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EDITORIAL – ENDOCRINE TUMORS

Editorial: Time to Surgery and Thyroid Cancer Survival in the United States

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The article entitled 'Time to Surgery and Thyroid Cancer Survival in the United States' is a retrospective cohort study by Fligor et al. that evaluates over 100,000 patients in the National Cancer Database (NCDB) with papillary thyroid cancer (PTC) from 2004 to 2016.[1] Cox proportional hazard models are used to evaluate risk-adjusted overall survival by time between diagnosis and surgery. Median follow-up time is 55.2 months (4.6 years), and overall survival in the analytic cohort is 94.7%. The study identifies a positive association between increasing time to surgery and the risk of mortality. Five-year overall survival is 95.7% in patients who received surgery within 90 days of diagnosis, 93.0% for those who underwent surgery 91–180 days after diagnosis, and 87.9% for those with delayed surgical intervention over 180 days. On subgroup analysis, increasing delays are associated with worse overall survival for T1, T2, and T3 tumors, but not for T4 tumors. No difference in survival exists for delayed treatment of micropapillary thyroid cancers.

Considerations of delay to treatment are particularly relevant in an era of quarantine for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, with reduced access to care due to office closures, patient preference to avoid exposures in the healthcare system, transition to telehealth practices,[2] and lack of insurance due to layoffs. Shannon et al. compare histologic factors of melanomas in patients before and during the SARS-CoV-2 pandemic. For patients evaluated by surgical oncologists, those evaluated during the pandemic exhibit melanomas with a higher median tumor Breslow depth, a higher mitotic count, and more frequent pT3/pT4 stage compared with melanomas in patients evaluated prior to the pandemic.[3] Tsang et al. have demonstrated a consistent decline in the number of fine needle aspirates to evaluate for thyroid cancer during the pandemic, with a monthly reduction between 59% and 63% for March through May 2020 compared with the same months the year prior.[4] The downstream consequences of these delays may be more significant than those reported by Fligor et al., as delays to diagnosis likely play an additional role in the long-term outcomes of thyroid cancer. With more than 25,000,000 individuals already infected with SARS-CoV-2 in the United States alone, the risk to thyroid malignancy remains to be fully elucidated as time elapses from infection.

SARS-CoV-2 is not the only condition associated with clinically indicated delays in the treatment of thyroid cancer. In pregnancy, thyroid resection is often postponed until the second trimester or after delivery to reduce the risks of spontaneous abortion and preterm labor. Moosa and Mazzaferri retrospectively evaluated 61 pregnant patients with thyroid cancer, 47 (77%) of whom delayed surgery until after delivery. The rate of metastases, recurrence, and death were not statistically significantly different between patients who underwent surgery during or after pregnancy and between the pregnant patients and 528 age-matched female controls.[5] The American Thyroid Association supports sonographic monitoring throughout pregnancy and post-partum resection for most cases of differentiated thyroid cancer, with consideration of surgical intervention in the second trimester for substantial growth

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(50% volume and 20% diameter in two dimensions), lymph node metastases, or high-risk histology.[6] Fligor et al. did not comment on the pregnancy status of subjects, precluding our ability to generalize their findings to this unique population.

As noted by Fligor et al., the major limitation of their article is the lack of disease-specific survival and cancer recurrence data in the NCDB. In this study, the adjusted overall survival in the most rapidly treated group is reported to be 89.6%, lower than typically reported for thyroid cancer survival. This suggests that patient factors, apart from thyroid cancer, are contributing to the reduced overall survival. The proportion of patients with multiple comorbidities and/or Medicaid insurance in the delayed groups is double, or nearly double, that in the timely treatment group, which likely explains some of the treatment effect noted in the study. It is plausible that these two factors and other unmeasured factors account for some of the observed effects of treatment delays on survival and even play a causal role in the treatment delays, which could be further evaluated by controlling for effect modification. Despite this limitation, others have examined cancer-specific outcomes and delays to treatment in thyroid cancer and found similar results. A 2010 Surveillance, Epidemiology, and End Results (SEER) database study of over 35,000 patients reported an estimated 20-year cancer-specific survival of 97% in patients with PTC limited to the thyroid who delayed intervention and 2% higher for those who received immediate, definitive treatment.[7] An earlier study on time to surgery as an outcome of thyroid cancer survival by Mazzaferri and Jhiang found that cancer mortality was 4% in patients who underwent initial therapy within 1 year, compared with 10% in the remaining patients.[8]

Fligor et al. raise an important question regarding the impact of delayed intervention for PTC on survival. Numerous factors in the delivery of care during a pandemic are impacting accessibility and prompt work-up and treatment. With a pandemic that has lasted well over the 180 days evaluated by Fligor et al., there may be further impacts on outcomes to the endocrine surgery population. For now, these data allow us to have important conversations with patients regarding the timing of their surgical treatment for known PTC.

In summary, until more definitive data exist regarding thyroid cancer-specific mortality, treatment within 90 days should be encouraged and, when delays are medically necessary, use of interval ultrasound examination can be used to drive decision making.

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