FU or capecitabine chemosensitization has been employed to reduce this risk. Neoadjuvant chemoradiotherapy is the standard of care for locally advanced (T3N0 or TanyN1 and higher) rectal cancer based on the German randomized trial demonstrating that preoperative chemoradiotherapy, incorporating infusional 5-FU and 50.4 Gy radiation therapy in 28 fractions, was superior to...
postoperative chemoradiotherapy with greater compliance, less toxicity, and lower local recurrence; however, a survival benefit was not confirmed.\textsuperscript{34} Neoadjuvant chemoradiotherapy is followed by total mesorectal excision and subsequent adjuvant chemotherapy.

Very little data are available to guide therapy in older adults; although the German trial included older patients, subset analyses are not yet available. A population-based study of 1,807 adults 65 and older with stage II or III rectal cancer from the SEER database reported that only 37% received chemoradiotherapy and that increasing age was associated with decreasing odds of treatment.\textsuperscript{35} In a small (36 patients) prospective cohort of older adults (70 and older, characterized as either “fit” or “vulnerable” based on comorbidities) with locally advanced rectal cancer who were receiving neoadjuvant chemoradiotherapy, all patients were able to complete full-dose radiation therapy but only 64% were able to complete all chemotherapy. Grade 3 to 4 gastrointestinal was less than 10% in both groups but chemotherapy regimens were not consistent.\textsuperscript{36}

Another option for neoadjuvant treatment is short-course radiotherapy, given as 5 Gy over five days without fluoropyrimidine immediately before surgery, as investigated in the Dutch Total Mesorectal Excision (TME) and Swedish Rectal Cancer trials.\textsuperscript{37,38} In a subset analysis of the Dutch TME trial, patients 75 and older had improved response to preoperative radiotherapy compared with younger patients, as well as improved cancer-specific survival which was not evident in the younger cohort.\textsuperscript{39} However, complications were increased in older patients (51% vs. 42%, \(p = 0.008\)) and were more likely to be fatal; 6-month mortality was increased because of both general (odds ratio [OR] 3.74, \(p = 0.002\)) and surgical complications (OR 4.93, \(p < 0.001\)) compared with younger patients. Increased mortality from this regimen has been linked to large treatment volumes and is likely mitigated by irradiating limited fields without loss of efficacy.\textsuperscript{37}

Although there is expert consensus that older fit patients should be considered for similar neoadjuvant therapy as younger patients, treatment for patients with vulnerability or frailty should be carefully considered based on life expectancy, patient preferences, and logistical issues (for example, willingness/ability to receive daily radiation and to travel to a high-volume cancer center).\textsuperscript{40} In addition, the local recurrence risk following modern TME is only 11%.\textsuperscript{38} Modern staging techniques can further stratify this risk, identifying a subgroup of patients with an exceptionally low risk of local recurrence.
recurrence. In those with a lower risk of local recurrence, such as high T3N0 cancers without threatened circumferential margin based on the distance of the tumor from the mesorectal fascia on MRI, careful consideration should be given to whether radiotherapy is necessary.\textsuperscript{41,42} However, given the catastrophic effect of local recurrence, neoadjuvant radiotherapy should be considered for all older patients with intermediate risk cancers. Adjuvant 5-FU decreases the risk of both local and systemic rectal cancer recurrence.\textsuperscript{33} The role of adjuvant oxaliplatin is currently being tested in large randomized trials, but given the marginal benefit in older adults with stage III colon cancer, adjuvant 5-FU or capcitabine may be the preferred choice given the substantial added toxicity of a trimodality rectal cancer regimen.

CONCLUSION

The majority of stage II and III colorectal cancers are diagnosed in older adults, but data to guide treatment decisions in this group are still limited. Choosing not to give neoadjuvant or adjuvant therapy to these patients may preclude a chance for cure. Population-based analyses indicate that older adults are far less likely to be given adjuvant therapy compared to younger cohorts. On the other hand, older adults are a heterogeneous population with widely variable levels of physiologic reserve and functional capacity. Treatment may lead to unacceptable levels of toxicity that subvert quality of life or even cause death, and these risks are particularly compelling in frail or vulnerable (prefrail) patients with competing risks for morbidity/mortality. Clearly, the risks of both undertreatment and overtreatment must be carefully weighed.

Before making any treatment decisions in older patients with stage II/III colorectal cancer, life expectancy should be estimated using available tools, and the patient’s goals and preferences should be elicited and discussed. An attempt should be made, in conjunction with life expectancy estimations, to determine the level of frailty, either by applying the criteria listed in Fig. 1, applying the Balducci frailty criteria, or using a screening instrument such as the VES-13. Patients that meet criteria for frailty should be referred to a geriatrician for comprehensive assessment and management of competing risks if the decision is made to pursue therapy.

Figure 2 outlines our recommendations for the adjuvant treatment of colon cancer in older adults, based on the evidence available. Data for the perioperative management of older rectal cancer are much more limited, but evidence suggests that age alone should not be the basis for treatment decisions. To better answer the questions facing oncologists, it is crucial that clinical trials are designed with older adults in mind. More descriptive data (for example, elements of the CGA) should be collected, and trials should be designed to include a more representative range of older adults.

References


11. Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey:


Achieving Health Equity in Colorectal Cancer: A Call to Action

Toni M. Cipriano, MA, and Blase N. Polite, MD, MPP

OVERVIEW

Whether defined by race, ethnicity, or socioeconomic status, there are clear health disparities in colon cancer—disparities that exist whether you measure screening, incidence, or mortality. Rather than rehash disparity statistics, the purpose of this educational article is to highlight important resources and how they can be used to help narrow these disparities. Although the logistics can be complex, the general solutions to eliminating colon cancer health disparities are not complex. They are as follows: Asymptomatic persons need to be screened. After being screened, they need to be diagnosed. After being diagnosed, they need to receive appropriate treatment in a timely fashion. After receiving treatment, they have to receive appropriate follow-up and information and advice on lifestyle changes. If we can implement these measures, then cancer-specific mortality disparities will be dramatically reduced, if not eliminated.

The black population is more likely to develop, and die as a result of, colon cancer than the white population, and to present at more advanced stages of disease. More concerning is that these trends are actually worsening rather than improving over time. For an in-depth look at these figures, an excellent resource is the American Cancer Society’s Cancer Facts & Figures for African Americans 2013–2014. A question that often arises is how much of the increased death rate is related to factors such as socioeconomic status (SES) and stage at diagnosis. Albeit dated, the U.S. National Cancer Institute’s Black White Cancer Survival Study remains one of the best studies addressing this question. The study found that overall the black population has a 50% higher hazard rate of death than the white population. Advanced stage at diagnosis explained approximately 60% of this difference. Socioeconomic status appeared to exert its influence on stage of diagnosis, because after stage was controlled for, SES had minimal impact and a 20% survival disparity persisted. This indicates that changing the stage distribution of cancer diagnosis will give us the greatest impact in reducing these disparities, but will still not completely solve the problem.

Additional updated longitudinal data (Fig. 1) suggest that these stage-specific survival trends not only continue but are worsening. Moreover, in a recent Journal of Clinical Oncology article by Robbins and colleagues, the growing survival disparity is most pronounced in the very area of colon cancer in which the greatest advancement has been made during the last decade: the metastatic setting. The tremendous advances being made in cancer care are not being broadly shared, and this remains one of the most difficult areas to understand and address.

ASYMPTOMATIC PERSONS NEED TO BE SCREENED

Colon cancer has the clear advantage over many other cancers in that screening can not only identify early cancers but actually identify precancerous lesions. That colon cancer screening saves lives is irrefutable. Unfortunately, black and Hispanic persons are less likely to be screened, and when they are screened black persons are less likely to be screened with colonoscopy. Insurance status and being in the health care system are particularly important. A 2001 California Health Interview Survey analysis found that only 26% of uninsured individuals ages 50 to 64 years with a primary care physician (PCP) had any screening for colon cancer and only 8% of uninsured individuals without a PCP were screened compared to 48% overall.

Providing this screening to all individuals and helping them navigate through the system can make a large difference. Both New York City and the state of Delaware implemented comprehensive public health solutions for colon cancer screening that included public health campaigns, access to colonoscopies, and patient navigation. In Delaware (Figs. 2-4), not only was the screening disparity eliminated, but stage and mortality disparities shrunk substantially. It is important to note that the public health solution was not merely to provide the colonoscopies, but also to educate the vulnerable populations and provide navigation through the system. Several high-quality studies, including several randomized interventions, have been published demonstrating the positive impact that navigation
services can have on colon cancer screening in underrepresented racial and ethnic minority populations.9

AFTER BEING SCREENED, PATIENTS NEED TO BE DIAGNOSED

Although this step might seem intuitive, it is important to understand that when using tests like fecal occult blood testing (FOBT) or sigmoidoscopy, an abnormal finding needs to be followed up with full colonoscopy for the screening to have any merit. Yet, in a Veterans Affairs study, fewer than half of the patients with a positive FOBT result underwent a full colon evaluation within 12 months.10 In another population-based study, 25% of physicians report using only in-office tests for FOBT and for those with a positive FOBT result, 18% recommended just repeating the test.11 On a positive note, this is an improvement from a previous study by the same group in which 30% of physicians recommended repeating the FOBT.12 Much of this is a systems issue because only 44% of physicians who use at-home FOBT as their screening method for colon cancer have reminder systems to ensure test completion and returns.12 With respect to follow-up after an abnormal flexible sigmoidoscopy, only approximately two-thirds of patients undergo appropriate diagnostic follow-up, and black patients are less likely than white patients to receive such follow-up (odds ratio [OR] = 0.88; 95% CI: 0.83 to 0.93).13 As we move to a more quality-based reimbursement system, appropriate follow-up for at-home tests such as FOBT or sigmoidoscopy must be part of our metrics. One could also make the strong argument that for a patient population that has numerous barriers to strict adherence to the conditions for a FOBT (yearly compliance, sample acquisition and return, follow-up testing if needed), a once-every-10-years colonoscopy has advantages.

AFTER BEING DIAGNOSED, PATIENTS NEED TO RECEIVE APPROPRIATE TREATMENT IN A TIMELY FASHION

Diagnosing a cancer is, of course, only part of the battle. If the cancer is not also treated in a timely fashion and by the appropriate physicians, then survival disparities will persist. Multiple studies have been published over the years showing that black patients are less likely to receive adjuvant treatment for stage III colon cancer.14-16 Probably the most in-depth study of this was published by Baldwin and colleagues in the Journal of the National Cancer Institute in 2005.14 In that study, even among black patients who were seen by a

KEY POINTS

- Health disparities in colorectal cancer not only persist, but are actually worsening over time.
- Disparities exist at every phase of the cancer care continuum.
- Successful solutions to reduce these disparities have been devised and implemented.
- If we have the will do so, cancer health disparities in colorectal cancer be reduced, if not eliminated, in this country.
medical oncologist, only 60% of black compared to 70% of white patients received chemotherapy. Perhaps most disturbing, among the youngest cohort of patients, those whom one would expect to receive the greatest benefit of treatment, 66% of black compared to 86% of white patients received chemotherapy. Involved are numerous system- and patient-level factors, which remain under investigation across fields. This is important because we know from both registry and clinical trial data that when black and white patients with colon cancer receive identical treatment in both the stage III and metastatic setting, their cancer-specific outcomes are the same.17-20

A final issue of note is the importance of where treatment is received. Although it is beyond the scope of this review to examine and synthesize the complex literature on the physician/hospital volume and quality relationships, it cannot be ignored as a factor in health disparities. To demonstrate, one analysis of California’s cancer registry data showed that individuals in lower-SES groups were more likely to receive rectal surgery in low-volume hospitals where fewer than seven such procedures were performed in a year, compared to those in the highest-SES group (30% compared to 13%), and that those who had their rectal surgeries performed in low-volume hospitals had higher 30-day mortality (OR = 2.6; 95% CI: 1.4 to 4.9) and overall mortality (OR = 1.3; 95% CI: 1.15 to 1.49).21 Again, as we think about designing a reward-based health care system in which quality of care matters, these are the type of issues we should address.


AFTER RECEIVING TREATMENT, PATIENTS HAVE TO RECEIVE APPROPRIATE FOLLOW-UP AND INFORMATION AND ADVICE ON LIFESTYLE CHANGES

In a Surveillance, Epidemiology, and End Results (SEER)-Medicare analysis, despite guideline recommendations and Medicare reimbursement, 25% of patients who undergo curative treatment for colon cancer do not receive surveillance examinations according to those guidelines, and minority patients are less likely than white patients to receive such surveillance.22

Another area receiving a great deal of attention in recent years is the role of lifestyle risk factors and modifications in determining not only the first onset of colon cancer but also recurrence of the disease. The areas that have received the greatest attention involve exercise, obesity, diet, aspirin use, and vitamin D levels. Numerous studies have linked obesity to colon cancer incidence, recurrence, and mortality.23,24 It is also well established that minorities, especially the black and Hispanic populations, have much higher rates of obesity and extreme obesity.25 Excellent work from Meyerhardt and colleagues from the Dana-Farber Cancer Institute (Boston, MA) have shed important light on the link between exercise and diet—particularly diets with lower glycemic loads—on colon cancer recurrence.26-29 Finally, emerging data show an association between low vitamin D levels and death as a result of...
colorectal cancer. This is particularly important for black and Hispanic patients, who naturally have much lower vitamin D levels than white patients. One study suggested that as much as 20% of the survival disparity for black patients could be explained by lower vitamin D levels. Whether vitamin D supplementation can alter that outcome is of course an open question, but one worthy of study.

CONCLUSION
Achieving health equity in colon cancer is possible and, in fact, already being done in certain areas of the country such as New York and Delaware. To get on a national level, our main focus needs to be on ensuring that all eligible patients undergo appropriate screening. Studies suggest that approximately 60% of our inequality could be solved there. This is not rocket science, but rather requires a concerted and dedicated public health effort across all geographic areas of our country.

The remaining 40% requires that we pay meticulous attention to every phase in the cancer care continuum. We need to continue to learn why treatment differences occur and develop interventions to eliminate them. We
also need to put further emphasis on survivorship care and develop culturally sensitive interventions with directed diet, exercise, and chemo-preventive pharmacologic strategies. I believe we have the tools to achieve health equity in colon cancer; the question remains, Are we willing to use them?

**Disclosures of Potential Conflicts of Interest**

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “Y” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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**References**

GASTROINTESTINAL (NONCOLORECTAL) CANCER

Rare but Real: Management of Small Bowel Cancer, Peritoneal Mesothelioma, and Cancer of Unknown Primary

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Cancer of unknown primary site (CUP) is a common heterogeneous clinicopathologic syndrome, but investigations and publications regarding these patients are rare. For the last 20 years, empiric “broad-spectrum” chemotherapy has been the standard therapy for the majority of these patients. More recently, improved immunocytochemistry and advent of gene-expression profiling have provided the diagnostic tools necessary to accurately define the tissue of origin in most patients. Molecular profiling assays complement standard pathologic diagnosis, and a recently reported large prospective study demonstrated an improvement in outcome for patients treated with site-specific therapy directed by the molecular assay diagnoses compared with empiric chemotherapy. Survival in molecularly diagnosed patients was as expected for those particular tumor types. The evaluation of patients has become more standardized. The empiric-chemotherapy era is ending and customized therapies based on accurate tissue of origin diagnoses have arrived. Eventually the recognition of the molecular aberrations responsible for the growth and metastasis of solid tumors, regardless of the tissue of origin, will lead to more precise and effective therapy for patients with advanced cancers.

CUP is defined as the presence of cancer without a clinically detectable anatomic primary tumor site of origin. The ability to accurately determine the tissue of origin has improved substantially by new diagnostic technologies. Global agreement of the diagnostic tests required at the time of clinical presentation is lacking, but becoming clearer. Most biopsies from these patients are carcinomas, and, rarely, other lineages are eventually diagnosed (lymphoma, melanoma, sarcoma). The management of patients with CUP has changed with the potential to diagnose the tissue of origin and treat with site-specific regimens.

DIAGNOSTIC ROLE OF IMMUNOHISTOCHEMISTRY (IHC) AND GENE-EXPRESSION PROFILING

The emergence of more precise IHC marker stains and gene expression/molecular profiling assays has changed the diagnostic approach. The identification of the tissue of origin in CUP is now more important than in the past, since the therapy for patients with many known advanced solid tumors has improved over the past several years. Furthermore, the stakes are likely to be even higher in the future, since more patients with CUP will have improved outcomes when treated with site-specific regimens effective for their particular tumor type.
Diagnosis of the tissue of origin in CUP has improved by the application of panels of IHC stains and molecular-profiling assays. Several rather specific IHC stains are available today. The IHC stains chosen for the initial diagnostic biopsy is based on the clinical findings, histologic diagnosis, and knowledge of the common occult tumors presenting as CUP with relatively diagnostic IHC profiles. Screening with selected staining is recommended on most biopsies (see Evaluation and Management in 2013 section) but indiscriminate use of multiple stains is expensive, it frequently exhausts the biopsy specimen, and is often not more revealing than a measured and rational step-wise approach.

Additional pathologic and clinical testing may be indicated, depending on the initial clinicopathologic findings. Several IHC staining profiles are highly suggestive of particular primary tumor types, but substantial variability remains. For example, false positives and negatives are well appreciated, and the absence of thyroid transcription factor-1 (TTF-1) or CDX-2 positivity in a minority of lung and colon adenocarcinomas, respectively, is well known. There are many different subsets within each category of specific carcinomas. Breast cancers are an example of heterogeneity in which staining for ER, PR, and HER2/neu may be positive, negative, or mixed. Further details regarding IHC are discussed later.

Gene-expression profiling assays to determine the tissue of origin in CUP have emerged in the last several years. Several commercial assays are available. The clinical value of these assays in CUP has been difficult to prove, but substantial data now validate the relative accuracy in predicting the tissue of origin.

The 92 gene reverse transcription polymerase chain reaction molecular profile assay is approximately 80% accurate in predicting the tissue of origin in CUP, as has been reported by using several correlative methods, and this accuracy is similar to that reported by the three commercially available molecular profile assays in known advanced primary cancers. Molecular assays complement standard pathology by providing a single diagnosis of the tissue of origin in most patients when diagnostic IHC staining is otherwise inconclusive.

Recently a large prospective study has been completed in CUP, looking at the outcomes or survival of patients treated with site-specific or customized therapies based on the molecular assay tissue of origin diagnosis. In 98% of tumors with successful assays, a single tissue of origin was predicted. A total of 194 patients received site-specific treatment. The median survival was 12.5 months, compared with the expected survival for patients with CUP receiving the same empiric therapy of about 9 months. Furthermore, the survival of 115 patients with molecular diagnoses of more responsive tumors (colorectal, breast, ovary, kidney, prostate, bladder, non-small cell lung cancer [NSCLC], germ cell, poorly differentiated neuroendocrine tumor, lymphoma, and small cell lung cancer) was significantly longer (13.4 months compared with 7.4 months; \( P = 0.04 \)) than the 79 patients with less responsive tumors (biliary tract, pancreas, gastroesophageal, liver, melanoma, sarcoma, cervix, carcinoid, endometrium, mesothelioma, skin, thyroid, head and neck, and adrenal).

Survival of patient subsets of molecularly diagnosed tumor types were as follows: biliary tract 6.8 months, pancreas 8.2 months, urothelium 8.4 months, renal 11.7 months, colorectal 12.5 months, NSCLC 15.9 months, ovarian 29.6 months, breast longer than 24 months (not yet reached). There is a survival advantage in CUP when patients receive site-directed therapy based on the molecular diagnosis, rather than the administration of empiric standard regimens (such as paclitaxel/carboplatin or gemcitabine/cisplatin) to all patients. Many of the molecularly diagnosed cancer types have relatively unresponsive tumor types to any chemotherapy, making the recognition of the more treatable or more responsive tumor types even more critical.

Data from several retrospective and prospective studies show that gene-expression profiling with any of the three commercially available assays of the biopsy specimen will provide a relatively accurate diagnosis of the tissue of origin. As discussed previously, customized or site-specific therapy in patients directed by the molecular diagnosis improves survival compared with empiric chemotherapy. All the clinicopathologic findings should be considered in conjunction with the molecular assay result, and this process improves the overall accuracy of tissue of origin prediction. The diagnosis of the tissue of origin in patients with CUP has changed the management for the majority of these patients.

**EVALUATION AND MANAGEMENT IN 2013**

An approach to the diagnosis in patients with suspected CUP is illustrated in Fig.1. An excisional, incisional, or core needle biopsy is necessary before continuing a more extensive evaluation. The clinical findings and histology of the
biopsy specimens suggest that additional clinical and/or specialized pathology testing is indicated. The evaluation initially recommended is outlined in Table 1. PET scanning may be useful in the evaluation of CUP, but with the exception of squamous cell carcinoma involving cervical lymph nodes, prospective data supporting primary site detection in large numbers of patients are lacking. Additional testing to attempt to find the anatomic tumor primary site or the tissue of origin is frequently suggested by the clinicopathologic findings. Table 2 lists additional supplemental-directed evaluation based on several initial clinicopathologic findings.

