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Challenging Cases

Scan? Cure? Sure!

Presentation of The Case

A 61-year-old man undergoes a sigmoid colectomy for a T3N1 (two of 18 nodes) adenocarcinoma of the sigmoid colon. He recovers well and receives 6 months of adjuvant FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) uneventfully. At his first follow-up visit, the oncologist recommended every 3 month visits for a physical, liver function tests, and carcinoembryonic antigen (CEA) measurement; every 6 month chest, abdomen, and pelvic computed tomography (CT) scans for 3 years; and aspirin, vitamin D supplementation, and exercise. Is CT scanning appropriate in the follow-up of colon cancer patients? (This case was presented at Massachusetts General Hospital Cancer Center.)

Pro

By Richard M. Goldberg
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Richard M. Goldberg, M.D.

Just recently, I reorganized my talking points about management of metastatic colorectal cancer. Now I focus those conversations, whether they occur in a lecture hall or a clinic exam room, around an AJCC (American Joint Committee on Cancer) unsanctioned but pragmatic new staging system, which I will call "UNC." With multidisciplinary input at the University of North Carolina (also, by coincidence, UNC), we sort patients into those "*unlikely (U)*" to undergo resection because of the extent of their metastatic disease or their comorbid conditions that make the risk of surgery prohibitive, those who can undergo resection "*now (N)*," and, those who *"could (C)"* after a response to medical treatment potentially undergo resection. We formulate management strategies that differ according to those categories. Currently, multidisciplinary teams can realistically offer the possibility of long-term disease-free survival to a subset of patients who fit into the N or C subcategories. How do we segregate patients into those categories? We book them an appointment for a CT scan because they seldom have symptoms or physical findings that reliably tell us how extensive their disease is [1].

After patients with stage II or III disease complete their initial therapy, it is common practice to do interval CT scans, CEAs, and colonoscopies aimed at early detection

Con

By David P. Ryan
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In medicine, we are taught to, above all, do no harm. My best friend and fellow chief resident in the mid-1990s at Columbia-Presbyterian Medical Center, Mat Maurer, summed it up best with his Golden Rule of Internal Medicine. There are only three reasons to recommend anything to a patient: to be cured, to live longer, and to feel better. I've kept this Golden Rule in mind particularly when it involves recommending chemotherapy in any setting. As post-treatment surveillance becomes an increasing component of our professional lives, it's worth applying this Golden Rule to seemingly innocuous recommendations such as vitamin D, aspirin, exercise, and, as our fellow asked, CT scans.

Let's start with the latter part of the Golden Rule. The practice of getting CT scans in the post-adjuvant surveillance period started in the 1990s for unclear reasons. It probably was an extension of the marketing push to get people to have colonoscopies so that we can "pick up cancer early." So, picking up metastatic cancer early must be a good thing, right? Unknown. There is no level 1 evidence showing that starting chemotherapy earlier for asymptomatic metastatic disease helps people live longer or feel better. In fact, many of us are proponents of chemotherapy holidays interspersed throughout the course of care for our patients with metastatic colon cancer. The number one

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of recurrent disease and new primary tumors. Guidelines issued by the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the Cochrane Collaboration reinforce this practice [2–4]. Are we fooling ourselves and our patients about the value of this approach in terms of lives saved or prolonged and money spent? My fiscally conservative crimson (Harvard's colors) friend and colleague Dr. Ryan suggests that we are and, from my vantage point on the opposite side of the color wheel (UNC's team color is sky blue), I disagree. Is there evidence on which to base a CT scan-based surveillance protocol?

The natural history of colorectal cancer stands out among solid tumors. Cohen and colleagues studied circulating tumor cells (CTCs) in patients with metastatic disease, proving that with current technology they could readily identify CTCs in a 10-ml aliquot of blood [5]. Yet in many patients, most of these potential seeds never grow and scans detect one or a few metastatic lesions. In patients with pancreatic cancer, resection of metastases is not curative. In many series, resection of limited hepatic and pulmonary metastases in colorectal cancer patients leads to a 30%–60% likelihood of long-term disease-free survival and to a substantial 5-year survival rate, even when surgery and drug therapy prove not to be curative [6]. Unfortunately, a substantial number of patients will subsequently relapse, some rapidly, and we need to discover molecular/genetic profiles that can help predict who among the patients with a single or small number of scan-identified lesions will likely benefit from curative resection and who will not. We hopefully can spare patients the pain and society the expense of fruitless surgeries once those data are available.

