The primary endpoint of this study was the recurrence-free survival which was defined as the interval between the date of surgery and the date of the recurrence of breast cancer or death. Recurrence of breast cancer was determined as local, regional or systemic and confirmed by radiologic or histologic examination.

The secondary endpoint was overall survival defined as the interval from the date of surgery to the date of death. We reviewed the electronic medical records of 7,678 patients who had breast cancer surgery between January 2005 and December 2013. After applying exclusion criteria, we finally included 5,331 patients for the analysis. After propensity score matching, 1,766 patients remained in each group with a good matching balance. We used propensity score matching to ensure that the IV and inhalation cohort shared a similar baseline characteristic and to reduce the potential confounding effect of each variable. The propensity score was defined as the probability of receiving inhalation anesthesia by logistic regression analysis. The variables used for matching were age, height, weight, ASA physical status, anesthetic time, postoperative use of ketorolac, transfusion, type of surgery, subtype of breast cancer, nonadherence to standard anticancer therapy, and year of surgery.

Propensity score matching was excluded from the model because all patients in the IV group received an opioid—remifentanil—intravenously. In the propensity-matched cohort, recurrence-free survival and other survival were estimated using the Kaplan-Meier survival cohort and two groups were compared using the log-rank test.

In addition, the Cox proportional hazards models for recurrence-free survival and other survival were constructed to assess the relationship between type of anesthesia and long-term outcomes after breast cancer surgery. The Cox proportional hazards regression model were also performed to identify risk factor for recurrence of cancer and all-cause mortality in propensity-matched cohort and total study cohort. All variables were (sounds like: first) into the multivariable model using the enter method which was used to fit the multivariable model.

Dr. James P. Rathmell: So, a pretty complex description there. But in the end of more than 7,000 patients having surgery for breast cancer during that time at Seattle University Hospital, you ended up with over 5,000 patients; 3,000-plus in the IV group and 2,200 or more in the inhalation group that were included in the final analysis. What did you find?

Dr. Jin-Tae Kim: We found no significant impact of total IV or inhalation anesthesia on recurrence of breast cancer and overall survival in patients with the disease. The Kaplan-Meier Curve and the log-rank test showed that there was no significant difference in recurrence-free survival or other survival between the two propensity-matched groups.

In the propensity-matched cohort, the Cox proportional hazard model for recurrence-free survival and other survival showed that there was no significant association between type of anesthesia and these long-term outcomes. Consistent risk factor for cancer recurrence and all-cause mortality in the propensity-matched cohort were age younger than 40 years, subtype of breast cancer other than Luminal A and nonadherence to standard anticancer therapy. But type of anesthesia was not a risk factor for cancer recurrence and all-cause mortality.

We also conducted Cox regression analysis for the total study cohort to determine risk factor for cancer recurrence and all-cause mortality, the secondary outcome of this study: age younger than 40 years, ASA physical status, status, mastectomy, subtype of breast cancer other than Luminal A and nonadherence to standard anticancer therapy were found to be associated with higher risk of cancer recurrence and all-cause mortality. But type of anesthesia was not a risk factor for cancer recurrence and all-cause mortality either.

Dr. James P. Rathmell: So, pretty reassuring that your model reiterated some of the standard risk factors like type of cancer, the disease burden, coexisting disease and health status prior to surgery is very reassuring that it pulled those out as risk factors, but it didn’t indicate that anesthesia was.

So, what did you conclude? What are your firm conclusions from the study and what are the biggest limitations of your study?

Dr. Jin-Tae Kim: Because there is no difference in long-term outcome between IV anesthesia and inhalation anesthesia, both anesthetic techniques can be used for breast cancer surgery and the choice of anesthetic agent should be made according to characteristics of the individual patient.
With the current evidence, selection of IV or volatile anesthesia for breast cancer surgery should be based on factors other than cancer recurrence. Regarding the limitations of this study, the biggest limitation of this study is attributed to its retrospective design; many patients were excluded because of missing variables relating to gene expression profile and use of adjuvant chemotherapy and radiation therapy. They were necessary to determine the subtype of breast cancer and nonadherence to standard anticancer therapy. In addition, we cannot exclude the possibility that the lack of the study’s cohort significance may have resulted from inadequate statistical power to detect a potential because we determined the sample size on the basis of the data of variable during the study period rather than by a prior calculation. Lastly, we cannot take into account the medical advances that took place during our relatively long study period.

Dr. James P. Rathmell: Well, pretty honest analysis of the retrospective study.

Dr. Riedel, I want to turn to your editorial view. You wrote this together with Dr. Daniel Sessler and it’s titled “Anesthesia and Cancer Recurrence: Context for Divergent Study Outcomes.” Your editorial walks through some of the reasons that have been put forward to explain why anesthesia might impact the long-term outcomes of patients having surgery for cancer resection.

Anesthesia and Cancer Recurrence: Can you walk us through some of those possible links between anesthesia and cancer outcomes?

Dr. Bernhard Riedel: Thank you, Dr. Rathmell. I think it’s an important study and it really does add to the current equipoise in our literature and it underlines and underpins the importance of a large prospective randomized study to (sounds relate this appropriately.