The gender of the patient and sites of metastasis are important to consider. The sites of metastasis in CUP as proven by necropsy series, in which the primary tumor site is identified, are often atypical for these primaries. For example, occult prostate carcinoma more often spreads to lymph nodes and/or lung initially than to bone; occult pancreatic carcinomas metastasize initially to bone and/or lung more often than expected from known pancreatic carcinoma. However, most occult primary carcinomas metastasize to regional nodes and to other typical well-appreciated sites in a fashion similarly to their counterparts with known primary cancers. The gender and metastatic sites are not specific but help in some patients in narrowing the diagnostic possibilities. Examples include

**FIG 1.** Evaluation and management of patient with possible CUP.
Features of lung cancer (hilar/mediastinal adenopathy; TTF-1+)
- Bronchoscopy

Features of colon cancer (liver/peritoneal metastases; CK20+; CK7-, CDX2+)
- Colonoscopy

Mediastinal/retroperitoneal mass
- Testicular ultrasound; Serum HCG, AFP

Women with features of breast cancer (axillary nodes, bone, lung, liver metastases, CK7+)
- Pelvic/intravaginal ultrasound; WT-1 stain

Predominant liver metastases (CK7+, CK20-)
- Serum AFP

Poorly differentiated carcinoma, with or without clear cell features
- Serum AFP if Hepa 1+; Octreotide scan if neuroendocrine stains

Any histology without a single site of origin predicted by IHC
- Molecular profile assay

Any histology with a very small biopsy specimen
- Molecular profile assay

**TABLE 2. Additional Evaluation of Specific Patient Subsets Defined by Initial Diagnostic Evaluation**

**Results of Initial Evaluation**
- Clinical Evaluation
- Specialized Testing of the Biopsy

**Abbreviations:** HCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; PLAP, placental alkaline phosphatase; FISH, fluorescence in situ hybridization; ER, estrogen receptor; RCC, renal cell carcinoma.

**TABLE 3. Immunohistochemical Staining Profiles Supportive of a Single Primary Site in CUP**

<table>
<thead>
<tr>
<th>Lung, adenocarcinoma/large cell</th>
<th>CK7+, CK20+, TTF-1+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung neuroendocrine (small cell/large cell)</td>
<td>Chromogranin+, Synaptophysin+, TTF-1+</td>
</tr>
<tr>
<td>Colorectal</td>
<td>CK7-, CK20+, CDX-2+</td>
</tr>
<tr>
<td>Breast</td>
<td>CK7+, ER+, GCDFP-2+, Mammoglobin+</td>
</tr>
<tr>
<td>Prostate</td>
<td>CK7-, CK20+, PSA+</td>
</tr>
<tr>
<td>Ovary</td>
<td>CK7+, ER+, WT-1+</td>
</tr>
<tr>
<td>Melanoma</td>
<td>S100+, Melan-A+, HMB45+</td>
</tr>
<tr>
<td>Renal</td>
<td>RCC+, Vimentin+, CD10+, PAX-8+</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepa 1+, CD10+, CD3+</td>
</tr>
<tr>
<td>Germ cell</td>
<td>PLAP+ and/or OCT-4+</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Alpha-inhibin+, Melan-A (A103)+</td>
</tr>
<tr>
<td>Thyroid (follicular/papillary)</td>
<td>TTF-1+, Thyroglobulin+</td>
</tr>
</tbody>
</table>

**Abbreviations:** CUP, cancer of unknown primary site; ER, estrogen receptor; PSA, prostate-specific antigen; RCC, renal cell carcinoma; PLAP, placental alkaline phosphatase; IHC, immunohistochemical.

*When the above IHC profiles are present in an appropriate clinical context, CUP should be designated as CUP breast profile, CUP-non-small cell profile, CUP-colorectal profile, etc. In patients without a single tissue of origin diagnosis by IHC, a molecular profile assay should be obtained. If the biopsy specimen is very small, a molecular profile assay should be considered before multiple IHC stains are performed.
A molecular profile assay appears to complement IHC in many patients with CUP. The molecular assay should be considered initially in patients with only small biopsy specimens or malignant effusions since an ideal IHC evaluation is usually not feasible on these specimens. In those rare patients with only poorly differentiated cancers without a lineage clearly defined by IHC, a molecular assay may be useful.

If an anatomic primary tumor site is not detected, the diagnosis of CUP is established. The IHC findings and/or molecular profiling assay may establish the tissue of origin or primary site, but patients without a demonstrable anatomic primary site should still be considered within the clinicopathologic syndrome of CUP. However, patients with IHC and/or a molecular profile assay highly suggesting a single primary site (CUP-colorectal, CUP-NSCLC, CUP-breast, etc.) should be treated with customized or site-specific treatment regimens, as recent data show their outcome is improved by such a tailored therapeutic approach. If future study verifies a similar survival for these patients as their counterparts with advanced known carcinomas, these patients with CUP may be definitely included as subsets of those same known advanced primary cancers.

In the past three decades several clinicopathologic “favorable subsets” (Table 4) of patients with CUP have been recognized (20% of all CUP). These patients have an improved prognosis with specific therapies, compared with the majority of the other patients (80%) with unfavorable prognostic features. These patients have a relatively poor prognosis, despite the past results with empiric chemotherapy (combinations of "broad-spectrum" antineoplastic agents). These oncogenic tumors delivered to patients with unfavorable prognostic features has been the standard therapy for about 20 years, and have modestly improved their overall long-term survival (40% at 1 year, 20% at 2 years, 10% at 3 years, and beyond). However, their median survival has been only about 9 months. The administration of empiric therapeutic regimens to all patients now is no longer appropriate, since a diagnosis of the tissue of origin is possible in most patients.

Patients with several known advanced carcinomas (including breast, NSCLC, ovary, colon, prostate, esophagus, stomach, anal canal, renal, bladder/renal pelvis/ureter, rectum, uterine cervix, liver, melanoma, hepatocellular, head and neck, and others) have had improvements made in their systemic therapy in the past 10 years. For example, in advanced colorectal carcinomas, the median survival has increased from 8 months to nearly 2 years. Several targeted drugs are now also indicated for several of these patients. There are now recognized subsets of colon cancer (Kras wild type), breast cancer (HER2-neu amplified), and non-small cell lung cancer (epidermal growth factor receptor mutation, anaplastic lymphoma kinase rearrangement, ROS1 rearrangement), which respond and benefit substantially from targeted agents.

A subset of patients with CUP with a colorectal profile (recognized by IHC and/or molecular profile assay) has been treated with site-specific colorectal therapy. Their response rate and survival appear similar to known patients with advanced colorectal cancer. When these patients were treated with empiric paclitaxel and carboplatin, the treatment did quite poorly with low-response rates and poor survival. This colorectal CUP subset may be recognized by IHC marker stains or molecular profiling assays, and their prognosis is considerably better when they receive site-directed therapy, rather than empiric chemotherapy. The CUP-colorectal subset is an example of colorectal carcinoma presenting as CUP, and their prognosis also appears similar to known advanced colorectal cancer after appropriate therapy.

Renal and hepatocellular carcinoma represent examples of solid tumors that targeted drugs improve overall patient

### TABLE 4. Favorable Subsets Identified by Clinical and Pathologic Features

<table>
<thead>
<tr>
<th>Histology</th>
<th>Clinical Subset</th>
<th>Therapy</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>Women, axillary node involvement</td>
<td>Treat as primary breast cancer</td>
<td>Survival improved</td>
</tr>
<tr>
<td></td>
<td>Women, peritoneal carcinomatosis</td>
<td>Treat as stage III ovarian cancer</td>
<td>Survival improved</td>
</tr>
<tr>
<td></td>
<td>Men, blastic bone metastases or high serum PSA/tumor PSA staining</td>
<td>Treat as metastatic prostate cancer</td>
<td>Survival improved</td>
</tr>
<tr>
<td></td>
<td>Single metastasis</td>
<td>Surgical resection and/or radiotherapy ± chemotherapy</td>
<td>Survival improved</td>
</tr>
<tr>
<td></td>
<td>Colon cancer profile (IHC and/or molecular assay)</td>
<td>Treat as metastatic colon cancer</td>
<td>Survival improved</td>
</tr>
<tr>
<td>Squamous Carcinoma</td>
<td>Cervical adenopathy</td>
<td>Treat as locally advanced head/neck primary</td>
<td>25%-30% 5-yr survival</td>
</tr>
<tr>
<td></td>
<td>Inguinal adenopathy</td>
<td>Inguinal node dissection, radiation therapy, ± chemotherapy</td>
<td>15%-20% 5-yr survival</td>
</tr>
<tr>
<td>Poorly Differentiated Carcinoma</td>
<td>Extragonadal germ cell syndrome</td>
<td>Treat as poor prognosis germ cell tumor</td>
<td>10%-20% cured</td>
</tr>
<tr>
<td>Neuroendocrine Carcinoma</td>
<td>Aggressive (small cell or large cell, poorly differentiated)</td>
<td>Treat as extensive-stage small cell lung cancer</td>
<td>High response rate/survival improved</td>
</tr>
<tr>
<td></td>
<td>Low grade</td>
<td>Treat as advanced carcinoid tumor</td>
<td>Indolent biology/long survival</td>
</tr>
</tbody>
</table>

Abbreviation: PSA, prostate-specific antigen.
TABLE 5. Clinical Landscape of CUP Over the Decades

<table>
<thead>
<tr>
<th></th>
<th>1976</th>
<th>1996</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Evaluation</strong></td>
<td>Rudimentary; CT not available yet</td>
<td>CT scans; endoscopies</td>
<td>Can be extensive; CTs, ultrasound, MRIs, PET, endoscopies</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>H and E, No IHC</td>
<td>Limited IHC</td>
<td>IHC evolving and panels useful; molecular assays useful</td>
</tr>
<tr>
<td><strong>Favorable Subsets</strong></td>
<td>Not appreciated</td>
<td>Multiple subsets appreciated with specific therapy (20% of all CUP)</td>
<td>Specific IHC and molecular diagnosis; Outcome improved with site-specific therapy</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Symptomatic/Supportive; no effective therapy; no specific diagnoses; empiric chemotherapy</td>
<td>Favorable subsets treatment helpful; empiric chemotherapy</td>
<td>Site-specific therapy; most CUP tissue of origin diagnosed</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Very poor; All patients lumped together; only a few advanced solid tumors had useful therapy</td>
<td>Good for favorable subsets; empiric regimens helpful to some</td>
<td>Improved with site-specific therapies based on diagnosis of tissue of origin; Poor for specific cancers with ineffective therapies</td>
</tr>
</tbody>
</table>

Abbreviations: CUP, cancer of unknown primary site; IHC, immunohistochemical.

CONCLUSION

The ability to make a diagnosis of the occult primary cancer or tissue of origin in CUP has greatly improved by the use of panels of IHC stains and molecular profiling assays. Molecular profile assays are relatively accurate, complement standard pathology, and frequently are diagnostic when IHC is inconclusive. A large prospective study of patients with CUP was recently published in which patients were treated with site-specific therapy based on the molecular assay diagnoses. The median survival was improved, and several subsets of diagnosed patients had survivals similar to their counterparts with known advanced cancer. In patients with responsive tumor types diagnosed by molecular assay, their survival was significantly superior to those diagnosed with less-responsive tumor types.

Site-specific and molecular-targeted therapies continue to improve for patients with several advanced solid tumors, and these therapies can be administered to patients with CUP, specifically defined by IHC profiles and/or molecular profile assays. Clinical oncology is an ever changing and fluid field, and useful new technology is often slow to be incorporated into clinical practice. The use of molecular profile assays in CUP represents an improved diagnostic test, but requires clinical judgment to interpret the results. This is similar for any other new technology in medicine. Additional clinical trials are necessary to better define the precise role of molecular diagnosis in CUP. Genomic investigations may also eventually find specific CUP genetic abnormalities which may explain the biology and perhaps provide additional clues to improve therapy. Empiric chemotherapy regimens in CUP have a role only in a small percentage of patients with CUP in whom the tissue of origin remains uncertain. As expected, patients with the more responsive tumor types will benefit most from discovery of their tissue of origin. A large minority of patients will not currently benefit from site-directed therapy, since effective therapy for their tumor types is not yet available. Confidence in the diagnosis of the tissue of origin will allow these patients to receive more effective therapy as the standard therapies for these tumor types improve. Patients with CUP will be treated in the future with therapy indicated for their specific tumor type or with other molecular targeted agents directed at critical genetic aberrations found in their tumors, regardless of their primary tumor site.
References


Peritoneal Mesothelioma: The Site of Origin Matters

Hedy Lee Kindler, MD

OVERVIEW

The etiology, gender distribution, pathology, natural history, and treatment options for mesothelioma (MM) differ substantially depending on the site of origin. Peritoneal mesothelioma (MPeM) is a rare disease, comprising only approximately 10% to 15% of the 2,500 cases of MM diagnosed in the United States each year. Patients with MPeM are younger than patients with pleural MM, and a higher proportion, mostly women, are long-term survivors. Most MPeM is caused by asbestos exposure. Germ-line mutations of BAP1 (BRCA associated protein 1) can predispose to MM, uveal melanoma, and potentially other cancers. MPeM can be challenging to diagnose, and cytology is rarely helpful. Review by an experienced pathologist using a panel of at least two positive and two negative immunohistochemical stains is essential. The three major pathologic subtypes are epithelial, sarcomatoid, and biphasic. Most cases are epithelial; the others have a dismal prognosis. Two indolent subtypes of borderline malignant potential—well-differentiated papillary mesothelioma and benign multicystic mesothelioma—are more common in the peritoneum and are treated surgically. In highly selected patients receiving treatment at experienced referral centers, an aggressive locoregional strategy that combines cytoreductive surgery to remove all gross disease and hyperthermic intraperitoneal chemotherapy to treat residual microscopic tumors yields a 3-year survival of 60% and a median survival approaching 5 years, far better than expected from historic controls. This approach also provides durable palliation of malignant ascites in nearly all patients. Pemetrexed is the only U.S. Food and Drug Administration (FDA)–approved systemic chemotherapy for pleural MM. Largely on the basis of data from pharmaceutical registry studies, the activity of pemetrexed-based chemotherapy appears to be similar in pleural MM and MPeM.

Peritoneal mesothelioma (MPeM) is a rare malignancy, comprising only 10% to 15% of the approximately 2,500 cases of malignant mesothelioma (MM) diagnosed in the United States each year. In the Surveillance, Epidemiology, and End Results (SEER) database, 10.5% of the MM identified between 1973 and 2005 was MPeM.1 MM is a heterogeneous disease, and the etiology, gender distribution, pathology, natural history, and treatment options can differ markedly depending on the site of origin. The vast majority of MM (85%) develop in the pleura; MM of the pericardium and tunica vaginalis are exceedingly rare.

Patients with MPeM are significantly younger than those with pleural MM (mean age, 63.3 vs. 70.8 years, respectively; p < 0.001).2 In historic series, patients with MPeM also have a shorter median survival, and women with MPeM live significantly longer than men (13 vs. 6 months; p < 0.001).1 There is greater variability in the survival of patients with MPeM compared to those with pleural MM, however, and a higher proportion of patients with MPeM, mostly women, are long-term survivors.2,3

Although men have a higher overall incidence of MPeM, a larger proportion of women develop MM that originates in the peritoneum. In the SEER database, women accounted for only 19% of pleural MM cases but comprised 44% of peritoneal MM cases.1 Most MM in males is caused by asbestos, with a 20- to 50-year latency following exposure. The attributable risk due to asbestos exposure is lower in women.4 MPeM may be associated with more prolonged, heavy asbestos exposure than pleural MM. In asbestos miners and insulators, for example, the proportion of MPeM is highest in those who have had the greatest cumulative asbestos exposure.5,6 Other potential causes of MPeM include thorotrast, erionite, therapeutic radiation, familial Mediterranean fever, and other causes of chronic peritonitis.6,7

Only a small fraction (< 5%) of those heavily exposed to asbestos will develop MM, yet the disease has been observed to cluster within families. This may be due to a newly described MM genetic susceptibility syndrome, in which germ-line mutations of BAP1 (BRCA associated protein 1) predispose to MM (including MPeM), uveal melanoma, other melanocytic tumors, and potentially other malignancies.8 MM is thought to predominate with asbestos exposure. Somatic mutations of BAP1 are also observed in approximately 23% of MM.
PRESENTATION, IMAGING, AND DIAGNOSIS

Most patients with MPeM present with vague, nonspecific abdominal symptoms, including increased abdominal girth, abdominal pain or discomfort, and weight loss. An umbilical or inguinal hernia may be present. Systemic symptoms can include fevers, night sweats, asthenia, nausea/vomiting, constipation, anorexia, and early satiety. Laboratory studies may reveal thrombocytosis.6,9-10

CT scan is the preferred initial imaging study, although it may underestimate the disease burden. It can demonstrate moderate to extensive ascites, diffuse peritoneal thickening, and nodular involvement of the omentum and mesentery.9-11 Most patients have diffuse peritoneal involvement, although localized MPeM can occur. Calcified pleural plaques can be observed in individuals with asbestos exposure. Liver metastases are exceedingly rare despite extensive intra-abdominal involvement. Pleural effusions and pleural-based tumors may develop later in the course of the disease, but other distant metastases are infrequent. MM may implant along needle tracts and surgical sites to produce painful subcutaneous nodules. Combined diffusion-weighted and gadolinium-enhanced magnetic resonance imaging may be more accurate than CT in quantifying the volume and extent of peritoneal tumor before surgical resection.12 There are limited data on the role of PET/CT in the management of MPeM, although it may be useful for the detection of recurrent disease.13

Ca-125 is commonly elevated in MPeM. Although it has no role in diagnosis, Ca-125 can be helpful in monitoring the disease course, particularly in patients without measurable tumor.6 There is less data for MPeM than for pleural MM regarding the utility of the recently described biomarkers serum mesothelin-related peptide (SMRP), osteopontin, and fibrin-3.14

Cytology is rarely helpful for diagnosis because the sensitivity of fluid cytology is low (32% to 76%),15 and the distinction between benign and malignant MM often depends on the degree of invasion, which cannot be ascertained by cytology. CT or ultrasound-guided needle biopsy or laparoscopy is generally required to establish the diagnosis.

Similar to pleural MM, the three principal histologic subtypes of MPeM are epithelial, sarcomatoid, and mixed (biphasic). In MPeM, however, biphasic tumors are infrequent, and pure sarcomatoid tumors are rare; both have a substantially worse prognosis than epithelial MPeM.15 The differential diagnosis of MPeM includes metastatic adenocarcinomas of the ovary, lung, or GI tract, as well as reactive mesothelium. No single immunohistochemical stain is pathognomonic of MM. Review by an experienced pathologist using a panel of at least two positive and two negative immunohistochemical stains is required to make a definitive diagnosis; the specific panel depends on the differential diagnosis. Common positive markers include calretinin, D2–40, CK 5/6, and WT-1; some frequently used negative markers include MOC-31, PAX8, BG8, Ber-EP4, B72.3, CEA, and CDX-2.15

Two distinct pathologic subtypes of borderline malignant potential are much more common in the peritoneum than in the pleura: well-differentiated papillary mesothelioma (WDPM) and benign multicystic mesothelioma (BMM).15-17 Both have relatively indolent behavior, are treated primarily with surgery, occur principally in women, and are not attributed to asbestos. WDPM commonly presents as an asymptomatic, incidental finding that can often be cured with resection alone. BMM, which consists of large grape-like cystic clusters, generally presents with an abdominal mass and abdominal pain, often in reproductive-age women with a history of endometriosis. Both entities can be locally recurrent, although this is much more common with BMM. Rare transformation to malignant mesothelioma has been reported for both WDPM and BMM, although in the case of WDPM this may reflect initial misdiagnosis or sampling error.

