

our study, rather than the increase by a factor of 2.4 in the relative risk. We observed no statistically significant difference between donors and nondonors in other important maternal and fetal outcomes, although the wide confidence intervals mean that a clinically important risk among donors was not ruled out. Donors should be carefully monitored during pregnancy, but such care is not routine in all countries. We agree with Lely et al. that all kidney donors should be encouraged to adopt a healthy lifestyle to minimize the risk of long-term health difficulties.

In our study, 16% of donated kidneys were from the right side, with too few patients to perform meaningful analyses on the basis of this characteristic. A difference between the two groups in the risk of gestational diabetes (as assessed with database codes) was neither expected nor observed. We agree with Jesudason and McDonald about the need to better understand the lifelong implications of preeclampsia in pregnancy after donation.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1501450

Esophageal Carcinoma

TO THE EDITOR: In their review of esophageal carcinoma, Rustgi and El-Serag (Dec. 25 issue)¹ do not recommend chemoradiotherapy for the treatment of unresectable disease on the basis of low efficacy and high rates of complications. However, we would like to note that the landmark Radiation Therapy Oncology Group (RTOG) 85-01 trial, which used definitive chemoradiotherapy with fluorouracil and cisplatin, was associated with a median survival of 14 months and a 5-year survival of 27%.² So it is not surprising to find that all guidelines recommend definitive chemoradiotherapy for patients with nonmetastatic unresectable disease and those not amenable for surgery.

In the Dutch Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial, chemoradiotherapy with the weekly administration of paclitaxel plus carboplatin had acceptable adverse events, with grade 3 or higher hematologic toxicity in 7% of patients and grade 3 or higher nonhematologic toxicity in less than 13%.³ Regarding dysphagia, chemoradiotherapy provides

durable palliation in most patients with unresectable disease who are treated with curative or palliative intent.⁴ Endoscopic esophageal stenting or brachytherapy should be considered for patients who cannot receive upfront chemoradiotherapy or who have a short estimated life expectancy.

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DOI: 10.1056/NEJMc1500692

TO THE EDITOR: As academic chairs in oncology, we would like to raise some questions about the review by Rustgi and El-Serag. We feel there are some inaccuracies, and we would particularly note that, surprisingly, the suggested approach given for stage III tumors in Table 1 of the article, which only refers to adenocarcinomas, is endoscopic palliation, when evident cure may be obtained either with definitive chemoradiotherapy or neoadjuvant chemoradiotherapy.¹ The authors state that minimally invasive esophagectomy does not provide any benefit over open surgery, yet two randomized trials have reported a reduction in postoperative complications.^{2,3} Furthermore, the authors state that palliative chemotherapy prolongs survival in patients with metastatic squamous-cell carcinoma. However, to our knowledge, no trial comparing chemotherapy with supportive care has been published, and a randomized trial (ClinicalTrials.gov number, NCT01248299) on this aspect of care is ongoing. Finally, it is noteworthy that trastuzumab reduces the risk of death by 26% among patients with adenocarcinomas that are positive for human epidermal growth factor receptor type 2 (HER2).⁴

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DOI: 10.1056/NEJMc1500692

TO THE EDITOR: Our multidisciplinary cancer team believes that the recommendations for the management of esophageal cancer do not conform to established evidence-based guidelines.¹ Table 1 of the article by Rustgi and El-Serag suggests that stage III disease should not be treated with a curative approach. In reality, the difference between stage II and stage III could be a single regional lymph node. The 2014 guidelines of the National Comprehensive Cancer Network (NCCN)² recommend treating patients with T1bN+ disease (primary disease invading submucosa with involved regional lymph nodes) or T2-T4a, N0-N+ disease (primary disease invading muscularis propria and beyond, with or without involved regional lymph nodes) with multimodality therapy, including esophagectomy when feasible. The authors recommend treating healthy patients who have mucosal tumors with endoscopic resection or esophagectomy and advise definitive chemoradiation for less healthy patients. We believe that this recommendation is counterintuitive. Usually, an endoscopic resection has fewer unacceptable side effects than definitive chemoradiation. Finally, the authors promote metal stents as the best management tool for obstructive symptoms, stating that “other methods are not recommended because of their low efficacy and high rates of complications.” The NCCN panel members concluded that “optimal treatment [for dysphagia] is still debated” and recommended “endoscopic lumen restoration, external beam RT [radiotherapy], chemotherapy or surgery” after careful assessment by a multidisciplinary team.

