Survival Outcomes in Stage IV Differentiated Thyroid Cancer After Postsurgical RAI versus EBRT

Yang Z, Flores J, Katz S, et al. Comparison of survival outcomes following postsurgical radioactive iodine versus external beam radiation in stage IV differentiated thyroid cancer. Thyroid 2017;27:944–52.

Study Overview

Objective. To evaluate survival trends and differences in a large cohort of patients with stage IV differentiated thyroid cancer treated with radioactive iodine (RAI), external beam radiation therapy (EBRT), or no radiation following surgery.

Design. Multicenter retrospective cohort study using data from the National Cancer Database (NCDB) from 2002–2012.

Setting and participants. The study group consisted of a random sample of all inpatient discharges with a diagnosis of differentiated thyroid cancer (DTC). This yielded a cohort of 11,832 patients with stage IV DTC who underwent primary surgical treatment with thyroidectomy. Patients were stratified by cancer histology into follicular thyroid cancer (FTC) and papillary thyroid cancer (PTC). Patients were additionally stratified into 3 substage groups: IV-A, IV-B, and IV-C. Administrative censoring was implemented at 5 and 10 year marks of survival time.

Main outcome measures. The primary outcome was all-cause mortality. Survival was analyzed at 5 and 10 years. Multivariate analysis was performed on a number of covariates including age, sex, race, socioeconomic status, TNM stage, tumor grade, surgical length of stay, and surgical treatment variables such as neck dissection and lymph node surgery.

Main results. Most patients (91.24%) had PTC and 8.76% had FTC. The average age of patients in the RAI group was younger (FTC, age 66; PTC, age 58) than patients in the EBRT (FTC, age 69; PTC, age 65) or no RT groups. (FTC, age 73; PTC, age 61). In contrast to FTC patients, a large majority of PTC patients underwent surgical neck dissection. There were no significant differences in sex, ethnicity, primary payer, median income quartile, or education level among the 3 groups for patients with FTC. However, in PTC there was a majority of female and ethnically white/Caucasian patients in all 3 groups. In addition, patients with PTC who did not receive RT or received RAI were more likely to have private insurance versus those who underwent EBRT, who were more often covered under Medicare. These differences in primary payer were statistically significant ($P < 0.001$).

Statistically significant differences in mortality were observed at 5 and 10 years in both papillary and follicular thyroid cancer among the 3 groups. In the PTC groups, patients treated with EBRT had the highest mortality rates (46.6% at 5 years, 50.7% at 10 years), while patients with PTC receiving no RT had lower mortality rates (22.7% at 5 years, 25.5% at 10 years), and PTC patients receiving RAI had the lowest mortality rates (11.0% at 5 years, 14.0% at 10 years). Similar results were seen in patients with FTC, in which patients treated with EBRT had the highest mortality rates (51.4% at 5 years, 59.9% at 10 years), while patient with FTC receiving no RT had lower mortality rates (45.5% at 5 years, 51% at 10 years), and FTC patients receiving RAI had the lowest mortality rates (29.2% at 5 years, 36.8% at 10 years).

Using univariate analysis, EBRT showed a statistically significant increase in 5- and 10-year mortality for patients with PTC stage IV-A and IV-B as compared with no radiation. This was demonstrated in both stage IV-A and IV-B subgroups at 5 years (EBRT 5-year HR PTC stage IV-A = 2.04, 95% confidence interval [CI] 1.74–2.39, $P < 0.001$; EBRT 5-year HR PTC stage IV-B = 2.23, 95% CI 1.42–3.51, $P < 0.001$; and 10 years [EBRT 10-year HR PTC stage IV-A = 2.12, 95% CI 1.79-2.52 $P < 0.001$; EBRT 10-year HR PTC stage IV-B = 2.03, 95% CI 1.33-3.10, $P < 0.001$). RAI showed a statistically significant decrease in 5- and 10-year mortality in both PTC and FTC compared with no radiation, regardless of

pathologic sub-stage. The largest reduction in risk was seen in FTC stage IV-B patients at 5 years [RAI 5 year HR FTC stage IV-B = 0.31, 95% CI 0.12-0.80, $P < 0.05$). Multivariate analysis was also performed and showed similar results to univariate analysis except that there was no longer a statistically significant difference in EBRT versus no RT in stage IV-A PTC at 5 and 10 years (EBRT 5-year HR PTC stage IV-A = 1.2, 95% CI 0.91–1.59, EBRT 10-year HR PTC stage IV-A = 1.29, 95% CI 0.93–1.79). Reductions in death hazard seen in all groups treated with RAI versus no RT previously observed in univariate analysis remained statistically significant in all groups on multivariate analysis.

Multivariate analysis revealed a number of significant covariates. Increase in age was noted to be associated with higher death hazard in all groups except FTC stage IV-B and stage IV-C. Every additional year of age increased the hazard of death by ~2% to 5%, up to a maximum of 9% per year. Females overall had a lower hazard of death compared with their male counterparts, most notably in PTC. African-American patients had improved survival in FTC (5 years) but lower survival in PTC (5 and 10 years) as compared with white patients. Tumor grade showed a dose response in models studied, with increasing death hazards with worsening tumor differentiation.

Conclusion. RAI was associated with improved survival in patients with stage IV DTC, while EBRT was associated with poorer survival outcomes.