KEY POINTS

- Mesothelioma (MM) is a heterogeneous disease, and the etiology, gender distribution, pathology, natural history, and treatment options can differ markedly depending on the site of origin. There is greater variability in the survival of patients with peritoneal mesothelioma (MPeM) compared to those with pleural MM, and a higher proportion of patients with MPeM, mostly women, are long-term survivors.
- A MM genetic susceptibility syndrome, in which germ-line mutations of BAP1 predispose to MM, uveal melanoma, other melanocytic tumors, and potentially other malignancies has recently been described.
- MM can be challenging to diagnose, and cytology is rarely helpful. Review by an experienced pathologist using a panel of at least two positive and two negative immunohistochemical stains is required for definitive diagnosis. It is important to recognize the two indolent subtypes of borderline malignant potential, well-differentiated papillary mesothelioma (WDPM) and benign multicystic mesothelioma, which are treated with surgery.
- An aggressive locoregional approach that combines cytoreductive surgery with hyperthermic intraperitoneal chemotherapy can achieve median survival approaching 5 years in highly selected patients at experienced referral centers, and can palliate symptomatic ascites in nearly all patients.
- Pemetrexed is the only FDA-approved systemic chemotherapy for pleural MM. Largely on the basis of data from pharmaceutical registry studies, the activity of pemetrexed-based chemotherapy appears similar in pleural MM and MPeM.

NATURAL HISTORY AND TREATMENT OPTIONS

A standard therapeutic approach is not well defined. Most treatment algorithms are extrapolated from data derived from highly selected patients in small, retrospective, single-center series at referral institutions with expertise in MPeM.
and other peritoneal malignancies, and from a few recent multicenter databases. There are infrequent clinical trials in MPeM; all are small and nonrandomized.

Compounding these inherent selection biases, the heterogeneous natural history of MPeM (especially by gender and histology), makes it even more challenging to determine the impact of a therapeutic intervention. Women with MPeM present with earlier-stage disease, have more favorable histology, and have a better prognosis regardless of stage, which may be related in part, to differences in causation. The prognosis of MPeM, particularly in women, is also quite variable. Although MPeM often behaves as aggressively as pleural MM, unlike in pleural MM, a substantial proportion of MPeM in women is fairly indolent. In one small series, patients otherwise similar in terms of age, symptoms, initial tumor burden, tumor morphology, and treatment were divided into those with survival less than 4 years (60%) and those with survival more than 4 years (40%). In the short-term survivors, median survival was 12 months, and 1-year survival was 67%, quite similar to survival for pleural MM. By contrast, median survival in the long-term survival group was 7 years (range, 5 to 15 years), which would not be expected in pleural MM. The median survival of untreated MPeM is about 6 months. The median survival of patients with MPeM in the 1980s and ’90s who received systemic chemotherapy or palliative surgery was less than 1 year (range, 9 to 15 months). This contrasts markedly with more contemporary series in patients who underwent aggressive locoregional treatment, in whom median survival approaches 5 years (range, 34 to 92 months).

**Surgery**

MPeM remains confined to the abdominopelvic cavity, with little invasion of the underlying organs and no metastatic spread until it is quite advanced. This natural history suggests that aggressive locoregional treatment may be appropriate, and in the absence of level 1 evidence, this is a preferred strategy that appears to improve survival over historic controls. Although the specifics of patient selection, surgical techniques, and chemotherapy agent, dose, and method of delivery differ by institution, the cardinal principle is that aggressive cytoreductive surgery (CRS) is required to remove all gross peritoneal disease. Residual microscopic tumors are treated intraoperatively with hyperthermic intraperitoneal chemotherapy (HIPEC). This is sometimes followed by early postoperative intraperitoneal chemotherapy (EPI) or, less commonly, whole-abdominal radiation or adjuvant systemic chemotherapy.

At laparotomy, the preoperative disease extent is determined by the peritoneal cancer index (PCI), which divides the abdomen into a grid of nine squares and the small bowel mesentery into quadrants. Tumor burden in each area is scored on a scale of 0 to 3 (e.g., no involvement to extensive), up to a cumulative score of 39.

The completeness of cytoreduction (CC) score quantifies residual disease after resection on the basis of the size of the remaining tumor nodules (CC-0: none, CC-1: < 2.5 mm, CC-2: 2.5 mm to 2.5 cm, and CC-3: > 2.5 cm or a confluence of tumor nodules at any site). Preoperative CT scan findings predictive of an adequate cytoreduction include the absence of a larger than 5-cm epigastric mass and no loss of normal architecture of the small bowel and its mesentery.

In a complete gross cytoreduction, the surgeon removes all visible abdominal and pelvic tumors and involved solid organs, performing a complete diaphragmatic, parietal, and pelvic peritonectomy, greater and lesser omentectomy, and when necessary, splenectomy, bowel resection, hysterectomy, salpingectomy, or oophorectomy. A complete peritonectomy is superior to partial peritonectomy, even when an area seems grossly uninvolved. Small tumor implants on the bowel serosa and mesentery are treated with electrofulguration. The morbidity of CRS in MPeM even in experienced centers ranges from 25% to 40% and mortality from 0% to 8%. Common complications include intestinal fistula, bleeding, embolism, wound infection, electrolyte abnormalities, and sepsis. Thus, selection of fit patients likely to achieve a complete cytoreduction is essential; they should be referred to experienced centers.

The optimal time to achieve uniform distribution of chemotherapy to the peritoneum is after the majority of tumor has been resected but before adhesions develop. Thus, once maximal cytoresection is attained, HIPEC is administered intraoperatively, delivering a high drug concentration directly to microscopic residual disease. Hyperthermia can be tumoricidal and augments chemotherapy cytotoxicity. Cisplatin, mitomycin, carboplatin, and doxorubicin are most commonly used.

Although selection criteria and treatment specifics vary widely between institutions, experienced investigators using this approach report an impressive median overall survival that seems superior to the expected natural history of MPeM (Table 1). The overwhelming majority of patients (86% to 94%) also achieve substantial, durable palliation of malignant ascites.

The largest surgical series in MPeM is a retrospective registry established in 2008 to collect data from 405 patients with MPeM at eight institutions in six countries between 1989 and 2009. Eligible patients were deemed candidates for CRS/HIPEC. As expected from a registry that spanned multiple continents and two decades, there was considerable variation in the HIPEC technique, specifically in the choice of cytotoxic agent, the degree of hyperthermia (40 to 43°C), the duration of the perfusion (30 to 120 minutes), and the exposure technique (open or closed). Nonetheless, this data set provides a wealth of valuable information about the toxicities and outcomes with CRS/HIPEC in selected patients with MPeM at experienced centers, establishing a benchmark against which other treatments can be compared.

HIPEC was administered in 92% of cases, 23% of patients received EPI (usually with paclitaxel), and 5% of patients received adjuvant systemic pemetrexed-based chemotherapy. The median age was 50 years, 56% of patients were male, and 79% of patients had epithelial histology. Only 6% had lymph node metastases. The mean PCI was 20; 46% of
patients achieved a CC-0/1. The mean surgical duration was 8 hours; the median length of hospital stay was 22 days. Perioperative complications occurred in 46% of all patients; 31% of all patients had grade 3/4 complications. Perioperative mortality was 2%. With a median follow-up of 33 months, the overall median survival was 53 months (range, 1 to 235 months). The 3- and 5-year survival rates were 60% and 47%, respectively. On multivariate analysis, epithelial histology, lymph node–negative disease, CC-0/1, and HIPEC treatment were independently associated with superior survival. There was no difference in outcome between chemotherapeutic regimens. As expected, women had substantially longer survival than did men (119 vs. 36 months; \( p < 0.001 \)).

A more recent analysis of 294 patients from this registry confirmed that female gender is a favorable prognostic factor.\(^{18}\) Three- and 5-year survival rates for women were 76% and 68%, respectively, compared to 50% and 39% for males. Women had a substantially lower PCI, lower-stage disease, and more favorable histology. Women older than age 55 had an inferior survival rate compared with younger women (\( p = 0.019 \)); there was no difference in outcome by age in men.

There is no official Tumor, Node, Metastasis (TNM) staging system for MPeM. A preoperative staging system has recently been proposed on the basis of this registry data.\(^{23}\) Seven prognostic variables were identified on univariate analysis: age 50 years or younger, female gender, epithelial subtype, PCI 1 to 10, absence of lymph node metastases, absence of extra-abdominal metastases (defined as penetrating the diaphragm or invading an abdominal wall scar), and CC-0/1. Because age, gender, and pathologic subtype are intrinsic, and CC score can be obtained only after surgery, these were not considered for preoperative staging; the three remaining prognostic determinants (PCI, lymph node status, and extra-abdominal metastases) were therefore selected. T stage is derived intraoperatively from the PCI (T1: PCI 1 to 10, T2: PCI 11 to 20, T3: PCI 21 to 30, T4: PCI 31 to 39). The N stage (N0, N1) and M stage (M0, M1) are defined as in other malignancies. This system successfully stratified survival by stage. One-year survival for patients with stage I (T1N0M0), stage II (T2–3N0M0), and stage III (T4 or N1 or M1) disease was 94%, 87%, and 66%, respectively; 5-year survival was 87%, 53%, and 29%, respectively.

**Systemic Chemotherapy**

Chemotherapy for MPeM is administered principally in patients with recurrent disease, and in those who are not appropriate candidates for aggressive surgery. At some centers, adjuvant chemotherapy is offered to patients with disease that is not optimally debulked or who are otherwise at a high risk for recurrence. Neoadjuvant chemotherapy is most commonly used in patients who are not candidates for immediate cytoreduction as a result of their disease burden, as well as in those with a poor prognosis (including those with nonepithelial histology, and, in some centers, male patients) to spare those with potentially aggressive disease from major surgery.

Most of what we believe about the activity of chemotherapy in MPeM is extrapolated from trials performed exclusively in patients with pleural MM because it is generally presumed, although certainly not proven, that most systemic chemotherapy drugs have similar efficacy in both sites. Because of the different natural history of pleural MM and MPeM, however, patients with MPeM are generally excluded from clinical trials of new agents in MM. Even the occasional trial that permits patients with MPeM enrollment very few. Patients with MPeM are frequently ineligible for clinical trials because their diffuse peritoneal disease is generally not measurable by Response Evaluation Criteria in Solid Tumors (RECIST). Available data on the activity of chemotherapy for MPeM come from several small retrospective analyses, a few case reports, and a few prospective observational series including two large pharmaceutical registry studies. The few prospective clinical trials are small, and there are no randomized studies.\(^{24}\)

The only FDA-approved drug for pleural MM is pemetrexed, an antifolate that inhibits thymidylate synthase, dihydrofolate reductase, and glycaminide ribonucleotide formyltransferase. The best level 1 evidence of the activity of any agent in pleural MM comes from a pivotal single-blind, placebo-controlled phase III trial, in which 456 patients were randomly assigned to receive cisplatin (75 mg/m\(^2\)) with or without pemetrexed (500 mg/m\(^2\)) every 21 days for up to six cycles. No patients with MPeM were enrolled. Patients who received pemetrexed/cisplatin experienced a longer median overall survival (12.1 vs. 9.3 months; \( p = 0.020 \)), a superior time to progression (5.7 vs. 3.9 months; \( p = 0.001 \)), a higher objective response rate (41% vs. 17%; \( p < 0.001 \)), and a superior quality of life compared to cisplatin alone.\(^{25}\) In a similar phase III trial, cisplatin with or without the antifolate raltitrexed achieved comparable outcomes in patients with pleural MM (median overall survival 11.4 vs. 8.8 months;
p = 0.048).26 This combination is approved for MM in some European countries; it has not been studied in MPeM.

Most of the available information on the activity of pemetrexed in MPeM is derived from Eli Lilly and Company’s (Indianapolis, IN) U.S. and International Expanded Access Programs (EAP) performed before regulatory approval.27,28 Although these provide valuable data, they should be interpreted cautiously; there is far greater heterogeneity in patient populations and less rigorous assessment and reporting of adverse events and clinical activity than in prospective clinical trials. Nonetheless, these data suggest that pemetrexed-based regimens have comparable activity in pleural MM and MPeM, as shown in Table 2.24

Of the 1,056 patients with MM in the U.S. EAP, 98 (9.3%) had MPeM. Most (58%) had received prior chemotherapy. Sixty-six patients received pemetrexed/cisplatin; the remainder, pemetrexed alone. The 73 patients assessable for response were a heterogeneous group: 28 were chemotherapy-naïve and 43 were previously treated; 47 received pemetrexed/cisplatin and 26 received pemetrexed. The overall response rate was 26%, and 45% of patients had stable disease, yielding a disease control rate of 71%. Response rates were similar in chemotherapy-naïve (25%) and previously treated patients (23%). Pemetrexed/cisplatin yielded a higher response rate (30%) than did pemetrexed alone (19%). Progression-free survival was not reported. Median overall survival had not been reached in the chemotherapy-naïve patients; it was 13.1 months in those previously treated.27

The International EAP demonstrated the activity and tolerability of pemetrexed alone or with cisplatin or carboplatin (area under the curve [AUC] 5) in an equally heterogeneous group of 109 patients with MPeM, who were evenly distributed among the three treatment regimens. Most of the patients who received platinum doublets were chemotherapy naïve, compared with only 21% of those who received single-agent pemetrexed. Although RECIST criteria were recommended, SWOG (formerly Southwest Oncology Group) or WHO response criteria were permitted. Response rates for pemetrexed, pemetrexed/cisplatin, and pemetrexed/carboplatin were 12.5%, 20%, and 24%, respectively; disease control rates were 50%, 80%, and 76%, respectively. For those receiving pemetrexed alone, the median time to progression was 6.2 months and the median overall survival was 10.3 months; these values could not be determined in the other treatment arms due to a high censoring rate.28

As part of the International EAP in Germany, 22 patients with MPeM received treatment at a single-center. Most (68%) were chemotherapy-naïve; 95% received pemetrexed/cisplatin. The objective response rate in 10 assessable patients was 36%; the disease control rate was 77%. Mean time to progression was 11.5 months, and mean overall survival was 13.7 months.29 In a tiny series typical of MPeM studies, Greek investigators treated six patients with MPeM with pemetrexed/cisplatin. All had undergone an exploratory laparotomy during which a cytoreductive surgery was attempted, but none had a complete cytoreduction. Two patients (33%) achieved a complete response (defined as resolution of all measurable disease or ascites and normalization of Ca-125), three patients (50%) had partial responses, and one had stable disease. Median time to disease progression was 9.5 months, median overall survival was 24 months, and three patients were alive at 40+, 48+, and 49+ months.30

Pleural MM patients who obtain durable disease control with first-line pemetrexed are commonly retreated with a pemetrexed-based regimen, since about two-thirds of those who achieve a progression-free survival lasting longer than 6 months from first-line pemetrexed have disease control upon retreatment, and 17% will have an objective response.31 It

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Abbreviations: EAP, Extended Access Program; NR, not reported.
may be reasonable to assume similar activity for pemetrexed in previously treated MPeM. Only a few other agents or combinations have even modest activity in pleural MM, including single-agent vinorelbine, and gemcitabine with cisplatin or carboplatin; none of these have been tested prospectively in MPeM.

The combination of gemcitabine (1250 mg/m² days 1 and 8) plus pemetrexed (500 mg/m², day 8) was evaluated in one of the largest prospective chemotherapy trials ever reported in MPeM. Twenty patients with MPeM were enrolled at 10 centers during a period of 17 months as part of a trial evaluating this combination in pleural MM. The primary endpoint was objective response rate, which was only 15%, comparable to single-agent pemetrexed. The disease control rate was 50%. Median time to progression was 10.4 months; median overall survival was 26.8 months. This combination produced substantial grade 3/4 toxicity, including neutropenia (60%), febrile neutropenia (10%), fatigue (20%), vomiting (10%), and dehydration (10%).

Although current data suggest that cytotoxic chemotherapy has similar activity in pleural MM and MPeM, this may not be the case with targeted agents, potentially reflecting differences in the biology of the two diseases. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, for example, are inactive in pleural MM, and EGFR mutations are rare (< 2%). EGFR mutations occur in 31% of MPeM, however. An ongoing University of Chicago phase II trial administers erlotinib to patients with MPeM who have activating EGFR tumors. Other potential therapeutic targets that are the subject of ongoing or planned clinical trials in MM include mesothelin, PI3kinase, MET, EphB4, and FAK.

CONCLUSION
MPeM is an uncommon but deadly disease with a variable natural history that remains localized to the abdominal cavity for most of its course. Select patients receiving treatment at specialized centers with an aggressive locoregional strategy of cytoreductive surgery and HIPEC can achieve prolonged survival. Pemetrexed-based chemotherapy appears to have similar activity in pleural MM and MPeM. A concerted international collaborative effort is essential to make further progress in the management of this rare malignancy.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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References


Rare but Real: Management of Small Bowel Adenocarcinoma

Michael J. Overman, MD

OVERVIEW

Despite representing the longest segment of the alimentary tract, small bowel adenocarcinomas are rare. The diagnosis of small bowel adenocarcinoma is frequently delayed because of the nonspecific clinical symptoms and the limitations of small bowel imaging. The majority of patients will present with either lymph node or distant metastatic disease. Though the role of adjuvant therapy for resected small bowel adenocarcinoma is unclear, recent research efforts have led to an improvement in our management of advanced disease. Prospective phase II studies have successfully enrolled patients with this rare tumor type and have established the combination of a fluoropyrimidine and oxaliplatin as the most appropriate front-line chemotherapy for patients with advanced disease. Currently, five prospective clinical trials have been designed for patients with small bowel adenocarcinoma and enrollment to these clinical trials should be encouraged.

Although adenocarcinomas have historically represented the most common histologic subtype of the small intestine, the rising incidence of carcinoids has recently made this subtype the most common. The estimated number of new cases of small bowel cancer for 2012 in the United States is 8,070, with a histologic distribution of carcinoid (44%), adenocarcinoma (33%), lymphoma (15%), and sarcoma (8%). The distribution of histologic subtypes varies across the small intestine, with adenocarcinoma representing the most common cancer of the duodenum. One of the more interesting observations regarding small bowel adenocarcinoma relates to its 50-fold lower incidence than large bowel adenocarcinoma. This discrepancy occurs despite the small intestine representing approximately 75% of the length and 90% of the surface area of the alimentary tract. Although a number of hypotheses have been proposed to explain the apparent resistance of the small intestine to carcinogenesis, limited experimental evidence exists to support any one theory. General postulates include (1) Rapid turnover of small intestine epithelium which precludes the accumulation of genetic damage, (2) Increased lymphoid tissue in the small intestine, providing increased mucosal immune surveillance, and (3) The inherent nature of the small intestine and its contents, which permits less exposure to carcinogenic agents in our diet as a result of rapid transit time, a dilute alkaline environment, and a lack of bacterial degradation activity.

ETIOLOGY AND PATHOGENESIS

Because of the rarity of small bowel adenocarcinoma, limited information is available regarding risk factors and pathogenesis of this disease. The majority of cases will be sporadic in nature, although a number of inherited cancer syndromes, such as hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatosis polyposis (FAP), and Peutz-Jeghers syndrome, are associated with an increased risk of small bowel adenocarcinoma. The two most common conditions linked to sporadic small bowel adenocarcinoma, Crohn’s disease and celiac disease, are both associated with small bowel inflammation. The risk from Crohn’s disease reflects both the location of small bowel involvement, with 70% of cancers developing in the ileum, and duration of disease, with an approximate risk of small bowel adenocarcinoma of 2% after 25 years.

