Reply. We are grateful for the interest others have shown in our paper, which allowed us to clarify critical aspects of the case-control study design and the nature of our study population.

First, why did so few of the patients with hepatocellular carcinoma (HCC) receive curative treatments? Does this suggest that screening benefit was not observed because curative treatments were not readily available in the Veteran's Affairs (VA) Healthcare System? It is important to recognize that the cases of HCC included in the study were, by definition, all fatal cases in whom the HCC was judged to have caused death. Therefore, one would expect very few of these patients to have received potentially curative treatments, even if they were readily available; if they had received a treatment that invariably cured HCC, they would not have died of HCC. For example, in our study population no patient with HCC who underwent liver transplantation during the study period subsequently died of HCC, and therefore no such patients were included in the study as cases. This finding is not a reflection of a lack of availability of curative treatments. The important point here is that the proportions of patients with fatal HCC who received different types of HCC treatment (shown in Table 2) are clearly not representative of the corresponding proportions among *all* patients with HCC in the VA Healthcare System.

In addition, the reason that many patients with early stage HCC do not receive potentially curative treatments is the stringent eligibility criteria for liver transplantation and many contraindications to surgical resection or even ablation, even among patients judged by the Milan criteria to have early-stage disease. For example, of 4867 unselected patients (ie, not necessarily fatal) diagnosed with early-stage HCC (within Milan criteria) in the Surveillance, Epidemiology, and End Results registry in 2010–2011, most

received no potentially curative treatment (65.3%) and only a small minority received local tumor destruction (14.4%), surgical resection (10.2%), or liver transplantation (10.2%).[1]

Second, why investigate receipt of screening over a 4-year period when screening is recommended every 6 months? We would like to emphasize that, in a case-control study, the time period over which screening histories are compared between cases and controls is not the same as the recommended screening interval. The 4-year period, known as the "detectable preclinical phase," was chosen because it was estimated to be the maximum time period during which the screening test could potentially have diagnosed an HCC before it presented clinically. This estimate was based on studies reporting that tumors with a median growth rate (ie, doubling time of 117 days) would take 3.2 years to grow from 1 cm (the minimum size potentially detectable by ultrasound) to 10 cm (a size generally expected to cause symptoms). We conducted additional analyses in which we considered screening tests performed within 1, 2, or 3 years from the index date. This was to account for the observation that, when different time periods yield different odds ratios, the lowest odds ratio (ie, the one that indicates the greatest survival benefit associated with screening) is likely to be the least biased.[2] However, there was no difference in receipt of screening between cases and controls during the 1, 2, 3, or 4 years before the index date.

Third, can we draw conclusions about the effectiveness of regular surveillance (ie, every 6 months) when the study patients received on average only 2.1 ultrasound examinations over a 4-year period? Focusing on the low average number of ultrasound examinations is misleading. When the average is 2.1 ultrasound examinations over 4 years, it means that some patients were getting no ultrasound examinations (indeed ~50% had no screening ultrasound examinations over 4 years), whereas many others received fairly frequent, "regular" ultrasound examinations. Therefore, indirectly the study did indeed compare patients getting no ultrasound examinations with those getting "regular" ultrasound examinations.

It is worth emphasizing that if all patients in the study were getting regular screening ultrasound examinations, we could not possibly have conducted the study. Any study of screening effectiveness requires a proportion of patients to be unscreened (ideally 50% for maximal power) so that they can be compared with those screened, ideally "regularly." This is indeed close to what we observed in our study.

The case-control study design has been used to study the effectiveness of the following screening tests, which were recommended at frequent intervals, just like HCC screening: fecal occult blood testing for colorectal cancer,[3] Pap smears for cervical cancer,[4] breast self-examination for breast ca,ncer[5] skin self-examination for melanoma,[6] and digital rectal examination for prostate cancer.[7] Some of these case-control studies reported associations between screening and lower cancer-related mortality (eg, fecal occult blood testing,[3] Pap smear,[4] skin self-examination[6]), others did not (eg, digital rectal examination[7]), and others had mixed findings (eg, breast self-examination[5]). Therefore, there is no inherent limitation in the case-control study design that precludes it from identifying a positive effect on cancer-related mortality of a screening test that is meant to be administered at frequent intervals, if such an effect truly exists.

Fourth, why not compare those who received no screening versus those who received screening twice per year as per American Association for the Study of Liver Diseases guidelines? We believe that a comparison between those receiving no screening versus screening twice per year would result in a spuriously low odds ratio associated with multiple (or "regular") screening even in the absence of any effective therapy for screen-detected cancers. This is explained in the Statistical Analysis section of our article and in our prior publications.[8,9]

Fifth, what if the quality of the ultrasound examinations or their interpretation was poor? It is impossible to retrospectively assess the quality of ultrasound examinations. What is highly likely is that the quality of the ultrasound examinations in our study, which were performed in a very large number of hospitals around the country, more closely reflects the quality of ultrasound examinations performed in contemporary clinical practice in the United States than, say, the quality of the ultrasound examinations performed by a single, dedicated expert radiologist in a clinical trial.

Sixth, was the study underpowered to look at screening by ultrasound examination and/or alpha fetoprotein? It was pointed out that we estimated in our power calculations that 70% of the controls would have received screening by serum alpha fetoprotein or ultrasound examination, whereas in fact the observed rate was 54%, and this was taken as evidence that the study must be underpowered. In fact, the opposite is true: a case-control study has the highest power for a given sample size when the frequency of exposure in the control group is close to 50%.

In summary, it is erroneous to attribute the lack of screening-related survival benefit in our study to lack of "regular screening" or unavailability of potentially curative treatments based on the reported results.

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Conflicts of interest
The author discloses no conflicts.