Commentary

Radioiodine therapy has been used for treatment of DTC since the 1940s. Radioactive iodine (I-131) is largely taken up by thyroid follicular cells via their sodium-iodide transporter causing acute thyroid cell death by emission of short path length beta particles [1].

External beam radiation therapy (EBRT) is the most common radiation therapy approach to deliver radiation from a source outside of the patient. EBRT machines produce radiation by either radioactive decay of a nuclide or by acceleration of charged particles such as electrons or protons. Using a linear accelerator, charged particles are accelerated to a high enough energy to allow transmission of particles as an electron beam or x-ray, which is subsequently directed at the tumor [2].

This study by Yang and colleagues aimed to examine survival differences in patients with stage IV DTC who received one of these adjuvant radiation modalities post-thyroidectomy. All treatment groups showed improved survival, with RAI with decreases in death hazard in both univariate and multivariate analysis. Patients with stage IV DTC prolonged their survival by a factor of 1.53–4.66 in multivariate models and 1.63–4.92 in univariate models. This clearly supports the effectiveness of RAI as an adjuvant treatment to DTC following surgical resection.

However, this study has several limitations. As this was a retrospective cohort study, the lack of randomization introduces a potential source of bias. In addition, since data was collected via the National Cancer Database, there was limited information that could be obtained on the subjects studied. Disease-specific survival and recurrence rates were not reported and even histological grades were missing more than 50% of the time. Finally, older age and more advanced stage in the EBRT cohorts were likely confounders in the results of increased death hazard and mortality that were observed. It should be noted, however, that attempts to adjust for these covariates were made by the authors by analyzing the data using multivariate analysis.

There are a number of potential reasons as to why the RAI-treated patients did significantly better than the EBRT-treated patients. Based on the current literature and guidelines, EBRT is mainly recommended as a palliative treatment of locally advanced, unresectable, or metastatic disease in primarily noniodine-avid tumors. Therefore, it is certainly feasible that patients in this study who underwent treatment with EBRT had more aggressive disease and were thus at higher risk to begin with. Perhaps the indications to treat with EBRT inherently confer a poorer prognosis in advanced DTC patients. In addition, RAI is a systemic treatment modality whereas EBRT is only directed locally to the neck and thus may miss micro-metastatic lesions elsewhere in the body.

Applications for Clinical Practice

Current standard practice in thyroid cancer management involve the use of radioiodine therapy in treatment of selected intermediate-risk and all high-risk DTC patients after total thyroidectomy. These patients are treated with 131-I to destroy both remnant normal thyroid tissue and microscopic or subclinical disease remaining after surgery. The decision to administer radioactive iodine post-thyroidectomy in patients with DTC is based on risk stratification of clinicopathologic features of the

tumor. The efficacy of RAI is dependent on many factors including sites of disease, patient preparation, tumor characteristics, and dose of radiation administered.

EBRT is currently used much less frequently than RAI in the management of differentiated thyroid cancer. Its main use has been for palliative treatment of locally advanced, unresectable, or metastatic disease in primarily noniodine-avid tumors. It has also been suggested for use in older patients (age 55 years or older) with gross extrathyroidal extension at the time of surgery (T4 disease), or in younger patients with T4b or extensive T4a disease and poor histologic features, with tumors that are strongly suspected to not concentrate iodine. The use of EBRT in other settings is not well established [3,4].

Treatment benefits of RAI in DTC have been extensively studied; however, this is the largest study that has examined long-term survival in a cohort of just under 12,000 patients with stage IV DTC. The results from this large cohort with advanced disease further demonstrates improved overall survival in stage IV DTC patients treated with RAI at 5 and 10 years. It is clear that RAI is the first-line adjuvant radiation therapy of DTC and should remain the standard of care in thyroid cancer management.

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References

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Inhaled Corticosteroid Plus Long-Acting Beta-Agonist for Asthma: Real-Life Evidence

Woodcock A, Vestbo J, Bakerly ND, et al. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. Lancet 2017.

Study Overview

Objective. To determine the effectiveness of asthma treatment using fluticasone furoate plus vilanterol in a setting that is closer to usual clinical practice.

Design. Open-label, parallel group, randomised controlled trial.

Setting and participants. The study was conducted at 74 general practice clinics in Salford and South Manchester, UK, between Nov 2012 and Dec 2016. Patients with a general practitioner's diagnosis of symptomatic asthma and on maintenance inhaler therapy (either inhaled corticosteroid [ICS] alone or in combination with a long-acting bronchodilator [LABA]) were recruited. Patients with recent history of life-threatening asthma, COPD, or concomitant life-threatening disease were excluded. Participants were randomly assigned through a centralized randomization service and stratified by Asthma Control Test (ACT) score and by previous asthma maintenance therapy (ICS or ICS/LABA). Only those with an ACT score < 20 were included in the study.

Intervention. Patients were randomized to receive either a combination of fluticasone furoate and vilanterol (FF/VI) delivered by novel dry powder inhalation (DPI) (Ellipta) or to continue with their maintenance therapy. General practitioners provided care in their usual manner and could continuously optimize therapy according to their clinical opinion. Treatments were dispensed by community pharmacies in the usual way. Patients could modify their treatment and remain in the study. Those in the FF/VI group were allowed to change to other asthma medications and could stop taking FF/VI. Those in the usual care group were also allowed to alter medications, but could not initiate FF/VI.