Although a number of molecular alterations are similar between small bowel and large bowel adenocarcinoma, such as 18q loss, p53 loss, and KRAS mutations; a dramatic difference exists in the rate of APC mutations, with one study finding a 0% rate of APC nonsense mutations in 48 patients with small bowel adenocarcinoma. The lack of APC mutations in conjunction with the infrequency of small bowel adenomas suggests that the incidence difference between small and large bowel adenocarcinoma may reflect a difference in the early initiation phase of carcinogenesis. A recent study comparing global DNA copy number alterations between small bowel, gastric, and colorectal cancers demonstrated that small bowel adenocarcinomas are more similar to colorectal cancers. In addition, small bowel adenocarcinomas demonstrate similar rates of microsatellite instability (MSI-high), 20%, and CpG island methylator phenotype (CIMP+), 27%, as seen in colorectal cancer. Interestingly, patients with celiac-related
small bowel adenocarcinoma have a relatively high rate of MSI-high tumors, with one study reporting a rate of 67%, all because of promoter methylation of the MLH1 gene.\(^5\)

**PRESENTATION AND DIAGNOSIS**

The median age at diagnosis for small bowel adenocarcinoma is 67, with over 85% of patients presenting after age 50.\(^8\) The most common symptoms are abdominal pain, nausea/vomiting, weight loss, and gastrointestinal bleeding. Stage presentation is 32% IV, 27% III, 30% II, and 10% I.\(^8\) This stage distribution contrasts with colon cancer, in which more patients (20%) present with stage I disease and less with stage IV disease (20%). This, in part, is likely a reflection of the lack of effective screening modalities for small bowel adenocarcinoma.\(^8\)

In the past, nonspecific clinical symptoms coupled with the limited sensitivity of an upper gastrointestinal series for small bowel neoplasms led to marked delays from symptoms to diagnosis.\(^9\) However, recent improvements in cross-sectional imaging, refinements in enteroscopy, and the development of wireless capsule endoscopy are all certain to improve the diagnosis of small bowel adenocarcinoma. For example, in a prospective study of CT enteroclysis with water in 219 patients with a clinical suspicion of a small bowel neoplasm, the sensitivity and specificity for detecting small bowel disease were 85% and 97%, respectively.\(^10\) Furthermore, until recently, endoscopic evaluation of the entire 7-meter-long small intestine could only be done at the time of surgical exploration. Now, both double balloon endoscopy and wireless capsule endoscopy are able to visualize the entire small bowel. Double balloon endoscopy uses two balloons in a push-and-pull technique to evaluate the entire small bowel; this requires significant expertise and is not widely available. Capsule endoscopy, first approved in the United States in 2001, has allowed markedly improved endoscopic imaging of the small intestine, although tissue acquisition is not possible with this modality and the presence of small bowel obstruction is a contraindication to this approach.\(^11\) In two large series of patients who underwent capsule endoscopy for a variety of reasons, small bowel tumors were identified in 76 of 978 patients (7.8%).\(^12,13\)

**PROGNOSIS**

In addition to stage, a number of additional factors have been associated with poor prognosis and include poor differentiation, positive margins, duodenal location, male gender, black ethnicity, and older age.\(^2\) Approximately 33% of small bowel adenocarcinomas present with poor differentiation, which is significantly higher than the 21% observed in colon cancer (\(p < 0.01\)).\(^8\) As seen with other tumor types, one of the most robust prognostic markers for resected cases is lymph node sampling. Recent data from the SEER database has demonstrated markedly improved outcomes for patients with increased nodal sampling, with one report finding eight lymph nodes\(^14\) and another finding 10 lymph nodes\(^15\) as the optimal number of sampled lymph nodes. For cases in which eight or more lymph nodes are assessed, the improvement in 5-year cancer-specific survival is 65.3% to 80.3% for stage I, 55% to 69.9% for stage II, and 40% to 45.1% for stage III disease.\(^14\) In a recent population-based comparison using the SEER database, even after accounting for lymph node sampling, small bowel adenocarcinoma demonstrated worse cancer-specific survival stage for stage than colon cancer.\(^8\) Interestingly, even when comparing stage I cases with adequate lymph node sampling, 5-year cancer-specific survival was significantly lower for adenocarcinomas of the jejunum/ileum (81.6%) than for colon (93.3%; \(p < 0.01\)). Such data suggest that a fundamental biologic difference exists between adenocarcinomas of the colon and small bowel.

**APPROACH TO TREATMENT**

### Locoregional Disease

Surgical resection is the mainstay of therapy for locoregional disease. Data investigating the effect of lymph node assessment has clearly shown that small bowel adenocarcinoma, and in particular duodenal adenocarcinoma, is markedly understaged.\(^14,15\) Such data support a more extensive surgical resection in order to obtain an adequate lymph node assessment. The relapse pattern for small bowel adenocarcinomas is predominantly systemic, with one large retrospective study reporting distant and locoregional relapses accounting for 86% and 18% of all recurrences, respectively.\(^16\) Although a higher rate of local recurrence is seen with duodenal primaries, systemic relapse still predominates.\(^17\)

At present, no randomized studies have been conducted evaluating the benefit of adjuvant chemotherapy in small bowel adenocarcinoma. A number of single-institution retrospective studies have not demonstrated a clear benefit from adjuvant therapy, but these studies have all been limited by their small sample size and selection bias favoring the use of

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**KEY POINTS**

- Despite representing the majority of the alimentary tract, the incidence of small bowel adenocarcinoma is 50-fold lower than colorectal adenocarcinoma and further research into understanding this great discrepancy is needed.
- For locoregional disease adequate lymph node assessment, 8 or more lymph nodes, strongly correlates with improved survival.
- The role of adjuvant therapy for small bowel adenocarcinoma has not been determined.
- The combination of a fluoropyrimidine and oxaliplatin represent the most appropriate front-line systemic chemotherapy.
- The role of biologic agents for this cancer are unknown, although a number of ongoing clinical trials are exploring this question.
adjuvant therapy in higher-risk patients.\textsuperscript{16,18} According to the National Cancer Database, the use of adjuvant chemotherapy has been increasing, with rates of 8.1% in 1985 to 22.2% in 2005 (p < 0.0001).\textsuperscript{2} In part, this likely reflects the poor outcome of high-risk patients who undergo resection, the known activity of systemic fluoropyrimidine-based chemotherapy in the metastatic setting, and extrapolation from the proven benefit of adjuvant treatment in colorectal cancer. Currently, there is an ongoing international effort as part of the Cancer Research United Kingdom/National Cancer Research Network/National Cancer Institute/European Organisation for Research and Treatment of Cancer Rare Cancers Initiative to initiate a large prospective randomized trial evaluating the effect of adjuvant chemotherapy in resected small bowel adenocarcinoma, termed the BALLAD study (A global study to evaluate the potential benefit of adjuvant chemotherapy for small bowel adenocarcinoma).

In duodenal cancer, its retroperitoneal location and resultant higher risk for locoregional failure has led to the frequent use of adjuvant chemoradiation. Although support for this approach is limited, one recent retrospective series from Duke University found a trend toward improved 5-year overall survival for those patients with an R0 resection who received adjuvant or neoadjuvant fluoropyrimidine-based radiation therapy compared with patients who underwent surgery alone (83% vs. 53%; p = 0.07).\textsuperscript{19} Of further note, neoadjuvant chemoradiation for duodenal adenocarcinomas has been shown to be safe, with a number of studies reporting evidence of robust tumor downstaging in the pathologic specimens.\textsuperscript{19,20} This approach deserves further investigation as cases of locally advanced unresectable disease have been converted to resectable disease following neoadjuvant therapy.\textsuperscript{20}

### Table 1. Studies of Systemic Chemotherapy for Advanced Small Bowel Adenocarcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>Tx Line</th>
<th>N</th>
<th>Chemotherapy</th>
<th>RR (%)</th>
<th>Median OS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McWilliams\textsuperscript{21}</td>
<td>2012</td>
<td>Phase II (NCCTG)</td>
<td>1st</td>
<td>28</td>
<td>Capecitabine + oxaliplatin + irinotecan</td>
<td>42</td>
<td>13</td>
</tr>
<tr>
<td>Xiang\textsuperscript{22}</td>
<td>2012</td>
<td>Phase II (China)</td>
<td>1st</td>
<td>33</td>
<td>FOLFIRI</td>
<td>49</td>
<td>15.2</td>
</tr>
<tr>
<td>Overman\textsuperscript{23}</td>
<td>2008</td>
<td>Phase II (MDACC)</td>
<td>1st</td>
<td>30</td>
<td>CAPOX</td>
<td>50</td>
<td>20.4</td>
</tr>
<tr>
<td>Gibson\textsuperscript{24}</td>
<td>2005</td>
<td>Phase II (ECOG)</td>
<td>1st</td>
<td>38</td>
<td>FAM</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Tsushima\textsuperscript{27}</td>
<td>2012</td>
<td>Retrospective</td>
<td>1st</td>
<td>60</td>
<td>Fluoropyrimidine monotherapy</td>
<td>22</td>
<td>13.9</td>
</tr>
<tr>
<td>Zhang\textsuperscript{28}</td>
<td>2011</td>
<td>Retrospective</td>
<td>1st</td>
<td>28</td>
<td>FOLFIRI/Capecitabine</td>
<td>32</td>
<td>14.2</td>
</tr>
<tr>
<td>Koo\textsuperscript{29}</td>
<td>2011</td>
<td>Retrospective</td>
<td>1st</td>
<td>40</td>
<td>Fluoropyrimidine based</td>
<td>11</td>
<td>11.8</td>
</tr>
<tr>
<td>Zaanan\textsuperscript{30}</td>
<td>2010</td>
<td>Retrospective</td>
<td>1st</td>
<td>48</td>
<td>FOLFIRI</td>
<td>34</td>
<td>17.8</td>
</tr>
<tr>
<td>Zaanan\textsuperscript{34}</td>
<td>2010</td>
<td>Retrospective</td>
<td>2nd</td>
<td>28</td>
<td>FOLFIRI</td>
<td>20</td>
<td>10.5</td>
</tr>
<tr>
<td>Overman\textsuperscript{31}</td>
<td>2008</td>
<td>Retrospective</td>
<td>1st</td>
<td>29</td>
<td>5-FU + platinum</td>
<td>41</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51</td>
<td>Various agents</td>
<td>16</td>
<td>12</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; CAPOX, capecitabine and oxaliplatin; ECOG, Eastern Cooperative Group; FAM, 5-FU, doxorubicin, mitomycin C; FOLFIRI, leucovorin, 5-FU, and irinotecan; FOLFOX, 5-FU and oxaliplatin; m, months; MDACC, MD Anderson Cancer Center; N, number of patients; NCCTG, North Central Cancer Treatment Group; OS, overall survival; RR, response rate; Tx, treatment.
similar to colorectal cancers than gastric cancers. Furthermore, a number of studies have shown that HER2 amplification or overexpression is extremely rare in duodenal adenocarcinoma. In an effort to determine whether small bowel adenocarcinomas are similar to gastric cancers in terms of responsiveness to taxanes, we are conducting a phase II study of nab-paclitaxel in small bowel adenocarcinoma (Table 2).

**CONCLUSION**

Research in rare tumor types is challenging and collaborative; multi-institutional efforts are needed. Although the molecular biology of small bowel adenocarcinoma is limited, the low rate of APC mutations stands out as an intriguing molecular difference in comparison with colorectal cancer. Further elucidation of the molecular underpinnings of small bowel adenocarcinoma may provide insights as to the protective factors responsible for the dramatic 50-fold difference in incidence between small bowel and large bowel cancers. This large difference in incidence does not justify screening for small bowel cancer in the general population. However, given the increased risk of small bowel adenocarcinoma among patients with celiac disease, Crohn’s disease, or HNPCC, screening studies which utilize newer diagnostic tools deserve investigation.

Surgical resection represents the mainstay of treatment for locoregional disease. Although no data support the use of adjuvant chemotherapy, the risk of distant relapse, the reproducible activity of systemic chemotherapy in the metastatic setting, and extrapolation of results from adjuvant therapy in colorectal cancer all support investigation of adjuvant fluoropyrimidine-based chemotherapy for small bowel adenocarcinoma.

Fluoropyrimidine and oxaliplatin represent the standard front-line chemotherapy combination. Given the rarity of this cancer, enrollment in clinical trials exploring novel agents is strongly encouraged. In the last 5 years, three prospective clinical trials in this disease have been reported, which contrasts with the one clinical trial in the preceding years, and represents a positive step forward. It is hoped that an improved molecular understanding of this cancer will enable a future generation of novel studies aiming to improve the outcomes for patients with this rare cancer.

**ACKNOWLEDGMENT**

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### TABLE 2. Current Clinical Trials for Advanced Small Bowel Adenocarcinoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Tumor Type</th>
<th>Tx Line</th>
<th>N</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPOX + bevacizumab</td>
<td>II</td>
<td>SBA +ampullary</td>
<td>1st</td>
<td>30</td>
<td>NCT00354887</td>
</tr>
<tr>
<td>Capecitabine/oxaliplatin/irinotecan</td>
<td>II</td>
<td>SBA</td>
<td>1st</td>
<td>33</td>
<td>NCT02435550</td>
</tr>
<tr>
<td>CAPOX + panitumumab (KRAS wild-type only)</td>
<td>II</td>
<td>SBA +ampullary</td>
<td>1st</td>
<td>20</td>
<td>NCT0202409</td>
</tr>
<tr>
<td>GEMOX + erlotinib</td>
<td>Ib</td>
<td>Duodenal +ampullary</td>
<td>1st</td>
<td>22</td>
<td>NCT00987766</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>II</td>
<td>SBA</td>
<td>≥ 2nd</td>
<td>10</td>
<td>NCT01730586</td>
</tr>
</tbody>
</table>

Abbreviations: CAPOX, capecitabine and oxaliplatin; GEMOX, gemcitabine and oxaliplatin; N, number of patients; SBA, small bowel adenocarcinoma; Tx, treatment. Chemotherapy dosing determined based upon UGT1A1 genotype.

### Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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### References

3. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The epidemiology and
GASTROINTESTINAL (NONCOLORECTAL) CANCER

The Many Faces of Hepatocellular Carcinoma: From Biology to Treatment

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How Do Mechanisms of Hepatocarcinogenesis (HBV, HCV, and NASH) Affect Our Understanding and Approach to HCC?

Philip J. Johnson, MD

OVERVIEW

The major etiologic factors for hepatocellular carcinoma (HCC), including chronic hepatitis B and C virus infections and nonalcoholic fatty liver disease, are now well established by epidemiologic investigations. The mechanisms by which these factors result in HCC have been extensively investigated but have not, to date, resulted in the development of specific therapeutic interventions. Other frequently occurring dysregulated pathways, including the Wnt/β-catenin signaling pathway, are proving difficult to target, but there are early suggestions that patients with “MET-high” HCC may benefit from the c-MET inhibitor tivantinib. Chronic inflammation and consequent cell damage and regenerative proliferation are common to all etiologic factors, and emerging evidence suggests that anti-inflammatory agents such as aspirin deserve further investigation as preventive agents.

It is the holy grail of translational research to show that understanding the molecular basis of cancer will lead to new or enhanced therapy. Such an approach is scientifically attractive and contrasts with cancer chemotherapy that uses cytotoxic drugs where the molecular mechanism of the available drugs is not well understood and where the drugs are seldom rationally designed. Furthermore, the “trial and error” approach conventionally applied to cancer chemotherapy that leads to regular but usually marginal improvements are again intellectually unsatisfying.

Clinical and epidemiologic approaches have, over the last 50 years, been very successful in identifying what might be called the “primary” etiologic factors for hepatocellular carcinoma (HCC)—namely the hepatitis C virus (HCV), the hepatitis B virus (HBV), and nonalcoholic steatohepatitis (NASH) as implied in the title of this review. Furthermore, it has to be noted that approaches to the prevention of HCC based on this understanding, even in the absence of any understanding of the downstream disease mechanisms, have had several major successes such as immunization against the HBV and antiviral therapy of chronic HBV and HCV.

The question that the title poses is how our understanding of the mechanism by which these agents cause cancer affects our clinical approach. The emphasis on mechanism is important. Certainly, etiology will have an impact on management. For example, if the etiology is HBV infection, it will be relevant to review other members of the family and here, as with hepatitis C, antiviral therapy will need to be considered. In the case of alcohol, abstinence with a view to improving, or at least avoiding further deterioration of liver function, is an important and effective intervention. None of these, however, relate to the mechanism of disease and, as such, are not considered further. There are some molecular pathways, the dysregulation of which form attractive and tractable targets, and these are mentioned only briefly as, again, at the present time they are not clearly related to a specific etiology.

Before reviewing each individual etiologic agent, there is one particular confounding factor that must be considered and that is the consistent association of HCC with chronic liver disease and cirrhosis.

DIRECT AND INDIRECT PATHWAYS TO HCC: THE ROLE OF CHRONIC LIVER DISEASE AND HEPATIC CIRRHOSIS

The hypothesis arises that, since all factors that cause chronic liver disease are associated with HCC, it is possible that it is the inflammation and consequent cell damage caused by these various risk factors that is implicated in the pathogenesis of HCC rather than any etiology-specific mechanism. In this respect, it is often postulated that this may not be the case since some cases of HCC arise in the absence of cirrhosis, often called “noncirrhotic HCC.” This diagnosis of noncirrhotic HCC is not as simple as it may at first seem. To some, the term simply means that the associated chronic liver disease has not reached the stage of cirrhosis; to others, it means...
that there is no underlying liver disease at all. When HCC arises in the latter situation, it is taken as evidence that any associated etiologic factor, such as HBV or HCV, is acting as a directly oncogenic agent.

Even then the term noncirrhotic may be a difficult diagnosis since it is often made on the basis of clinical features. For example, in the classic study by Beasley and colleagues, which showed the magnitude of the risk of HCC in carriers of HBV, it was noted that although many HCC cases were classified as “noncirrhotic” on entry into the study, based on the lack of any clinical features of cirrhosis, among those who came to autopsy most actually had cirrhosis. Furthermore, although it is clear that when HCC is diagnosed it is usually within a cirrhotic liver, this does not mean that the liver was cirrhotic when the cancer first developed, most likely several years before presentation. The reader should, therefore, exercise caution when the suggestion oncogenic potential is based on finding of cases in the noncirrhotic setting unless that latter term is very clearly defined. The fact remains that the great majority of HCC cases arise in the setting of chronic liver disease and usually present when that disease process is at a cirrhotic stage.

THE HEPATITIS B VIRUS

Hepatitis B virus is the most common cause of HCC on a worldwide basis, being responsible for approximately 75% of cases; over 80% of the annual burden of around 750,000 cases are reported to occur in China, Southeast Asia, or Sub-Saharan Africa. It is important to note that the virus is contracted at birth or during the first few years of life in these high-risk areas, and that the risk is exacerbated by exposure to the carcinogen aflatoxin, derived from the mold aspergilum fumus. Thus exposure to the etiologic agent (HBV) is usually for a much longer period than is the case with other factors.

HBV is a hepadnavirus family. It is not a retrovirus despite using reverse transcription in its complex replication pathway. The virion consists of an outer lipid envelope and protein core. The genome is packaged as partially double-stranded DNA, 3.5 kb in length. There are four genes encoded by the genome. Gene C encodes the core protein, HBcAg; the P gene encodes the DNA polymerase; the S gene encodes the surface antigen (HBsAg); and the X gene encodes a protein HBx, the “x” referring to its uncharacterized function. Its possible role in hepatocarcinogenesis is discussed below.

The mechanism by which HBV results in HCC has been intensively investigated for more than 40 years but remains unclear. Most authorities have concluded that there are multiple pathways involved, including the accumulation of genetic damage due to immune-mediated hepatic inflammation, more virus-specific mechanisms involving, for example, the viral gene X (HBx), and insertional mutagenesis with integration of HBV DNA into the host genome to alter the function of endogenous genes or induce further chromosomal instability.

Early studies suggested that viral integration into the host gene seemed the most likely mechanism, but consistent integration sites were not detected and the studies were not able to identify any preferred site or gene for HBV integration; HBV integration seemed to occur randomly. Later studies revealed a small number of “recurrent” integration sites, typically close to or inside of the certain targeted genes, such as the telomerase reverse transcriptase (TERT) gene and MLL4 gene. These have recently been confirmed using whole genome sequencing during which several other recurrent sites have been discovered suggesting that viral integration in the vicinity of genes controlling cellular proliferation and differentiation, may indeed be involved directly in hepatocarcinogenesis.

HBx is a 115 amino acid pleiotropic transactivator. In the cytoplasm it activates mitogenic signaling cascades and in the nucleus it modulates gene expression via interaction with numerous transcription factors including NF-κB, NF AP, and AP 1, thereby dysregulating several cellular processes, including signaling pathways, cellular proliferation, and apoptosis. In a transgenic mouse model (where the transgene incorporates the region encoding amino acids 58 –154 of the HBV X protein and the murine c-myc gene) the sequential development of HCC has been clearly demonstrated.

In the absence of any common target for therapeutic intervention based on the above studies and in the face of growing evidence suggesting that treatment with nucleoside analogs and universal vaccination at the time of birth may decrease the risk of HBV-related HCC development irrespective of how the virus results in HCC, therapeutic approaches based on analysis of underlying mechanisms must remain prospects for the future.

KEY POINTS

- The major etiologic factors for hepatocellular carcinoma, including chronic hepatitis B and C virus infections and nonalcoholic fatty liver disease, are now well established by epidemiologic investigations.
- Most cases arise in the setting of chronic liver disease and present at the stage of cirrhosis.
- Despite extensive investigations, the molecular mechanisms of hepatocarcinogenesis remain unclear, and their study has not yet resulted in etiology-specific approaches to treatment.
- Although the Wnt/β-catenin pathway is aberrant in most HCCs, it has proved difficult to target, but patients classified as “MET-high” appear to benefit from the c-MET kinase inhibitor, tivantinib.
- Anti-inflammatory drugs such as aspirin warrant further investigation as agents that may prevent progression of chronic liver disease to HCC.
**THE HEPATITIS C VIRUS**

Extensive and convincing epidemiologic evidence suggest that chronic infection with the hepatitis C virus is responsible for a significant proportion of HCC.14

Unlike HBV, HCV is a positive stranded RNA virus that replicates in the cytoplasm and does not have the potential to integrate into the host genome. There is no doubt that HCC arises mainly in those with chronic liver disease. It is presumed that chronic persistence of the virus results in immune-mediated chronic inflammation that stimulates progressive fibrosis implying that an indirect mechanism is at play. After entry into the hepatocyte, the HCV core protein enters the host cell and activates several signaling pathways such as p38 MAPK and NF-κB, which in turn leads to cytokine production and consequent inflammation and disruption of apoptotic pathways. Other pathways that may induce inflammation include the nonstructural proteins NS3 and NSSA acting via oxidative stress. To this extent it appears that the mechanism of HCV-related hepatic carcinogenesis is likely to be similar to that in other types of cirrhosis related HCC.15,16

However, other lines of evidence have been proposed that suggest a direct role for HCV,15,16 including the higher rate of HCC in the HCV-infected liver than in other types of cirrhosis, such as autoimmune hepatitis, although the major risk factors for HCC are increasing age and male gender, and autoimmune hepatitis is predominantly a disease of younger females. More convincing is the occurrence, in the noncirrhotic liver, of HCC in some strains of transgenic mice.