An expert multidisciplinary committee that included several individuals whose prior published work included recommendations against routine surveillance CT scanning (Loprinzi, Virgo) wrote the most recent 2005 ASCO guidelines that endorse follow-up CT scan screening for patients with stage II and III colorectal cancer [2]. An exhaustive review of the literature available at that time convinced the panel of the value of scans. The review included three meta-analyses, all of which they classified as "highest quality" using the metrics defined by the Oxmann-Guyatt Overview Quality Questionnaire. These three meta-analyses reported a 20%–33% reduction in the risk of death from all causes in the groups of patients who had scans as a routine part of follow-up [4, 7, 8]. Interestingly, this reduction in the odds of death is nearly identical to that reported by Moertel and colleagues for adjuvant therapy of stage III colon cancer [9]. The data on the benefit of adding oxaliplatin to fluorouracil-based therapy provides a lesser incremental benefit [10]. Presumably, Dr. Ryan does offer adjuvant therapy with predictor of survival is sensitivity to chemotherapy, not how early one receives it.

The crux of the argument for CT scans involves the first part of the Golden Rule. Approximately 30% of patients with metastatic colon cancer can be cured by surgical resection if the disease is isolated to the liver or lung when it recurs. Is it reasonable to presume that we can pick up more isolated disease by CT scanning? There have been three randomized studies of postoperative surveillence CT scans [1–3]. None of these studies demonstrated a statistically significant survival advantage, but all were done in the era prior to the understanding that isolated disease was potentially curable. There have been two meta-analyses of studies that compared intensive surveillance strategies, including the CT studies mentioned above with lax surveillance strategies [4, 5]. They demonstrated a statistically significant advantage in terms of mortality for intensive follow-up. Given the number of design flaws in the individual studies that made up the meta-analyses, this was really making lemonade out of lemons.

A retrospective analysis recently contributed to the argument in favor of CT scans. Chau and colleagues demonstrated that patients with metastatic disease picked up by CT scan as opposed to CEA measurement or symptoms were more likely to be operated on for cure and were more likely to survive [6]. Despite the retrospective nature and the tremendous opportunity for bias, particularly in an era when not all oncologists agree on resecting metasatic colon cancer with curative intent, the ASCO guidelines now recommend yearly chest, abdomen, and pelvic CT scans in the postoperative setting.

The cost in terms of toxicity may not be trivial. The incidence of contrast allergic reactions is low, but contrast nephropathy can occur in up to 2% of cases and there may be toxicity from cumulative radiation exposure [7, 8]. In addition, the cost of getting just the three CT scans for the approximately 50,000 people in the U.S. is nearly 120 million dollars. This does not take into account the need to get endless 3 month follow-up CTs or magnetic resonance imaging (MRI) scans for the "ditzel" that gets picked up in liver, lungs, or marginally enlarged lymph nodes. Finally, the added anxiety to the patient goes unmeasured.

But, let's assume that CT scans work at curing patients. For every 100 patients with stage 3 disease, 70 are cured. For the 30 that present with metastatic disease, three to six (10%–20%) present with isolated disease and are candidates for resection already. For the 24 to 27 (80%–90%) who present with unresectable disease, let's assume that the impact of CT scans is robust, as was seen in the Chau et al. [6] study and converts nine (30%) to resectable by picking up the disease earlier. Because we can cure only 30% of pa-

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FOLFOX to his patients with stage III colon cancer after resection. Finally, I am having a hard time with the validity of the cost estimates that Dr. Ryan offers. In summary, I believe the data support CT scan surveillance for patients with stage II or III colorectal cancer and the management of those patients found to have recurrent disease using the "UNC" approach.

Disclosures

Richard M. Goldberg: *Research funding/contracted research:* Pfizer.

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tients with isolated disease, at most three extra people will be cured of every 100 with stage 3 disease. If one takes into account the added MRIs, positron emission tomography (PET) scans, and surgeries, it's easy to assume that the practice of getting CT scans costs millions of U.S. dollars for every life that is theoretically saved.

So, does CT scanning in the postoperative surveillance period meet the Golden Rule? I say "no"; but, even if it does, at what cost?

Disclosures

David P. Ryan: *Consultant/advisory role:* Threshold Pharmaceuticals, Array Bioscience, Millennium Pharmaceuticals.

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