It also highlights the most important fact in that it’s the cancers outcomes are really determined by the underlying type of cancer and that’s illustrated by the high (inaudible) ratio between the non-Luminal A cancers and the adherence to postoperative adjuvant therapies and with the largely driven (inaudible) patient comorbidity factors.

So, as perioperative physicians, I think we can add incremental value to the cancer journey of patients. For example, we can ensure that patients are optimized for surgery; for example, prehabilitation, that there are pathways to ensure that they have timely return to the postoperative adjuvant therapies.

In terms of the links between anesthesia and cancer outcomes, I think it’s important to understand that cancers are largely driven by adrenergic and inflammatory processes and it’s these processes that drive the tumor microenvironment and they facilitate cancer growth.

Now, surgery, per se, imposes a period of significant biological perturbation with a significant increase in adrenergic inflammatory mediated release. And then on top of that it impairs the immune system and suppresses amongst others natural killer cell function for up to a week after surgery. I think it’s important to understand that surgeries have different magnitude and I think breast cancer surgery, as we’ve moved into an era of a lesser insult is significantly lower than other cancer types.

In terms of overall survival, there are eight studies that we’ve pooled together, 1,878 patients, and the pooled hazard ratio may be .78 which where they’re statistically significant.

In terms of overall survival, there are eight studies that showed improved overall survival with propofol anesthesia in esophagectomy, testicular cancer and colon resection. And I think it’s important to recognize that what we’re referring to here is these patient populations and surgical procedures that have a high biological perturbation, so there’s a strong adrenergic inflammatory response to surgery.

Dr. James P. Rathmell: So, what do you take away from this new study by Dr. Kim and his colleagues? And what’s your overall take from the data you’ve seen to date on the link between anesthesia and cancer recurrence writ large?

Dr. Bernhard Riedel: I think importantly these all-retrospective studies, they’ve all controlled for underlying cancer types and comorbid factors to varying degrees. I think Dr. Kim’s one of the more very robust studies and so it’s important to take notice of their findings and I really think it does – that there’s equipoise in the literature.

And so it’s with the suggestion I think that we need to really send a message to (inaudible); I don’t think we have enough data yet to change practice, but it’s important that we do proceed with large prospective randomized studies to answer this question.

And I’m aware of a number of prospective studies around the globe. I think there’s one being conducted in New York, there’s one in Sweden, there’s one in China and here in Australia we’ve recently been funded to undertake a large prospective randomized (inaudible) and I’m happy to go into that in more detail if you want.

Dr. James P. Rathmell: Just give us a basic construct of this new trial that you’re launching.

Dr. Bernhard Riedel: (Inaudible) is a randomized controlled study with a 2x2 factorial design and what we’ve appended on is the fact that we’ve seen this differential effect of propofol involatile in the literature. But there’s also interesting data coming out that suggests that lidocaine may have some protective properties. We know it’s a (sounds like: zircon) ACE inhibitor, it may preserve natural killer cell function, it’s got anti-inflammatory properties. So, the 2x2 factorial design will have volatiles versus propofol with an (inaudible) a second randomization chose lidocaine over placebo. We have
estimated that it needs about 957 events of (sounds like: failed disease presurvival) and to achieve it we probably have to study and randomize 5,700 patient. So, that gives you an idea of the magnitude of study size that's required to demonstrate and have adequate power to demonstrate the finding.

The prime targets that we – or cancer types that we are targeting are colorectal cancer and lung cancer because this is the cohort that had roughly about 50% to 60% five-year survival.

Dr. James P. Rathmell: Well, fantastic. We’ll look forward to seeing the results in the future. Dr. Kim, congratulations again on the publication of your work. What comes next for you and your research team?

Dr. Jin-Tae Kim: I believe the influence of the type of anesthesia on the recurrence of cancer will depend on the type of surgery, the type of cancer and genetic factors. So, we currently are investigating the fact of type of anesthesia on cancer recurrence and different type of cancer focusing on genetic factors.

In addition, influence of regional anesthesia and inflammation on cancer recurrence will be our next research topic.

Dr. James P. Rathmell: Terrific. I hope today’s discussion will lead many of you listening to read this new article and the accompanying editorial view that appear in the January 2019 issue of Anesthesiology where you can learn more about anesthesia and the risk of cancer recurrence.

Dr. John Wanderer from Vanderbilt University and I also created an infographic that appears in the January 2019 issue titled "Operation Cancer Resection: Does Anesthetic Approach Matter?" and it illustrates the contradictory findings about anesthesia and cancer recurrence described in Dr. Riedel’s editorial.

Drs. Kim and Riedel, thank you for joining me today and for the terrific explanations about cancer, recurrence and the influence of anesthesia.

Dr. Bernhard Riedel: Thank you, Dr. Rathmell.

Dr. Jin-Tae Kim: Thank you, Dr. Rathmell and Dr. Riedel.

Dr. Bernhard Riedel: Thank you, Dr. Kim.

Host: You’ve been listening to the Anesthesiology journal podcast, the official peer-reviewed journal of the American Society of Anesthesiologists. Check anesthesiology.org for an archive of this podcast and other related content.