Several transgenic mouse lines that express HCV protein have been developed, although it should be noted that in such models there is no virus replication. Some of these, particularly where core protein and/or envelope proteins E1 and E2 are expressed highly, consistently develop HCC, with steatosis in the absence of any inflammatory response thereby suggesting a direct role for HCV. However, in a detailed and balanced review of this evidence, McGovern and Lemon conclude that although in some phenotypes both structural and nonstructural HCV proteins appear to be involved, it is “disconcerting” that there is considerable variation in the lineages and that no single protein consistently causes cancer when expressed at levels seen in the human situations.15,16

With rapidly improving antiviral therapy for chronic HCV infection and increasing evidence that this dramatically reduces the incidence of HCC,17 it seems likely that this approach will be favored over the next decade. Although there are clearly cost implications for antiviral therapy, it must be remembered that it has benefits not just on HCC development but on other forms of HCV-related mortality and morbidity, and any therapeutic approach based on an understanding of HCV-related pathways is likely to be just as expensive.

**NONALCOHOLIC FATTY LIVER DISEASE**

There is a strong association between obesity and HCC and in an early large-scale study, the relative risk of dying from liver cancer was 4.5 for men with a body mass index of 35 kg/m² or above compared to those with a normal body mass index.18 Obesity is, in turn, associated with the metabolic syndrome of insulin resistance and type 2 diabetes. In a population-based study including 14% of the United States population, diabetes conferred a 3-fold risk of HCC.19 The hepatic manifestation of obesity and metabolic syndrome is nonalcoholic fatty liver disease. Although most individuals with NAFLD have isolated steatosis, approximately 20% of all cases present as steatohepatitis (NASH), which is microscopically defined and consists of steatosis, hepatocellular injury, parenchymal and portal inflammation, and variable degrees of fibrosis with the potential to progress to cirrhosis. Based on its prevalence and natural history, NAFLD in developed countries may become the primary source of HCC and offset the impact of successful measures on reducing the incidence of hepatitis C virus–related liver cancer.

**Mechanism of Carcinogenesis in NAFLD**

The most convincing hypothesis is that it is the low-grade systemic inflammatory response to obesity that initiates the metabolic syndrome and encourages progression from steatosis to NASH.20 Excessive fat in the liver promotes the release of pro-inflammatory cytokines, which are central to the pathogenesis of NASH and its sequelae. Tumor necrosis factor, in particular, activates pro-oncogenic pathways involving NF-κB, JNK, the mammalian target of rapamycin and extracellular signal-regulated kinases. Interleukin-6 (IL-6) is also involved and exerts proliferative and antiapoptotic effects through activation of STAT3. Animal models have recently been developed and these confirm the importance of TNF and other cytokines.20-22

**Other Nonetiologically Related Targets**

The Wnt/β-catenin signaling pathway is dysregulated in the majority of cases of advanced HCC23; though inhibition of this pathway has antitumor effects in HCC cell lines, practical molecular targeting is proving challenging.24 Nonetheless, encouraging results are starting to be seen using agents specific to a particular dysregulated molecular pathway. One of the best examples is tivantinib, although the relevant trial focused on patients with advanced HCC irrespective of the etiology. Thus, in a small subset of patients in a randomized phase II study that compared tivantinib, a c-MET tyrosine kinase inhibitor, to best supportive care in the second-line setting for patients with advanced HCC, patients with “MET-high” HCC (MET ≥ 2 in >50% of tumor cells by immunohistochemistry) saw improvement in progression-free survival (PFS). There was preliminary evidence of an overall survival (OS) trend favoring tivantinib despite the fact that cross-over to open-label tivantinib was allowed after progressive disease.25 A prospective randomized phase III trial is currently underway, again targeting patients with “MET-high” HCC.

Sorafenib is the current standard of care for patients with advanced cancer. There are now three large phase III clinical trials in which sorafenib has been used either as the trial agent (The SHARP study, sorafenib vs. placebo) or as the control arm (against sunitinib and brivanib).26-28 In all of these, the
survival was greater in the patient subgroup, which had chronic HCV than in the alternative arm of the trial. However, it must be emphasized that these were not preplanned analyses and thus must be considered with great caution; sorafenib should not be considered an etiologically targeted agent on the basis of present data.

Recent studies report that aspirin (and perhaps NSAIDs [nonsteroidal anti-inflammatory drugs]) decreases the risk of HCC among patients with chronic liver disease. Aspirin nonselectively inhibits both COX-1 and COX-2 and presumably acts in an anti-inflammatory role. Since chronic inflammation and consequent cell damage/death and resultant cellular proliferations seem to be common to all the etiological factors for HCC, aspirin might be considered as a therapeutic approach that does indeed target the pathways of carcinogenesis driven by the recognized etiological agents. Many remain skeptical although this report is only one of an increasing number of methodologically rigorous studies suggesting a role for aspirin in cancer prevention, even suggesting that aspirin may have an impact on disease progression. The accompanying editorial gives a well-balanced assessment of the implications of this research. Other reports that statins may decrease the risk of HCC in HBV patients should also be noted.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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References


Novel Therapeutics in Hepatocellular Carcinoma: How Can We Make Progress?

Robin K. Kelley, MD, and Alan P. Venook, MD

OVERVIEW

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death globally, and its prevalence and impact are even more profound because sorafenib is the only systemic therapy proven to prolong survival in patients with advanced disease. Randomized phase III trials of other novel targeted agents including sunitinib, linifanib, brivanib, and the combination of sorafenib plus erlotinib have failed to improve overall survival compared with sorafenib as a single agent in the first line setting, as well as compared with placebo in the second-line setting, in the case of brivanib. These negative studies are a sobering reminder of the challenges to clinical research in HCC, including the competing comorbidity of liver dysfunction, marked clinical and biologic heterogeneity, and the unreliability of surrogate endpoints to accurately predict survival. To address these challenges, HCC-specific phase I/ib cohorts must be used to define the maximum tolerated dose and drug exposure in this organ dysfunction population with high background rates of adverse events and little tolerance for superimposed treatment-related toxicity. Pooled analyses of contemporary randomized trials and database studies should be undertaken to define the strongest prognostic factors for stratification in future phase III studies. Research blood and archival tumor specimens should be collected from patients on clinical trials to intensify the search for biomarkers of responsive or resistant subsets, in parallel with ongoing efforts to improve on radiographic response assessment. Collectively, these and other new strategies are needed to make progress in identifying active novel therapeutics for patients with HCC.

Despite its enormous global impact as the third leading cause of cancer death worldwide, treatment options for advanced HCC remain extremely limited and outcomes grim. The multikinase inhibitor sorafenib is the only agent known to confer a survival benefit in advanced HCC, modestly prolonging overall survival compared with placebo (10.7 vs. 7.9 months, p < 0.001) in the SHARP trial. The failure of sunitinib, linifanib, brivanib, and the combination of sorafenib plus erlotinib to improve on sorafenib alone, and of brivanib to improve on placebo after first-line therapy, in recent comparative trials is a sobering reminder of the complexities of treating patients with HCC.

ACCOUNTING FOR THE COMPETING COMORBIDITY OF LIVER DISEASE IN CLINICAL TRIALS

A fundamental challenge in HCC is the coexistence of underlying liver injury and hepatic dysfunction as the premalignant environment in greater than 80% of patients. This pervasive problem is a competing cause of death but also has the potential to substantially affect drug metabolism and toxicity, as well as to increase the risk for a wide array of unrelated adverse events.

It is often difficult to discern the relationship of treatment to toxicity in HCC studies in the setting of hepatic dysfunction. Serious adverse event (SAE) rates (all-cause) reported in patients treated with single-agent sorafenib range from 36% to 55% in recent phase III trials, although this is not dissimilar to the rates of SAE reported in patients on placebo arms in these studies (45% to 57%). Overall, however, treatment-related event rates other than SAE generally appear higher in the experimental arms than the placebo arms across studies, though they have not been formally compared (Table 1). In recent sorafenib-controlled studies, toxicity in the experimental arms appears to parallel the experience in the placebo-controlled studies, with higher rates of toxicity.
and/or treatment discontinuation in experimental arms observed in relation to controls (Table 1).3,4,6,7

Adverse events (AE) in HCC trials result in frequent dose-reductions, delays, and discontinuations across studies, which collectively suggest the potential to affect efficacy outcomes and mask identification of active therapies (Table 2). In the SHARP trial experimental and placebo arms, respectively, AE resulted in dose reductions in 26% and 7% and drug discontinuation in 38% and 37% (with 11% and 5% attributed as treatment-related events in each arm).2 The GIDEON registry (a global survey of the real-world use of sorafenib) findings corroborate that over one-third of patients with Child Pugh A (37%) require dose reductions.11 Similarly, sorafenib-controlled studies show that dose modifications also are required in a substantial proportion of all patients, perhaps more so in the experimental arms (Table 2).3,4,6,7 These trends further support the hypothesis that treatment-related toxicity, superimposed on high rates of background adverse events in liver dysfunction patients, may substantially affect dose intensity and exposure to novel therapeutics in clinical trials and confound efficacy analyses.

Acknowledging liver disease as an immutable baseline factor in HCC populations, how can we reduce the degree of superimposed treatment-related toxicity in HCC clinical trials? In the trials cited in Tables 1 and 2, the high rates of all-cause and treatment-related toxicity and dose modifications occurred despite stringent eligibility criteria, which restricted enrollment to patients with Child-Pugh A liver disease, a clinical trial strategy to minimize background comorbidity rates in HCC clinical trials.12 Though improved tools to risk-stratify baseline liver disease could reduce the competing comorbidity of liver disease in patients entering clinical trials, such approaches, which further winnow the eligible HCC population, would adversely affect accrual rates as well as limit the applicability to the broader advanced HCC population.

Instead, these data suggest that the maximum tolerated dose (MTD) in all-comer phase I trials may exceed that in HCC populations. This hypothesis supports disease-specific dose-finding and pharmacokinetic (PK) and pharmacodynamics (PD) studies in HCC cohorts, instead of the conventional model of extrapolating from doses and PK/PD data in all-comer phase I studies. Conventionally, phase II and III efficacy studies in patients with HCC have been undertaken by using doses identified from all-comer phase I studies, without HCC-specific phase I studies. It is certainly possible that assessment of efficacy could be confounded by administration of doses exceeding the MTD in an HCC population.

Another important question pertaining to the study of investigational therapeutics in populations of patients with HCC is whether all-cause organ dysfunction studies accurately recapitulate the cumulative effect of cirrhosis on hepatic metabolism across drugs and metabolic pathways. The

### TABLE 1. Adverse Event Rates in Randomized Phase III Trials in HCC

<table>
<thead>
<tr>
<th>RP3 Study and Treatment Arms</th>
<th>All-Cause SAE (p)</th>
<th>AE Differences Between Treatment Arms (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOR versus placebo (SHARP)2</td>
<td>52% versus 54% (NS)</td>
<td>45% versus 32% (p = 0.04) (all-cause, treatment-emergent)</td>
</tr>
<tr>
<td>SOR versus placebo (Asia-Pacific)3</td>
<td>47.7% versus 45.3% (NS)</td>
<td>81.9% versus 38.7% (NR) (treatment-related, all grades)</td>
</tr>
<tr>
<td>SUT versus SOR4</td>
<td>44% versus 36% (NR)</td>
<td>82% versus 73% (NR) (all-cause, ≥ grade 3)</td>
</tr>
<tr>
<td>LIN versus SOR5</td>
<td>52.4% versus 38.5% (p &lt; 0.001)</td>
<td>85.3% versus 75.0% (p &lt; 0.001) (all-cause, ≥ grade 3)</td>
</tr>
<tr>
<td>SOR vs ERLOT versus SOR6*</td>
<td>58% versus 54.6% (NS)</td>
<td>95.0% versus 95.2% (NS) (treatment-related, all grades)</td>
</tr>
<tr>
<td>BRIV versus SOR (BRISK-FL)7*</td>
<td>59% versus 52% (NR)</td>
<td>NR</td>
</tr>
<tr>
<td>BRIV versus placebo (BRISK-PS)8</td>
<td>63% versus 57% (NR)</td>
<td>92% versus 62% (NR) (treatment-related, all grades)</td>
</tr>
</tbody>
</table>

Abbreviations: HCC, hepatocellular carcinoma; RP3, randomized phase III; SAE, serious adverse event; AE, adverse event; NS, not significant; NR, not reported; SOR, sorafenib; SUT, sunitinib; LIN, linifanib; ERLOT, erlotinib; BRIV, brivanib.

* Discontinuation rate due to adverse events was numerically higher on experimental arm (see Table 2).

Note: p values are provided only when reported.
original studies of chemotherapeutics (paclitaxel and gemcitabine) in patients with organ dysfunction led the National Cancer Institute Organ Dysfunction Working Group (ODWG) to define liver dysfunction by aspartate aminotransferase and bilirubin levels in all-cause hepatic dysfunction populations. These criteria show modest association with Child Pugh score but have not been comprehensively examined for association with toxicity, PK, or PD in cirrhotics compared with patients with other causes of liver dysfunction (such as hepatitis, metastatic disease, biliary obstruction, or hepatotoxicity from previous chemotherapy). This important unanswered question suggests a role for future studies to determine concordance of ODWG criteria with the degree of hepatic dysfunction in HCC and cirrhotic populations in general.

### CLINICAL HETEROGENEITY OF HCC: TO LUMP OR TO SPLIT, AND HOW?

Identifying active novel therapeutics in advanced HCC is also obscured by the marked heterogeneity in outcomes across populations and studies. This heterogeneity prohibits meaningful cross-study comparisons and mandates randomized trials to interpret efficacy end points. There is no more graphic example of the hazards of cross-study comparison in HCC than when comparing the SHARP trial with the contemporary Asia-Pacific study. Both were phase III trials of sorafenib compared with placebo in advanced HCC patients, but were conducted in mostly Western compared with Asia-Pacific populations, respectively. Despite the two studies' shared industry sponsorship, trial design, and eligibility, along with the achievement of nearly identical positive hazard ratios (HRs) for improvement in overall survival (HR 0.69 and 0.68, respectively), their absolute outcomes diverged substantially, with median overall survival for sorafenib compared with placebo arms of 10.7 compared with 7.9 months in SHARP by comparison to 6.5 compared with 4.2 months in the Asia-Pacific study. It remains unknown whether this disparity is a result of inherent differences in HCC biology dependent on etiology of liver disease (e.g., hepatitis B compared with C virus infection, alcoholism, nonalcoholic fatty liver disease), pharmacogenetic differences between Asian and Western populations, variations in regional practice patterns in early-stage disease and/or post-sorafenib, or a complex interplay of these and many other factors.

This finding exemplifies why stratification within randomized trials is particularly important to ensure that clinical and pathologic prognostic factors are balanced. In the phase III BRISK-PS trial of brivanib compared with placebo after failure of sorafenib therapy in advanced HCC after first-line therapy, an imbalance between experimental and placebo arms on vascular invasion (31% compared with 18% favoring placebo arm) was identified despite stratification on extrapathic spread and/or vascular invasion, raising the question of whether this imbalance could have contributed to the failure of brivanib to demonstrate survival benefit in this study—something we will never know.

Collectively, these examples underscore the potential effect of stratification factors on outcomes in HCC efficacy studies. From these contemporary randomized phase III datasets, retrospective pooled subset analyses as well as longitudinal database studies of putative and known clinical and pathologic prognostic factors should be undertaken to inform selection of the most impactful stratification factors in future HCC phase III trials. There remains also the important but unanswered question of whether future phase III trials of novel therapeutics in HCC should be conducted separately in Asian and Western populations, and if so, how should these populations be defined?

### COMPLEX TUMOR BIOLOGY: A GOOD BIOMARKER IS HARD TO FIND

Complex tumor biology in HCC underlies the well-characterized clinical heterogeneity of HCC. HCC tumors demonstrate a high degree of genetic instability and heterogeneity attributed to longstanding inflammation and hepatocyte regeneration in the setting of chronic liver injury. Gene expression profiling in HCC suggests the existence of common molecular subclasses in HCC, including distinct groups with greater genetic instability, high grade histology, and poor clinical outcome. Recent comprehensive genotyping efforts in HCC tumors have identified a high rate of

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**TABLE 2. Dose Reductions, Delays, and Discontinuations Due to AE in Randomized Phase III Trials in HCC**

<table>
<thead>
<tr>
<th>RP3 Study</th>
<th>Dose Reductions (p)</th>
<th>Discontinuations (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOR versus placebo (SHARP)²</td>
<td>26% versus 7% (NR)</td>
<td>38% versus 37% (all-cause) (NR), 11% versus 5% (related) (NR)</td>
</tr>
<tr>
<td>SOR versus placebo (Asia-Pacific)³</td>
<td>30.9% versus 2.7% (NR)</td>
<td>19.5% versus 13.3% (all-cause) (NR)</td>
</tr>
<tr>
<td>SUT versus SOR⁴</td>
<td>47% versus 69% (NR)</td>
<td>26% versus 23% (all-cause) (NR)</td>
</tr>
<tr>
<td>LIN versus SOR³</td>
<td>45.3% versus 31.2% (p &lt; 0.001)</td>
<td>36.3% versus 25.4% (all-cause) (p &lt; 0.001)</td>
</tr>
<tr>
<td>SOR + ERLOT versus SOR⁶</td>
<td>NR</td>
<td>34.0% versus 23.8% (all-cause) (NR) (withdrawals after 1 cycle)</td>
</tr>
<tr>
<td>BRIV versus SOR (BRISK-FL)⁷</td>
<td>NR</td>
<td>43% versus 33% (all-cause) (NR)</td>
</tr>
<tr>
<td>BRIV versus placebo (BRISK-PS)⁵</td>
<td>NR</td>
<td>23% versus 7% (related) (NR)</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse events; HCC, hepatocellular carcinoma; RP3, randomized phase III; NS, not significant; NR, not reported; SOR, sorafenib; SUT, sunitinib; LIN, linifanib; ERLOT, erlotinib; BRIV, brivanib.

Note: p values are provided only when reported.
somatic mutation without frequently recurring activation of known driver oncogenes; however, a sobering common theme in carcinogen-induced cancers. An update on the complex mechanisms of hepatocellular carcinogenesis is presented separately in Dr. Philip Johnson’s companion manuscript in this Educational Book.

In the setting of complex tumor biology, the paucity of available tumor tissue for the identification of biomarkers of response or resistance in HCC makes matters worse. The difficulty in obtaining research tumor specimens in HCC can be attributed, in part, to the acceptance of radiographic diagnosis without biopsy in HCC as well as to the scant material often obtained from fine needle aspirations when biopsies are performed, because of concerns for bleeding and biopsy track seeding. The SHARP trial again serves as an informative example, having successfully collected baseline and on-treatment research blood samples for biomarker research in 81.6% and 50.7% of the overall study population, respectively, by comparison with collection of archival tumor tissue samples in only 18%. These specimens should be obtained not only in the context of embedded research biopsies for clinical trials under the auspices of informed consent, but also as a standard of care if criteria for radiographic diagnosis are not stringently met.