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DOI: 10.1056/NEJMc1500692

TO THE EDITOR: The review of esophageal cancer by Rustgi and El-Serag is comprehensive. However, we question their statement about the role of human papillomavirus (HPV) in esophageal squamous-cell carcinoma. According to a meta-analysis of 132 studies, Hardefeldt et al. found very solid evidence that there is an increased risk of esophageal squamous-cell carcinoma among patients with HPV infection, with odds ratios ranging from 2.05 to 3.54.¹ More than 100 types of HPV have been identified to date. Among these types, HPV types 16 and 18 are the most important strains in cervical cancer.² HPV types 16 and 33 were the most commonly detected types in invasive laryngeal cancers diagnosed in the United States.³ However, in cases of esophageal squamous-cell carcinoma, HPV type 16 was the most frequent type detected.^{1,4} The above-mentioned studies confirm an increase in the prevalence of HPV infection in esophageal squamous-cell carcinoma.

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DOI: 10.1056/NEJMc1500692

THE AUTHORS REPLY: We think that Essadi et al. may have misread our recommendation. We stat-

ed that definitive chemoradiation was not preferred for patients with resectable cancer. We agree with their statement on dysphagia treatment, especially for patients with squamous-cell carcinoma, and therefore had included chemotherapy or chemoradiation therapy as a recommendation for patients with advanced disease (Table 1 of our article).

We would point out to Adenis et al. that in Table 1 of our article there are two lines for treatment for advanced tumors (including stage III), one for endoscopic palliation and the second for chemotherapy or chemoradiotherapy. Concurrent chemoradiotherapy without surgery is accepted for esophageal squamous-cell carcinoma; however, local control and dysphagia are significantly better with surgery. The response rate among patients with adenocarcinoma is even lower than that for squamous-cell carcinoma. One randomized, controlled trial showed a lower rate of pulmonary complications with minimally invasive esophagectomy than with open esophagectomy, whereas the second study cited by Adenis et al. on minimally invasive esophagectomy remains in abstract form. However, a recent systematic review of 28 comparative studies did not support a clear benefit for minimally invasive esophagectomy.¹

Our statement on the benefit of chemotherapy in advanced disease was qualified by the use of “may” because of the lack of randomized trials against usual care. We concur that multidisciplinary teams and individual management are ideal, but we also state and cite the evidence in a recent Cochrane review that endoscopic palliative therapy and brachytherapy have garnered the most convincing evidence for efficacy in relieving obstructive symptoms in patients who are not candidates for surgery and believe that complications are reduced with endoscopic stenting.²

We agree with Mitin et al. and had recommended multimodal therapy with esophagectomy when possible for patients with T3N1 disease (which encompasses all the criteria that they mention except for T4a disease). We maintain the soundness of our recommendation for patients with early-stage esophageal cancer. Potentially curative therapy with endoscopic or surgical resection should be offered to patients who can tolerate and accept it. The potential for cure is less with chemoradiotherapy and thus, we believe,

should be a second-line therapy, especially since surgery after the failure of chemoradiation is generally not successful.

In response to Wu and Chen: we maintain that the association between HPV and squamous-cell carcinoma is inconsistent and generally weak, and this heterogeneity reduced our confidence in the pooled odds ratio reported by Hardefeldt et al.³ We therefore conclude that HPV cannot be considered as a definitive causal risk factor. This interpretation is generally shared.⁴

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DOI: 10.1056/NEJMc1500692

Expanded Access to Investigational Drugs

TO THE EDITOR: Darrow et al. (Jan. 15 issue)¹ highlight the challenges posed by expanded patient access to unapproved drugs, including an application process that may have been complicated by the time and complexity for physicians to complete the form currently used by the Food and Drug Administration (FDA) and multiple associated documents.² On February 4, 2015, the FDA published draft guidance on a streamlined process for individual-patient expanded-access submissions by physicians treating single patients with investigational drugs.³ The process continues to protect patients while not undermining clinical-trial enrollment. Feedback from academia, physicians, patients, advocacy groups, and industry helped the FDA to revise and clarify the process, including creating what will be a substantially simplified form (currently estimated to take 45 minutes to complete) and reducing the number of required attachments from seven to one. The FDA also redesigned its expanded-access webpage (www.fda.gov/expandedaccess) to include information about the proposed new process for individual-patient submissions.⁴

The FDA welcomes stakeholder input in our ongoing efforts to balance potential benefits of expanded access to investigational therapies against their potential risks. The comment period for the draft guidance and form closes on April 13, 2015 (<https://federalregister.gov/a/2015-02561>).

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4. Expanded access (compassionate use). Silver Spring, MD: Food and Drug Administration (<http://www.fda.gov/expandedaccess>).

DOI: 10.1056/NEJMc1501823

THE AUTHORS REPLY: The move by the FDA to further limit bureaucratic preconditions to expanded access to investigational drugs for appropriate patients is a welcome development.^{1,2} In streamlining the expanded-access application process, the FDA needs to ensure that such a pathway will not provide a “back door” to unjustified use of treatments that do not meet its stan-