The selective MET inhibitor, tivantinib (ARQ 197) is an example of a novel therapeutic with potential activity identified by a tumor tissue biomarker enrichment strategy in HCC. In a randomized phase II study, patients with high MET expression by immunohistochemistry (IHC) treated with tivantinib (22 patients) compared with placebo (15 patients) had significantly longer time to progression (TTP) (2.7 vs. 1.4 months, p = 0.03). Based on this randomized phase II data, a phase III trial of tivantinib compared with placebo in second-line HCC patients with high MET expression is ongoing (NCT01755767). Another example of a promising biomarker in HCC is glypican-3 (GPC3), being examined in a randomized, placebo-controlled phase II trial (NCT01507168) as a predictive marker for a recombinant monoclonal antibody targeting GPC3, GC33, based on phase I data suggesting longer TTP in patients with GPC3-high disease. Table 4 presents a selection of new targeted agents under study in HCC. These examples in HCC highlight the potential of biomarker enrichment to identify active novel therapeutics and again underscore the importance of "

### Table 3. Response-Derived Endpoints and Overall Survival in Randomized Phase III Trials in HCC

<table>
<thead>
<tr>
<th>RP3 Study</th>
<th>DCR (p)</th>
<th>TTP (p)</th>
<th>OS (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOR versus placebo (SHARP)²</td>
<td>43% versus 32% (p = 0.002)</td>
<td>5.5 versus 2.8 mo. (p &lt; 0.001)</td>
<td>10.7 versus 7.9 mo. (p &lt; 0.001)</td>
</tr>
<tr>
<td>SOR versus placebo (Asia-Pacific)³⁰</td>
<td>35.3% versus 15.8% (p = 0.0019)</td>
<td>2.8 versus 1.4 mo. (p = 0.0005)</td>
<td>6.5 versus 4.2 mo. (p = 0.014)</td>
</tr>
<tr>
<td>SUT versus SOR⁴</td>
<td>NR</td>
<td>4.0 versus 4.1 mo. (NS)</td>
<td>81 versus 10.0 mo. (p = 0.0019)</td>
</tr>
<tr>
<td>LIN versus SOR⁵</td>
<td>13.0% versus 6.9% (NR)</td>
<td>5.4 versus 4.0 mo. (p = 0.001)</td>
<td>91 versus 9.8 mo. (NS)</td>
</tr>
<tr>
<td>SOR + ERLOT versus SOR⁶</td>
<td>43.9% versus 52.5% (NR)</td>
<td>3.2 versus 4.0 mo. (p = 0.91)</td>
<td>95 versus 8.5 mo. (p = 0.2)</td>
</tr>
<tr>
<td>BRIV versus SOR (BRISK-FL)⁷</td>
<td>12.0% versus 8.8% (NR)</td>
<td>4.1 versus 4.2 mo. (p = 0.85)</td>
<td>95 versus 9.9 mo. (NS)</td>
</tr>
<tr>
<td>BRIV versus placebo (BRISK-PS)⁸</td>
<td>79.2% versus 49.1% (p &lt; 0.0001)</td>
<td>4.2 versus 2.7 mo. (p = 0.0001)</td>
<td>9.4 versus 8.2 mo. (p = 0.33)</td>
</tr>
</tbody>
</table>

Abbreviations: HCC, hepatocellular carcinoma; RP3, randomized phase III; NS, not significant; NR, not reported; DCR, disease control rate; TTP, time to progression; OS, overall survival; mo., months; SOR, sorafenib; SUT, sunitinib; LIN, linifanib; ERLOT, erlotinib; BRIV, brivanib.

Note: p values are provided only when reported.

### Table 4. Selected New Agents and Targets in Clinical Development in HCC

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Trial Design*</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine deprivation</td>
<td>ADI-PG20 (pegylated arginine deiminase)</td>
<td>RP3</td>
<td>NCT01287585</td>
</tr>
<tr>
<td>GPC-3</td>
<td>GC33 (anti-glypican 3 Ab)</td>
<td>RP2, stratified on GPC-3 IHC</td>
<td>NCT01507168</td>
</tr>
<tr>
<td>Immune modulation</td>
<td>JY-594 (oncolytic poxvirus) Lenalidomide (IMiD) Tremelimumab (anti-CTLA4 Ab)</td>
<td>RP2, Phase II</td>
<td>NCT0378555</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT01545804</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT0008358</td>
</tr>
<tr>
<td>MET</td>
<td>Cabozantinib (multikinase inhibitor) Tivantinib (MET inhibitor)</td>
<td>RP3, Phase II</td>
<td>NCT pending</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT0177397</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT01035229</td>
</tr>
<tr>
<td>mTOR</td>
<td>CC-223 (TORC1/2 inhibitor) Everolimus (mTOR inhibitor)</td>
<td>Phase II/II</td>
<td>NCT pending</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT01040347</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Cabozantinib (multikinase inhibitor) Ramucirumab (anti-VEGFR Ab)</td>
<td>RP3, Phase III</td>
<td>NCT pending</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT01040347</td>
</tr>
</tbody>
</table>

Abbreviations: HHC, hepatocellular carcinoma; RP3, randomized phase III; RP2, randomized phase II; Ab, antibody; IHC, immunohistochemistry; VEGFR, vascular endothelial growth factor receptor. Targets and agents are listed alphabetically. Key: * = All studies listed are for ≥ second-line therapy.
obtaining tumor tissue specimens from patients enrolled on therapeutic clinical trials.

INCONSISTENT SURROGATE ENDPOINTS IN HCC TRIALS

The negative trials of linifanib, brivanib, sunitinib, and sorafenib plus erlotinib collectively draw attention to the definitions of go/no-go signals in phase II efficacy studies in HCC. To address the common criticism that these trials did not use randomization in phase II before proceeding to phase III, it is important to note that, even in the larger randomized phase III studies, conventional phase II response-based surrogate end points did not reliably predict overall survival and were sometimes discordant, even within the same study population (Table 3).3,7

Why are drugs failing to improve overall survival despite trends toward or even achieving an improvement in response-based end points? One possible explanation is simple: the drugs truly are not sufficiently active to improve survival and the surrogate end point failed as a result of limitations of standard imaging to discern response compared with progression in HCC, compounded by the inherent inability to adequately blind treatment arms when treating with drugs which confer characteristic symptomatic toxicities. The limitations of conventional response imaging in HCC are widely recognized, which is a discussion beyond the scope of this manuscript.12 Another possible explanation for the unreliability of surrogate end points in HCC hearkens back to the discussion above on the competing comorbidities of liver disease in HCC: perhaps the drugs or combinations do have activity as suggested by response-based end points, but dose modifications and discontinuations as a result of toxicity have contaminated the overall survival results. This concern reinforces the need for disease-specific phase I/Ib trials in HCC in an effort to minimize the effect of differences in drug exposure on efficacy outcomes. A third possibility is that the drugs or combinations may have activity only in subsets and that this activity is obscured by the heterogeneity of randomized phase III populations. This hypothesis supports the need to optimize stratification and identify biomarkers of responsive or resistant subpopulations as discussed above, as well.

Most likely, a complex combination of these factors is at play, which may vary according to individual drugs and clinical trials. Although a clear go/no-go signal for phase II trials in HCC remains difficult to define in the absence of reliable surrogate end points, an appropriate interim strategy is to use randomized phase II designs, careful stratification and biomarker efforts, and attention to overall survival as a secondary end point to inform the interpretation of phase II trial findings.

CONCLUSION

In summary, future progress in HCC clinical research requires a multifaceted approach to address the unique challenges in this disease including underlying liver dysfunction, the high degrees of clinical and biologic heterogeneity, and inconsistent surrogate end points for survival. HCC-specific phase I/Ib cohorts should be used instead of extrapolating from all-comer phase I data to define MTD, PK, and PD in this organ dysfunction population with high background rates of adverse events and little tolerance for superimposed treatment-related toxicity. Pooled analyses of contemporary randomized trials and database studies should be undertaken to define the strongest prognostic factors for stratification in future phase III studies. Research blood and archival tumor specimens must be collected from patients on clinical trials to intensify the search for biomarkers of responsive or resistant subsets, in parallel with ongoing efforts to improve on radiographic response assessment.

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References

5. Llovet JM, D-L Raoul, E Boucher, et al. Brivanib versus placebo in patients with advanced hepatocellular carcinoma (HCC) who failed or were intolerant to sorafenib: results from the phase 3 BRISK-PS study. 2012 International Liver Congress, European Association for the Study of the Liver; Barcelona, Spain.
randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with hepatocellular carcinoma (HCC). 2012 37th ESMO Congress; Vienna, Austria. European Society of Medical Oncology.


GASTROINTESTINAL (NONCOLORECTAL) CANCER

Unresolved Questions in the Management of Gastroesophageal Junction Tumors: Practical Issues in Diagnosis and Treatment

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Despite a plethora of data, the optimal surgical approach to invasive adenocarcinoma of the gastroesophageal (GE) junction remains controversial. To quote Dr. Valerie Rusch, “Strong individual preferences and some degree of surgical mystique often govern the selection of operation for resection of GE junction adenocarcinomas.” The first of these controversies is whether the optimal open surgical approach should be via the transabdominal, transthoracic (two-incision Ivor Lewis or three-incision McKeown), or transhiatal route. Proponents of the transthoracic or transhiatal routes have voiced strong opinions on the potential advantages and disadvantages of each approach (Table 1). It is clear from most large retrospective series that, in experienced hands, excellent results can be achieved by either approach. The principal advantage of the transthoracic route is the ability to perform a radical mediastinal lymphadenectomy en bloc with the primary tumor, the theory being that a more aggressive lymph node dissection would be associated with an improved long-term outcome. To date, however, this association of a more aggressive lymphadenectomy with improved outcome has remained elusive in most gastrointestinal malignancies, including esophageal cancer. Proponents of the transhiatal approach cite similar lymph node retrieval rates, the potential for lower short-term morbidity, and the potential for similar long-term outcomes. With the advent of newer technology, the controversy regarding the optimal surgical approach to adenocarcinoma of the GE junction has evolved in yet another direction, with proponents of a minimally invasive approach, citing even lower perioperative morbidity and mortality, again with comparable or even superior long-term oncologic results.

In this section we will review the high-level evidence summarizing retrospective studies and prospective clinical trials performed to define the optimal open surgical approach, as well as those aimed at defining the role of minimally invasive surgery in the surgical management of patients with invasive adenocarcinoma of the GE junction. Finally, we will emphasize the absolute importance of both surgical expertise and hospital volume in minimizing perioperative morbidity, and perhaps maximizing long-term oncologic outcome.

**CLASSIFICATION OF GE JUNCTION TUMORS**

The most recent version of the AJCC staging system has redefined any cancer involving the GE junction to be an esophageal tumor. This change now groups together tumors of varying epidemiology and pathogenesis into a single category. Siewert has proposed a more useful and therapeutically relevant classification. Siewert type I tumors involve principally the distal esophagus, and are almost invariably associated with chronic Barrett’s changes of intestinal metaplasia and dysplasia, usually caused by chronic GE reflux. These tumors may be associated with potentially premalignant changes in the esophageal mucosa well up into the mediastinum. Although early esophageal dysplasia and even noninvasive mucosal cancers in this location may be successfully managed with endoscopic techniques (resection and/or ablation) combined with effective antireflux procedures, resection of invasive type I adenocarcinoma generally requires removal of the entire esophagus with adjacent primary draining mediastinal lymph nodes; this requirement effectively precludes a transabdominal approach. Siewert type II tumors have their epicenter at the GE junction, with variable degrees of extension both up into the esophagus and down into the proximal stomach. The ability to achieve a negative proximal esophageal margin via a transabdominal approach depends largely on the proximal extent of Siewert type II tumors; it is technically almost impossible to achieve an R0 resection with type II tumors that extend to less than 38 cm from the incisors. The primary lymphatic drainage of these tumors is equally toward the mediastinum and the celiac axis; any procedure that provides access to both regions is appropriate. Finally, as most patients with Siewert type II tumors are treated with radiation as a component of their neoadjuvant therapy, resection of part or all of the thoracic esophagus enables reconstructive anastomosis to nonirradiated esophagus in the neck or upper chest. Siewert type III tumors are true...
gastric cardia cancers involving principally the proximal stomach, up to and including the GE junction. In addition to relatively little esophageal involvement, these tumors have primarily intra-abdominal lymphatic drainage. These tumors are best managed by an abdominal approach, usually by total gastrectomy with en bloc regional perigastric lymphadenectomy.

**OPEN SURGICAL APPROACHES**

Sasako and colleagues reported on the first planned interim analysis of a prospective randomized clinical trial, which assigned patients with cardia and subcardia cancers that could be resected via the transabdominal route to resection via either the transabdominal or left thoracoabdominal approach. After accrual of 167 of a planned 302 patients, the investigators found the left thoracoabdominal approach to be associated with substantially increased morbidity and mortality, with no improvement in survival. With a less than 4% probability of ever being able to show that the more morbid thoracoabdominal procedure would result in a significantly better survival, the trial was closed to further accrual. Of note, the transabdominal approach achieved a comparable number of negative proximal margins, a comparable number of R0 resections, and a comparable number of dissected nodes. The investigators concluded that, for tumors of the cardia and subcardia amenable to resection via the transabdominal route, the left thoracoabdominal approach could not be routinely justified.

There is an abundance of both prospective and retrospective studies describing experience with transthoracic resection, transhiatal resection, as well as experience with both procedures. These studies have been nicely summarized in two large meta-analyses. The first, by Rindani, summarized 44 series describing 2,675 patients undergoing transhiatal and 2,808 patients undergoing transthoracic (Ivor-Lewis) esophagectomy. This study found no significant difference in postoperative morbidity with respect to pulmonary complications, cardiovascular complications, wound infection, or chylous leak. The transhiatal resection group had a higher incidence of anastomotic leaks (16% vs. 10%), anastomotic strictures (28% vs. 16%), and recurrent laryngeal nerve injuries (11.2% vs. 4.8%). The 30-day operative mortality was lower following transhiatal resection (6.3% vs. 9.5%). There was no difference in long-term survival between the two groups. The authors postulated that the differences between these two procedures were so small that a prospective randomized trial with 3,100 patients per arm would be required to define the minor observed differences to be statistically significant. Hulscher and colleagues performed a systematic review of 24 studies comparing transthoracic to transhiatal resections, 15 studies describing transthoracic resections, and 11 studies describing transhiatal resections only. This review included data on 7,527 patients. Compared to patients undergoing transhiatal resection, patients undergoing transthoracic resection had a higher postoperative mortality (9.2% vs. 5.7%), increased blood loss (1000 mL vs. 728 mL), increased pulmonary complications (18.7% vs. 12.7%), increased chylous leak (2.4% vs. 1.4%), increased

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**TABLE 1. Potential Advantages and Disadvantages of the Transthoracic and Transhiatal Approaches to Resection of Invasive Adenocarcinoma of the Esophagus and Gastroesophageal Junction**

<table>
<thead>
<tr>
<th>Potential Advantages</th>
<th>Potential Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transthoracic</td>
<td></td>
</tr>
<tr>
<td>More thorough lymph node dissection</td>
<td>More perioperative morbidity</td>
</tr>
<tr>
<td>Better circumferential margin</td>
<td>Anastomotic leaks more serious</td>
</tr>
<tr>
<td>Fewer anastomotic leaks</td>
<td>Longer operation</td>
</tr>
<tr>
<td>Fewer anastomotic strictures</td>
<td>More blood loss</td>
</tr>
<tr>
<td>Better oncologic outcome (?)</td>
<td>Longer ventilation, ICU and hospital LOS</td>
</tr>
<tr>
<td>Transhiatal</td>
<td></td>
</tr>
<tr>
<td>Lower pulmonary morbidity</td>
<td>More recurrent laryngeal nerve injuries</td>
</tr>
<tr>
<td>Shorter operation</td>
<td>Inadequate lymph node dissection</td>
</tr>
<tr>
<td>Less blood loss</td>
<td>Potential for tracheal injury</td>
</tr>
<tr>
<td>Lower operative mortality</td>
<td>More anastomotic leaks</td>
</tr>
<tr>
<td></td>
<td>More anastomotic strictures</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; LOS, length of stay; QOL, quality of life.

---

**KEY POINTS**

- Transthoracic and transhiatal esophageal resection have different profiles of short-term perioperative morbidity.
- Perioperative mortality is similar after transthoracic or transhiatal esophagectomy in experienced centers.
- Minimally invasive esophagectomy is emerging as a credible alternative to open esophagectomy.
- Hospital volume is a primary determinant of short-term perioperative mortality.
- High hospital volume may be associated with improved long-term outcome.
wound infection (7.7% vs. 4.3%), increased length of ICU stay (11 days vs. 9 days), and an increased length of hospital stay (21 days vs. 18 days). Patients undergoing transthoracic esophagectomy had a lower incidence of cardiac complications (6.6% vs. 19.5%), a lower incidence of anastomotic leakage (7.2% vs. 13.6%), and a lower incidence of vocal cord paralysis (3.5% vs. 9.5%). As in the Rindani’s study, Hulscher found no improvement in cancer-specific survival associated with one surgical approach or the other.

Chang and colleagues performed a large population-based study of outcomes following transhiatal or transthoracic esophagectomy, using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. This study included 225 patients undergoing transhiatal resection and 643 patients undergoing transthoracic esophagectomy. Operative mortality was significantly lower after transhiatal resection (6.7% vs. 13.1%, p = 0.009). Patients undergoing transhiatal esophagectomy were more likely to require endoscopic dilation within 6 months of surgery (43.1% vs. 34.5%, p = 0.02).

After adjusting for differences in tumor stage, patient and provider factors, there was no significant improvement in long-term survival associated with either approach.

There have been five prospective randomized clinical trials comparing the transthoracic to the transhiatal approach in the management of esophageal cancer (Table 2a-c). The first three trials, all reported in the 1990s, were all underpowered; all three studies focused principally on patients with squamous cell carcinoma. More recently, two publications have appeared describing the long-term results of a much larger prospective randomized clinical trial of transhiatal versus transthoracic resection in patients with adenocarcinoma of the GE junction, 80% Siewert type I and 20% Siewert type II. The initial publication focused on morbidity and mortality, whereas the more recent publication focused on long-term cancer-specific outcome. In this prospective trial, pulmonary complications (including atelectasis) were seen more frequently with transthoracic esophagectomy (57% vs. 27%). Transthoracic esophagectomy was associated with

### TABLE 2. (A,B,C): Summary of Results from Prospective Randomized Clinical Trials Comparing TT to TH Resection of Cancer of the Esophagus and Gastroesophageal Junction. Statistically significant differences are noted in bold.

#### 2A.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Patients</th>
<th>Pulmonary Morbidity (%)</th>
<th>CV Morbidity (%)</th>
<th>Vocal Cord Paresis (%)</th>
<th>EBL (cm³)</th>
<th>Leak (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldminc et al.</td>
<td>1993</td>
<td>67</td>
<td>SCC mid-distal 1/3</td>
<td>20</td>
<td>19</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Chu et al.</td>
<td>1997</td>
<td>39</td>
<td>SCC distal 1/3</td>
<td>No difference</td>
<td>16</td>
<td>15</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Jacobi et al.</td>
<td>1997</td>
<td>32</td>
<td>SCC: 6 Adenoca</td>
<td>50</td>
<td>25</td>
<td>18.8</td>
<td>31.3</td>
<td>-</td>
</tr>
<tr>
<td>Hulscher et al.</td>
<td>2002</td>
<td>220</td>
<td>Adenoca mid-distal 1/3</td>
<td>57</td>
<td>27</td>
<td>26</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Chou et al.</td>
<td>2009</td>
<td>87</td>
<td>71 mid:16 distal</td>
<td>12.8</td>
<td>10</td>
<td>0</td>
<td>2.5</td>
<td>-</td>
</tr>
</tbody>
</table>

#### 2B.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Patients</th>
<th>Chylos Leak (%)</th>
<th>OR Time (Minutes)</th>
<th>Ventilation (Days)</th>
<th>ICU Stay (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldminc et al.</td>
<td>1993</td>
<td>67</td>
<td>SCC mid-distal 1/3</td>
<td>-</td>
<td>-</td>
<td>360</td>
<td>240</td>
</tr>
<tr>
<td>Chu et al.</td>
<td>1997</td>
<td>39</td>
<td>SCC distal 1/3</td>
<td>-</td>
<td>-</td>
<td>210</td>
<td>174</td>
</tr>
<tr>
<td>Jacobi et al.</td>
<td>1997</td>
<td>32</td>
<td>SCC: 6 Adenoca</td>
<td>-</td>
<td>-</td>
<td>330</td>
<td>190</td>
</tr>
<tr>
<td>Hulscher et al.</td>
<td>2002</td>
<td>220</td>
<td>Adenoca mid-distal 1/3</td>
<td>10</td>
<td>2</td>
<td>360</td>
<td>210</td>
</tr>
<tr>
<td>Chou et al.</td>
<td>2009</td>
<td>87</td>
<td>71 mid:16 distal</td>
<td>-</td>
<td>-</td>
<td>385</td>
<td>264</td>
</tr>
</tbody>
</table>

#### 2C.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Patients</th>
<th>LOS (days)</th>
<th>Mortality (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldminc et al.</td>
<td>1993</td>
<td>67</td>
<td>SCC mid-distal 1/3</td>
<td>18</td>
<td>20.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Chu et al.</td>
<td>1997</td>
<td>39</td>
<td>SCC distal 1/3</td>
<td>27</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Jacobi et al.</td>
<td>1997</td>
<td>32</td>
<td>SCC: 6 Adenoca</td>
<td>21</td>
<td>23</td>
<td>6.3</td>
</tr>
<tr>
<td>Omloo et al.</td>
<td>2007</td>
<td>205</td>
<td>Adenoca mid-distal 1/3</td>
<td>19</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Chou et al.</td>
<td>2009</td>
<td>87</td>
<td>71 mid:16 distal</td>
<td>34</td>
<td>22</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Abbreviations: CV, cardiovascular; EBL, estimated blood loss; ICU, intensive care unit; LOS, length of stay; OR, operating room; SCC, squamous cell carcinoma; TH, transhiatal; TT, transthoracic.
more blood loss (1900 mL vs. 1000 mL), a longer OR time (360 minutes vs. 210 minutes), an increased incidence of chyloous leakage (10% vs. 2%), a longer mechanical ventilation time (2 days vs. 1 day), a longer ICU stay (6 days vs. 2 days), and a longer hospital stay (19 days vs. 15 days). There were no significant differences in the incidence of cardiac complications, anastomotic leaks, recurrent laryngeal nerve injury, wound infection, or operative mortality. Transthoracic esophagectomy was associated with increased cost.

In the initial report, there was an insignificant trend toward improved outcome in patients undergoing transthoracic esophagectomy. In a follow-up study, the authors confirmed no significant overall survival benefit associated with either approach. In subset analysis, among 90 patients with Siewert type I adenocarcinoma, there was an insignificant trend toward improved survival seen with the transthoracic approach (51% vs. 37%, p = 0.33). In a post hoc subset analysis, among 104 patients with one to eight positive nodes, there was an improvement in 5-year locoregional disease-free and overall survival associated with transthoracic resection (DFS: 64% vs. 23%, p = 0.02; OS 38% vs. 20%, p = 0.05).

There was no survival advantage associated with either approach in patients with negative nodes, or in patients who had more than eight positive nodes.

MINIMALLY INVASIVE ESOPHAGECTOMY

With improvements in technology and surgical instrumentation, enthusiasm for the application of minimally invasive techniques (laparoscopic, thoracoscopic, robotic) in upper GI surgery has steadily increased. The term “minimally invasive” embraces a broad variety of surgical approaches, including hybrid approaches of laparoscopy in the abdomen with open thoracotomy, open laparotomy with thoracoscopy, or entirely laparoscopic and thoracoscopic procedures, or any of these procedures with some component being performed robotically. With increasing experience, the anastomosis to restore GI continuity may be made either in the neck or in the chest. Although there is a learning curve associated with any new surgical technique or technology, with the advent of robotics, minimally invasive approaches are now within the capability of many surgeons who understand the principles of the operation, but who may have not obtained specific advanced laparoscopic/thoracoscopic skills.

The advantages of the minimally invasive approach are self-evident: the same operation can be done with less surgical trauma. These operations hope to achieve at least similar oncologic outcomes with less immediate postoperative morbidity when compared to open surgical approaches. The decreased perioperative morbidity should counterbalance the increased cost of these new technologies, although studies to define this are ongoing.

Dr. James Luketich has led the effort to develop and refine the operation of minimally invasive esophagectomy, a procedure originally described by Cuschieri in 1992. He recently presented his initial experience with minimally invasive esophagectomy on 1,011 patients. Early on in his series, the anastomosis was performed in the neck (MIE-neck, 481 patients); more recently he prefers to perform the anastomosis of the chest (MIE-chest, 530 patients). In this series he describes an overall 30-day operative mortality of 1.7%. Vocal cord paresis was seen in 4%, more often in the MIE-neck (8% vs. 1%, p < 0.001). Anastomotic leak was observed in 5% of patients. In all patients, an average of 20 lymph nodes were retrieved, and 98% of patients achieved a negative histologic margin. The average length of stay was 8 days, with an average ICU length of stay of 2 days. These figures speak to what can be achieved in the context of a dedicated program with substantial experience and expertise in the refinement of a new surgical approach.

In the background of this encouraging experience, a number of centers around the world have embraced this approach, with a corresponding dramatic increase in the number of publications about the procedure.

Biere and colleagues have reported on the initiation of a prospective randomized phase III (MIRO) trial, comparing outcomes of patients with adenocarcinoma or squamous cell carcinoma of the middle or lower third of the thoracic esophagus, randomly assigned to laparoscopic gastric mobilization with open thoracotomy, or to open gastric mobilization with open thoracotomy. All anastomoses will be performed in the neck. The primary endpoint of the study is major postoperative 30-day morbidity; 200 patients are planned to be enrolled in this study.

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quality-of-life indicators showed improvement in the minimally invasive group compared to the open surgery group. Of note, to participate in this trial, surgeons needed to have completed at least 10 minimally invasive esophagectomies and were required to work in institutions where more than 30 esophagectomies per year were performed. The authors concluded that, in experienced hands and in experienced centers, there are short-term advantages to the minimally invasive approach.

Finally, the advent of surgical robotics has opened the field of minimally invasive upper gastrointestinal surgery to a broader array of surgeons. This technology offers improved vision and vastly improved kinetics in comparison to laparoscopy and thoracoscopy. Recently, another prospective randomized clinical trial (the ROBOT trial) has opened. This is a single-center trial being performed in the Netherlands, in which only two experienced surgeons will perform the surgery. Patients with resectable squamous cell or adenocarcinoma of the intrathoracic esophagus will be randomly assigned to an open three-stage transthoracic esophagectomy with cervical anastomosis, or to a robotic-assisted minimally invasive thoraco-laparoscopic esophagectomy during which the thoracic component of the procedure is performed robotically and the abdominal component is performed laparoscopically. The final anastomosis in this group will also be performed in the neck. The primary endpoints of this study are postoperative complications, blood loss, length of stay, and quality of life, with at least similar oncologic outcomes.

OTHER SURGICAL ISSUES
In addition to the optimal open surgical approach, and the role of minimally invasive surgery, there are many other controversial technical aspects of esophagectomy that have been studied. These include the effect of cervical/upper mediastinal lymphadenectomy, the optimal route of esophageal re-construction (posterior mediastinal vs. substernal), the optimal level of anastomosis (cervical vs. thoracic), the optimal anastomotic technique (hand-sewn vs. stapled; one-layer or two-layer hand-sewn; continuous vs. interrupted sutures), the optimal diameter of the anastomosis, the optimal width of the gastric tube, the importance of a pedicled omental flap to protect the anastomosis, the importance of a pyloroplasty, the importance of a drain in the cervical anastomosis, and the role of fibrin glue in minimizing anastomotic leak. Although beyond the scope of this review, data from many prospective clinical trials addressing these issues have been comprehensively summarized by Lagarde.

THE CRITICAL EFFECT OF SURGICAL VOLUME ON OUTCOME
There is an increasingly frequent and very consistent observation that hospital volume has a substantial effect on perioperative morbidity and mortality following complex surgical procedures. This effect is perhaps most dramatically seen following esophagectomy. In a review of the SEER-Medicare database, Begg and colleagues observed a reduction in 30-day mortality from 17.3% to 3.9% following esophagectomy when comparing hospital volumes of 1–5 cases per year to 6–10 cases per year. Birkmeyer, in a review of the national Medicare Claims database and the Nationwide Inpatient Sample, observed a clear trend in reduction of 30-day mortality among 6,337 patients undergoing esophagectomy, from 20.3% in hospitals performing less than two procedures a year, down to 8.4% in hospitals performing over 19 procedures a year. Although the 8.4% mortality figure reported in high-volume hospitals is substantially higher than contemporary high-volume centers are reporting, the trend is clear and consistent across all studies. Markar and colleagues confirmed this in a meta-analysis of series published on surgery for esophageal malignancy. They noted a very clear and consistent trend of reduction in in-hospital mortality, 30-day mortality, length of stay, and postoperative complications when comparing high- to low-volume institutions. In a more recent follow-up study of mortality trends for high-risk surgery, Birkmeyer’s group found a significant reduction in 30-day risk adjusted mortality among Medicare patients undergoing esophagectomy, from 10% to 8.9%, comparing cohorts from 1999–2000 to 2007–2008 (p < 0.001). They attributed at least 32% of this reduction in operative mortality to redistribution of patients to higher-volume hospitals.

Of even more interest, Birkmeyer and colleagues recently reported on long-term cancer related outcomes following cancer surgery in high- vs. low-volume hospitals. The absolute difference in 5-year survival following esophageal resection in a high-volume hospital was substantially higher than after resection in a low-volume hospital (34% vs. 17%). After adjusting for patient characteristics and adjuvant therapy, the hazard ratio of mortality after esophageal resection in a high-volume hospital compared to a low-volume hospital was 0.71 (95% CI 0.54 – 0.92). From this analysis, hospital volume is as or more important to long-term survival than surgical technique or even adjuvant/neoadjuvant therapy.

Evidence on the relationship between individual surgeon experience and short-term outcome is less abundant, but is generally consistent with the hospital-outcome data. Birkmeyer looked at outcomes following esophagectomy stratified by a combination of both hospital and surgeon volume, and found that the odds ratio for perioperative mortality for a surgeon performing less than two procedures a year was 2.3 compared to a surgeon who performed more than six procedures per year. He calculated that 46% of the effect of hospital volume was attributable to individual surgeon volume. Gopaldas looked at individual surgeon case-mix as a surrogate for surgical specialty, and how this parameter interacted with short-term outcome after esophagectomy in a large cohort identified from the Nationwide Inpatient Sample. Although this study did not directly address individual surgeon volume, it found that, while the rate of complications after esophagectomy was similar among groups characterized as general, cardiac, or thoracic surgeons, increased operative mortality (adjusted for other factors contributing
to mortality) was independently associated with procedures performed by general surgeons. The authors interpreted the discrepancy between equivalent morbidity and increased mortality as an increased failure of general surgeons to rescue after a postoperative complication.

**SUMMARY AND CONCLUSIONS**

There is an abundance of data from large single-center retrospective reviews, population-based studies, meta-analyses, and prospective randomized clinical trials to inform the discussion about the optimal surgical management of invasive adenocarcinoma of the GE junction. Collected reviews of retrospective series have shown a fairly consistent trend toward increased mortality associated with transthoracic compared to transhiatal resection, with a different spectrum of, and less consistent association with, increased morbidity. Among the five prospective randomized clinical trials comparing transthoracic to transhiatal resection, only the largest study was able to demonstrate increased morbidity associated with the transthoracic procedure. Beyond post hoc subset analysis, none of the prospective trials has demonstrated a significant improvement in cancer-specific survival to be associated with either approach.

Minimally invasive esophagectomy, via any combination of laparoscopy, thoracoscopy or robotics, is being rapidly and widely adopted in many centers. There is a fairly consistent trend of these procedures being associated with less early short-term morbidity and mortality in comparison to open procedures. Ongoing prospective clinical trials are trying to define the cost:benefit ratio of these procedures in the face of increasing marketing pressures and public demand.

There are strong and consistent data attesting to the relationship between increased hospital volume and decreased perioperative mortality. The magnitude of this volume:outcome effect in many instances exceeds the magnitude of the most optimistic estimates of the effect of combined modality neoadjuvant or postoperative adjuvant therapy. There are emerging data to suggest that the advantage of high-volume centers may extend beyond lower operative mortality to improved long-term stage-specific cancer-specific survival. These observations clearly require confirmation. Fewer data exist on the effect of individual surgeon volume on outcome; where available, trends in short-term perioperative events are similar to those seen in high-volume hospitals.

Although outcome of patients with adenocarcinoma of the GE junction is largely determined by tumor biology and proper patient selection, the technical details of treatment are important. In the ideal world, these patients would be evaluated and treated by a multidisciplinary team according to consistent evidence-based guidelines, tempered by experience and sound clinical judgment.

**Disclosures of Potential Conflicts of Interest**

The author(s) indicated no potential conflicts of interest.

**References**

1. Rusch VW. Are cancers of the esophagus, gastroesophageal junction, and cardia one disease, two, or several? *Semin Oncol.* 2004;31:444-449.


The Rationale and Evidence for Radiotherapy in the Management of Gastroesophageal Junction Tumors

Karin Haustermans, MD, PhD

OVERVIEW

Adenocarcinoma of the gastroesophageal junction (GE-junction) is a frequent disease with a rising incidence. The optimal treatment of localized disease is the subject of many randomized trials and meta-analyses studying the role of preoperative chemotherapy or preoperative chemoradiation compared with surgery alone. A complicating factor in interpreting the results of these trials is the fact that GE-junction tumors are sometimes regarded as esophageal tumors, although in other studies they are regarded as gastric cancers. A thorough review of the literature including meta-analyses clearly indicates that there is a role for preoperative chemoradiation in locally advanced GE-junction tumors. Based on the available evidence a surgery alone arm in future randomized trials for locally advanced GE junction tumors can no longer be regarded as a standard arm.

Esophageal and gastroesophageal-junction (GE-junction) cancers are deadly malignancies with around 460,000 new diagnoses and more than 380,000 deaths per year globally. The incidence of adenocarcinoma of the esophagus has been rising at a rate of 5% to 10% per year since the mid-1970s. Several studies have investigated the role of chemoradiation in locally advanced GE-junction cancer. Thanks to optimized locoregional treatment distant metastasis is becoming the most common site of recurrence.

THE RATIONALE

The primary goal of preoperative treatment is to downsize and downstage the primary tumor to allow the surgeon to obtain an R0 resection. The latter is an important prognostic factor for patient outcome. Moreover, the upfront use of chemotherapy theoretically allows eradication of microscopic tumor deposits at a distance of the primary tumor. By combining chemotherapy with radiation, the chance to reach the primary goal increases as both modalities will cause tumor-cell kill. It has also been shown that several cytostatic agents have radiosensitising properties and in that way increase the cell killing effect of radiation.

Several studies have shown that adenocarcinoma is a radiosensitive tumor with almost 20% of patients obtaining a pathologic complete remission after preoperative chemoradiation in adenocarcinoma of the rectum.

Tumors located at the GE-junction can be treated by radiation and, as in contrast to adenocarcinomas of the stomach, the motion of the primary tumor is limited. This allows the irradiated volume to be limited, which leads to manageable side effects. In addition, preoperative therapy may be better tolerated than postoperative therapy and a pathologic evaluation of response to preoperative chemoradiation offers important prognostic information.

Each daily fraction of 2 Gy reduces tumor cell survival to approximately 50%. The larger the tumor the more tumor cells to be killed and thus, the higher the total dose required and the higher the risk of complications. Radiotherapy can eliminate large tumors but it is better at eradicating small tumors and subclinical tumor deposits. Conversely, surgery is excellent for removing masses, but its therapeutic ratio in subclinical disease is usually low. Surgery and radiotherapy are therefore mutually beneficial in that less radical treatments each achieve equivalent or better tumor control rates and fewer side effects. In many settings, chemotherapy and radiotherapy can consolidate the cytotoxic achievements of one another; this is well-established for GE-junction tumors.

THE EVIDENCE

Several studies have looked at the role of preoperative chemoradiation in esophageal cancer. According the Union for International Cancer Control classification, the GE-junction is part of the esophagus. For that reason, phase III studies on preoperative chemoradiation in esophageal cancer will be discussed. Most of these studies include squamous cell carcinoma and adenocarcinoma. An overview is given in Table 1.
A small randomized study of surgery alone compared with preoperative concurrent chemoradiation (40 Gy in 15 fractions of 2.67 Gy) with cisplatin and 5-fluorouracil (5-FU) in patients with esophageal adenocarcinoma showed a notable improvement in overall survival at 3 years (32% vs. 6%, p = 0.01). However, the surgery-only arm in this study showed extremely poor results, which questioned the value of the study.

Two other small randomized phase III studies did not show a notable survival advantage with preoperative chemoradiation. Urba and colleagues randomly assigned 100 patients with locoregional esophageal squamous cell or adenocarcinoma (n = 75) to preoperative cisplatin, 5-FU, and vincristin concurrently with twice daily radiation to a total dose of 45 Gy in 1.5 Gy per fraction, or to surgery alone. Although a statistically significant improvement in locoregional control was seen in the preoperative chemoradiation group, the difference in overall survival (OS) did not reach significance (3-year OS 16% vs. 30% with chemoradiation, p = 0.15). A pathologic complete response was obtained in 28% of the patients, 3-year overall survival was 64% in this selected patient group.

Burmeister and colleagues studied 256 patients, of whom 62% had adenocarcinoma. 128 patients were randomly assigned to surgery alone and 128 patients to surgery after 80 mg/m² cisplatin on day 1, 800 mg/m² fluorouracil on day 1 through 4, with concurrent radiotherapy of 35 Gy given in 15 fractions of 2.34 Gy. The trial reported a notable increase in the R0 resection rate (80% vs. 59%, respectively).

The Cancer and Leukemia Group B (CALGB) 9781 trial was closed prematurely because of slow accrual. This trial was initially designed to randomize 475 patients with resectable esophageal squamous cell and adenocarcinomas to surgery or preoperative cisplatin 100 mg/m², 5-FU 1000 mg/m²/day for 4 days and concurrent radiation (50.4 Gy in 1.8 Gy per fraction) and accrued only 56 patients. A statistically significant overall survival benefit was seen at 5 years (39% vs. 16%, p = 0.002) in favor of those receiving trimodality therapy, with a pCR rate of 40%.

The most definitive results in support of the use of chemoradiation for patients with locally advanced esophageal and GE junction cancer come from the CROSS trial.13 This phase III randomized trial compared 41 Gy in 23 fractions of 1.78 Gy plus weekly carboplatin and paclitaxel followed by

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**TABLE 1. Overview of Phase III Randomized Studies**

<table>
<thead>
<tr>
<th>HAUSTERMANS</th>
<th>Number of Patients</th>
<th>Study Treatments</th>
<th>Regimen</th>
<th>Histology</th>
<th>Median Survival (Months)</th>
<th>Overall Survival (%)</th>
<th>PCR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walsh et al, 1996</td>
<td>103</td>
<td>Surgery versus surgery and CRT</td>
<td>Concurrent cisplatin + fluorouracil and RT to 40.0 Gy</td>
<td>103 (100%) adenocarcinoma</td>
<td>11.0 versus 16.0</td>
<td>(3-yr) 6% versus 32%*</td>
<td>25</td>
</tr>
<tr>
<td>Urba et al, 2001</td>
<td>100</td>
<td>Surgery versus surgery and CRT</td>
<td>Concurrent cisplatin + fluorouracil + vincristine and RT to 45.0 Gy</td>
<td>25 (25%) SCC, 75 (75%) adenocarcinoma</td>
<td>17.6 versus 16.9</td>
<td>(3-yr) 16% versus 30%</td>
<td>28</td>
</tr>
<tr>
<td>Burmeister et al, 2005</td>
<td>256</td>
<td>Surgery versus surgery and CRT</td>
<td>Concurrent cisplatin + fluorouracil and RT to 35.0 Gy</td>
<td>95 (37%) SCC, 158 (62%) adenocarcinoma, 3 (1%) mixed or other</td>
<td>22.2 versus 19.3</td>
<td>NR</td>
<td>16</td>
</tr>
<tr>
<td>Tepper et al, 2008</td>
<td>56</td>
<td>Surgery versus surgery and CRT</td>
<td>Concurrent cisplatin + fluorouracil and RT to 50.4 Gy</td>
<td>14 (25%) SCC, 42 (75%) adenocarcinoma</td>
<td>21.5 versus 53.8</td>
<td>(3-yr) 16% versus 39%*</td>
<td>40</td>
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<tr>
<td>van Hagen et al, 2012</td>
<td>368</td>
<td>Surgery versus surgery and CRT</td>
<td>Concurrent carboplatin + paclitaxel and RT to 41.4 Gy</td>
<td>84 (23%) SCC, 275 (75%) adenocarcinoma, 12 (2%) undifferentiated</td>
<td>49.4 versus 24.0</td>
<td>(3-yr) 47% versus 34%*</td>
<td>29</td>
</tr>
<tr>
<td>Macdonald et al, 2001</td>
<td>556</td>
<td>Surgery versus surgery and adjuvant CRT</td>
<td>Sequential and concurrent CRT with fluorouracil</td>
<td>556 (100%) adenocarcinoma (445 (80%) stomach, 111 (20%) gastro-oesophageal junction)</td>
<td>27 versus 36</td>
<td>(3-yr) 4% versus 50%*</td>
<td>NA</td>
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Abbreviations: CRT, chemoradiotherapy; NR, not reported; pCR, pathologic complete response; RT, radiotherapy; SCC, squamous cell carcinoma.

*Significant difference in favor of neoadjuvant chemoradiotherapy.

**KEY POINTS**

- There is a strong rationale and scientific evidence to treat locally advanced adenocarcinoma of the gastroesophageal junction with preoperative chemoradiation.
- Classically, the radiation is combined with 5-fluorouracil and cisplatinum, but carboplatin and paclitaxel have shown high response rates in one randomized study (CROSS trial).
- Ideally, doses of 45 Gy in 1.8 Gy per fraction, five fractions a week, with an overall treatment time of 5 weeks should be delivered.
- Careful target delineation and dose planning should be performed using high-energy photon beams in order to adequately cover the tumor while optimally sparing the surrounding normal tissues.
surgery, to surgery alone. Median overall survival was notably improved, from 26 months in the control arm to 49 months in the combined modality arm. The reported rate of R0 resection was higher in the chemoradiation arm compared with the surgery-alone arm (92% and 65%, respectively). Several meta-analyses of randomized trials of trimodality therapy compared with surgery support the use of trimodality therapy.10,11 The most recent meta-analysis by Sjoquist and colleagues suggests a 9% reduction in overall mortality at 2 years.12

The U.S. GI Intergroup (INT 0116/SWOG 9008) studied the use of adjuvant chemoradiation in locally advanced gastric adenocarcinoma.13 Patients with GE-junction tumors extending at least 2 cm into the stomach and those with proximal gastric cancers accounted for 20% of the patients randomly assigned. Patients were randomly assigned after surgery to observation or adjuvant chemoradiation in which 5-FU was followed by 45 Gy of radiation (1.8 Gy per fraction) concurrently with 5-FU, followed by additional cycles of 5-FU chemotherapy. A statistically significant improvement in disease-free and median overall survival (36 months vs. 27 months) was observed. This study has been criticized for inadequate extent of lymphadenectomy. Only 10% of patients received the recommended D2 dissection, and more than half the patients received less than a formal D1 dissection.

Data comparing chemotherapy and chemoradiation in the preoperative setting are limited. Stahl and colleagues randomly assigned 126 (of 354 planned) patients with adenocarcinoma of the esophagus or GE-junction to 16 weeks of neoadjuvant cisplatin and 5-FU or 12 weeks of the same regimen followed by 3 weeks of cisplatin and etoposide with concurrent radiotherapy (30 Gy in 2 Gy per fraction) before surgical resection.14 Those treated with chemoradiation did not have a notable increase in R0 resection, but did have a higher pathologic complete response rate (15.6% vs. 2%) and tumor-free lymph nodes (64.4% vs. 37.7%) at resection. There was a trend toward improved 3-year overall survival.

There are very few randomized data available on definitive chemoradiation in adenocarcinoma of the GE junction. Most trials looking at definitive chemoradiation versus preoperative chemoradiation included squamous cell carcinoma only. From these studies it is clear that response to initial chemoradiation is a good prognostic factor. So patients in which surgery is not an option could be offered chemoradiation as an alternative treatment strategy.

**TARGET VOLUME, DOSE, AND FRACTIONATION**

When delineating the clinical target volume (CTV) for GE-junction cancer, the radiation oncologist should make sure that the volume treated adequately encompasses the tumor, the pathologic lymph nodes, and the lymph nodes at risk for microscopic disease. Because of the anatomy of the esophagus, this will lead to rather large radiation volumes. However, many of these nodes are only microscopically invaded and the total dose given to these regions at risk does not need to be as high as the dose needed to treat macroscopic disease. Nevertheless, the toxicity and morbidity of such treatment is substantial as radiation needs to be combined with chemotherapy.

Esophageal cancer is notorious for its ability to spread intramurally distant from the main lesion. Not infrequently, primary tumors with multicentric lesions and spread are encountered, and a 5 cm margin may not be sufficient. However, with new advances in endoscopic and radiological techniques, the tumor extent and spread, together with synchronous lesions, are frequently accurately detected.

The European Organization for Research and Treatment of Cancer-Radiation Oncology Group (EORTC-ROG) developed guidelines for target volume definition in preoperative chemoradiation of adenocarcinomas of the GE junction.15 Doses to be administered in the preoperative phase vary between 40 Gy and 45 Gy in 1.8 Gy to 2 Gy fractions in combination with chemotherapy. The dose administered in the postoperative phase varies between 45 Gy and 50.4 Gy in fractions of 1.8 Gy combined with chemotherapy.

All patients get a computed tomography (CT) scan in the treatment position (defined by the location of the primary tumor) with IV contrast. The slice thickness must not be larger than 3 mm. Patients should be treated supine. Legs should have knee support, and arms should be lifted above the head. On this CT scan, the CTV and organs at risk are delineated (lungs, spinal cord, heart, liver, and kidneys). A three dimensional-conformal radiation plan or intensity modulated radiation plan is made, dose volume histograms (DVHs) are calculated for CTV and organs at risk to judge on the feasibility of delivering the prescribed dose in combination with chemotherapy.

The planning target volume (PTV) is defined as the internal target volume (ITV) plus the set-up margin. The ITV takes into account organ motion in particular respiratory motion to ensure adequate CTV coverage. Lymph node stations to be included are numbers 1 to 20 including the supradiaphragmatic lymph nodes according to the JGCA classification.16 Dose constraints for the organ at risk are well described in the EORTC-ROG guidelines.

**CONCLUSION**

The optimal treatment strategy for localized GE-junction tumors is still under discussion. Radiation therapy has made major progress, not only in the complexity of the treatment machines and treatment-planning computers, but also in the understanding of the biologic processes that underlie radiation responses. The manipulation of these characteristics to increase the therapeutic differential between normal tissues and tumor to provide safer, more comfortable, and more effective cancer treatment is the goal of further research in this disease.
Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

References


Unanswered Questions in the Management of Gastroesophageal Junction Adenocarcinoma: An Overview from the Medical Oncologist’s Perspective

Manish A. Shah, MD

OVERVIEW

Patients with gastroesophageal junction (GEJ) adenocarcinoma have multiple treatment options; however, are victims of lack of consensus and wide variation in treatment, sometimes within the same hospital. While there is a consensus that surgery alone is inadequate for locally advanced disease, locoregional treatment has become the point for debate. Only in 2010 was the reclassification of GEJ cancers as esophageal cancers. Treatment options remain as varied as the classification of GEJ cancers: preoperative chemoradiotherapy, definitive chemoradiotherapy, perioperative chemotherapy, and resection followed by postoperative chemoradiation. Several studies have examined the varying treatment paradigms; however, many fall short due to methodology or sample size. The MAGIC study determined perioperative chemotherapy to be an acceptable standard treatment option for patients with gastric cancer, although a significant portion of enrolled patients had distal esophageal and GEJ adenocarcinoma. The CROSS study concluded combination chemotherapy and radiation before resection beneficial. Preoperative therapy in cases of GEJ is beneficial for survival, but not as much impact is seen as in esophageal SCC, which exhibits an increased sensitivity to CRT. There is concurrence with two phase III studies from Japan and Korea on the role of adjuvant chemotherapy for gastric cancer. However, the applicability of these studies to GEJ adenocarcinoma remains a question, especially with the significantly different epidemiology of increased proximal and GEJ tumors in the West compared to Asia. To move forward with this increasingly prevalent disease, we will need to do more than understand the multiple treatment paradigms—we will need to select a strategy and examine it.

Cancers of the upper gastrointestinal (GI) tract form a heterogeneous group of diseases for which treatment paradigms for localized disease continue to emerge. The management for localized disease is complex and involves multidisciplinary consideration. For patients without evidence of metastases, the mainstay of treatment almost always involves surgical resection. However, those patients with locally advanced disease have a high chance of a positive margin, local-regional recurrence, and a high risk of distant micrometastatic disease resulting in a high risk for systemic recurrence. For this reason, additional therapy has been investigated. The success of the MAGIC study revealed the benefit of perioperative chemotherapy for locally advanced gastroesophageal carcinoma. Although there is now acceptance that surgery alone is inadequate therapy for patients with locally advanced disease, the management of local-regional disease, particularly with regard to the gastroesophageal junction (GEJ), remains an area of controversy. In the past several years, the epidemiology and biology of GEJ tumors has led to their reclassification as esophageal cancer.1 As per the National Comprehensive Cancer Network Guidelines for esophageal carcinoma in patients with localized disease who are medically fit for resection, several standard treatment options are acceptable, including preoperative chemoradiotherapy, definitive chemoradiation, preoperative chemotherapy (for adenocarcinoma), and resection followed by postoperative chemoradiation.2 One might ask, however, is this really progress? Which option do we choose? In our session, “Unanswered questions in the management of Gastroesophageal Adenocarcinoma,” we will review the diverse management options for these malignancies, including an important review of the considerations for surgery (given by Dan Coit, MD, Memorial Sloan-Kettering Cancer Center) and a viewpoint from radiation oncology (given by Karin Haustermans, MD, Leuven Kankerinstituut).

THE MAGIC OF MAGIC: USHERING IN A NEW ERA OF ADJUVANT THERAPY

The first large random assignment study evaluating preoperative chemotherapy was the U.S. RTOG study, which
randomly assigned 440 patients from 1990 to 1995 to preoperative cisplatin/fluorouracil chemotherapy, followed by surgery (213 patients), or to surgery alone (227 patients). Notably, this was an esophageal cancer study, with inclusion of the GEJ. The epidemiology of this study was of a different era for esophageal cancers, with 46% of the patients having a squamous cell carcinoma and the remainder (54%) having adenocarcinoma. The treatment was marginally effective, with 7% of patients having a clinical complete response (as assessed by barium-contrast enhanced radiography) and 12% having a partial clinical response. 2.5% of patients (5/202 who received at least one treatment cycle) had a complete pathologic response, and 133 patients (65.8%) had an R0 resection. Notably, the R1 (microscopic margin rate) was improved with preoperative chemotherapy (15% in surgery alone arm vs. 4% in the preoperative chemotherapy arm, p = 0.001). Unfortunately, this was a negative study with no notable difference in survival. Median survival was 14.9 months and 16.1 month for preoperative chemoradiotherapy and surgery alone, respectively.

However, subsequently, the MAGIC study demonstrated a clear benefit of perioperative therapy. In this study, 503 patients were randomly assigned from 1994 to 2002 to receive perioperative epirubicin, cisplatin, and infusional fluorouracil (ECF; 250 patients) or to surgery alone (253 patients). In this study, 26% of the enrolled patients had tumors of the distal esophagus or GEJ, and unlike the previous study, all patients had adenocarcinoma. A greater proportion of patients (90.7%) completed perioperative therapy, and among the 209 patients who underwent surgery in the perioperative chemotherapy arm, only 65.6% received postoperative therapy. There was evidence of downstaging with preoperative chemotherapy, with a notably greater proportion of patients receiving perioperative chemotherapy having early T (T1 or T2–51.7% vs. 36.8%, p < 0.002) and N (N0 or N1–70.5% vs. 84.4%, p = 0.01). Those individuals randomly assigned to perioperative chemotherapy had a higher likelihood of survival (5-year survival of 36% compared with surgery’s 23%, 95% CI, p < 0.001). This study was supported by another study performed by the French MultiCenter group, in which 224 patients were randomly assigned to two or three cycles of cisplatin 100 mg/m² and fluorouracil 800 mg/m²/d for 5 days and surgery (113 patients) or to surgery alone (111 patients). 75% of randomly assigned patients were of the lower esophagus or GEJ, with 100% of adenocarcinoma histology. The surgery group presented a 5-year survival rate of 24%, compared with the chemotherapy group with 38% (hazard ratio [HR] 0.69, p = 0.02). Although grade 3 and 4 toxicity presented in 38% of patients receive chemotherapy, morbidity remained comparable. Based on the later two studies, perioperative chemotherapy has evolved to an acceptable standard treatment option for patients with GEJ adenocarcinoma, although it has been applied more frequently to gastric adenocarcinoma, with deference to chemoradiation.

**CHEMORADIATION BEFORE SURGERY: DO NOT CROSS THIS OUT!**

There have been several studies examining preoperative chemoradiation for patients with locally advanced esophageal and GEJ carcinoma. These studies have been victimized, plagued by methodological issues and sample size limitations that have made the application of preoperative chemoradiation a point of ongoing discussion. The CROSS study is a well-designed large study that examined the effects of preoperative chemoradiotherapy in advanced esophageal cancer. This study found that a combination regimen of chemotherapy and radiation before resection is superior to surgery alone. In this study, 364 patients from the Netherlands presenting with resectable esophageal adenocarcinoma or squamous cell carcinoma (SCC) from 2004 to 2008 were randomly assigned to receive combined-modality therapy of chemoradiotherapy (CRT) followed by surgery or surgery alone. Notably, 75% of the patients enrolled had adenocarcinoma of the distal esophagus or GEJ. The other notable feature of this study was that only 16% of patients enrolled were lymph node-positive. Preoperative CRT consisted of weekly paclitaxel 50 mg/m² and carboplatin dosed at area under the curve 2 for 5 weeks with concurrent 41.4 Gy radiation administered in 23 fractions. Following CRT, patients underwent resection within 6 weeks of preoperative therapy completion. Ninety-two percent of patients receiving preoperative chemoradiation had an R0 resection, as compared with 69% of the surgery alone group (p < 0.001). Although 28.6% of patients (46/161 randomly assigned to receive preoperative chemoradiation) had a complete pathologic response, there was a notably greater proportion for esophageal SCC (49% vs. 23%, p = 0.008). The median survival of patients who received chemoradiation and surgery was 49 months, compared with 24 months for those who received surgery alone (HR = 0.657, p = 0.003). However, although both adenocarcinoma and SCC appeared to have a notable benefit, it appears that the benefit of chemoradiation was primarily derived in patients with esophageal SCC. Patients with

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**KEY POINTS**

- Patients with locally advanced gastroesophageal junction (GEJ) adenocarcinoma who are proceeding to surgery require additional treatment in addition to surgical resection including (a) preoperative chemoradiation, (b) perioperative chemotherapy (without radiation), and (c) postoperative chemoradiation.
- Patients with locally advance GEJ adenocarcinoma who may not proceed to surgery should receive definitive chemoradiation.
- Disease biology across the upper gastrointestinal tract (esophagus, GEJ, and stomach cancer) will define treatment paradigms in the future.
- Squamous cell carcinoma esophagus-chemoradiation (either preoperative or definitive) is preferred.
esophageal SCC observed an adjusted HR of 0.422 (95% CI 0.226 – 0.788), whereas patients with esophageal adenocarcinoma had an adjusted HR of 0.741 (95% CI 0.536 – 1.024). To place these data sets into context with other randomized studies that predominantly included distal esophageal and gastroesophageal junction carcinoma, as well as a recent updated meta-analysis, if surgery is decided as part of the treatment plan for a patient with localized GEJ adenocarcinoma, applying preoperative therapy may confer a survival advantage, but not as striking or clear as that seen for esophageal SCC, which seems to be more sensitive to CRT. In addition, Mariette and colleagues demonstrated that there appears to be no added benefit of CRT to surgical resection for early-stage esophageal adenocarcinoma.

**ADJUVANT CHEMOTHERAPY: CAN YOU STOMACH IT?**

The CLASSIC study was a randomized phase III evaluation of postoperative chemotherapy with capecitabine and oxaliplatin compared with observation in resected gastric cancer. In this study, 1,035 patients with stage II-III gastric cancer who had a D2 (i.e., extended lymphadenectomy) surgical dissection were randomly assigned to receive either observation alone (515 patients) or eight cycles of chemotherapy (520 patients) that consisted of oxaliplatin 130 mg/m² plus capecitabine 1,000 mg/m² twice daily for 14 days repeated every 3 weeks. The investigators met their prespecified primary endpoint of improving 3-year disease-free survival.

<table>
<thead>
<tr>
<th>Year</th>
<th>Disease Type</th>
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<th>Hazard Ratio (HR), p</th>
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<td>CRT (41.4 Gy) + surgery versus surgery</td>
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<td>49 mo vs 26 mo</td>
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**TABLE 1. Selected Phase III Studies in Patients with Localized Esophagogastric Carcinoma**

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**TABLE 2. Medical Oncology Considerations for the Various Treatment Options Available for GEJ Adenocarcinoma**

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<tr>
<th>Approach</th>
<th>Evidence For Approach</th>
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| Pre-operative/Peri-operative chemotherapy | MAGIC5, Ychou et al6 | • Certainty of subsequent surgery  
• Pts who may not be good surgical candidates should consider chemo/RT as possible definitive therapy.  
• Histology: SCC responds better with chemo/RT.  
• Location: If the tumor extends into the esophagus more than a few cm, an esophagectomy may be required. Consider chemo/RT.  
• May salvage a positive margin (sometimes) with post-op chemo/RT |
| Pre-operative chemoradiation | CROSS Study7 | • Toxicity—although it is feasible to get patients through, chemotherapy may be better tolerated.  
• Risk of systemic disease  
• The CROSS study predominantly included node-negative disease.  
• T4 disease—the addition of RT will likely improve the chance of an R0 resection. |
| Post-operative chemoradiation | MacDonald (INT-0116)77 | • Location—85% of patients enrolled in this study were gastric tumors. Proximal stomach/GEJ tumors may better be served by other treatment paradigms. |

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</table>
| Pre-operative/Peri-operative chemotherapy | MAGIC5, Ychou et al6 | • Certainty of subsequent surgery  
• Pts who may not be good surgical candidates should consider chemo/RT as possible definitive therapy.  
• Histology: SCC responds better with chemo/RT.  
• Location: If the tumor extends into the esophagus more than a few cm, an esophagectomy may be required. Consider chemo/RT.  
• May salvage a positive margin (sometimes) with post-op chemo/RT |
| Pre-operative chemoradiation | CROSS Study7 | • Toxicity—although it is feasible to get patients through, chemotherapy may be better tolerated.  
• Risk of systemic disease  
• The CROSS study predominantly included node-negative disease.  
• T4 disease—the addition of RT will likely improve the chance of an R0 resection. |
| Post-operative chemoradiation | MacDonald (INT-0116)77 | • Location—85% of patients enrolled in this study were gastric tumors. Proximal stomach/GEJ tumors may better be served by other treatment paradigms. |
vival, demonstrating 74% 3-year disease-free survival with adjuvant chemotherapy compared with 60% with observation alone, HR 0.56 (Table 1). These data are consistent with the previous adjuvant S1 study reported by Sakuramoto and colleagues and, bolstered by the pooled individual patient-data meta-analysis, further support the use of postoperative chemotherapy alone. The applicability of the recent large phase III studies from South Korea and Japan to a Western patient population remains a question, especially with notably different epidemiology of increased proximal and GEJ tumors in the West compared with Asia. Even when controlling for the extent of surgical resection, apparent differences in outcomes persist. Therefore, despite the recent compelling phase III data, treatment paradigms in the West for locally advanced gastric/GEJ adenocarcinoma currently involve either preoperative or perioperative chemotherapy, or postoperative chemoradiation. In the initial phase III study evaluating postoperative follow-up/radiation therapy (FU/RT), 14% of patients had tumors of the GEJ. More recently, the addition of epirubicin and cisplatin did not improve standard adjuvant FU/RT. Furthermore, when comparing postoperative chemo/RT with postoperative chemotherapy alone (ARTIST study), the additional benefit of RT was not seen in the entire (intention-to-treat) population, but a posthoc analysis suggested a possible benefit in patients with node-positive disease (HR 0.687, 95% CI 0.474–0.995, p = 0.047).

Thus, adjuvant chemotherapy appears to be promising, however, has only been proven as such in gastric cancer studies done in Asia, with little emergence in the West. Virtually no gastroesophageal carcinoma patients have enrolled in these studies, and those that have are combined with patients with gastric cancer. Therefore, we are forced to conclude that, in regards to GEJ, we just do not have the data to accept adjuvant chemotherapy as a stand-alone treatment for gastroesophageal carcinoma.

CONCLUSION
Where do we go from here? First, as a community, we need to come to a consensus, for research purposes, to acknowledge and classify gastroesophageal junction adenocarcinomas as such, and report findings accordingly. Second, as medical oncology treatment paradigms are defined on a global basis, it will be important to understand the global heterogeneity of these diseases. The epidemiology, risk factors, and patterns of care for cancers of the upper gastrointestinal tract are substantially different across the globe. Disease biology in the various regions around the world may also be different, although this needs to be more thoroughly investigated. Table 2 illustrates a few thoughts to consider when devising a treatment strategy for patients with locally advanced gastroesophageal junction tumors. Important issues include the tumor location within the GEJ and extension into the esophagus or stomach, tolerance of preoperative chemoradiation, and likelihood of subsequent surgery. We hope, that as we refine our treatment paradigms, that targeted therapies (such as the addition of trastuzumab or the use of PET scans to select therapy) will make our treatment options more clear and uniform.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.


References


18. Fuchs CS, Tepper JE, Niedzwiecki D, et al. Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LV before and after CRT: Intergroup trial CALGB 80101. *J Clin Oncol.* 2011;29 (suppl; abstr 4003).