Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2010 - 12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814 935 1081

5. **Grant SAP Number:** 4100050904

6. **Project Number and Title of Research Project:** 28. Outcomes for Recurrent Thyroid Cancer in the Elderly

7. **Start and End Date of Research Project:** 9/1/2010 - 6/30/2012

8. **Name of Principal Investigator for the Research Project:** Christopher S. Hollenbeak, Ph.D.

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 31,656

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Boltz, Melissa	Resident	10%	$6,443
Schaefer, Eric	Statistician	10%	$8,308

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Hollenbeak, Christopher	Professor	2.5%
Goldenberg, David	Professor	1%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No_____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If

you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes____X____ No_____

If yes, please describe your plans:

We are in the process of writing a grant to study in greater depth treatment selection for thyroid cancer and its impact on outcomes and costs.

12. Future of Research Project. What are the future plans for this research project?

From our perspective, this research project is complete. We have achieved our specific aims and we have published two papers in reputable, peer-reviewed journals. The next step is to expand our research based upon the knowledge gained from this work. This expansion includes: 1) studying how well the definition of recurrence used in this study translates to other cancers, such as oral cavity and oropharyngeal cancers, and 2) studying other dimensions of thyroid cancer outcomes, such as factors that drive treatment selection and how treatment selection relates to economic outcomes.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes_____ No____X_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other				
Unknown				
Total				

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No____X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes____X____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

This project enhanced the human capital for research of one of our surgery residents. Dr. Boltz leveraged her knowledge and skills obtained while working on this research project to write and publish another paper related to thyroid cancer in adolescent women. This article is forthcoming:

Boltz MM, Enomoto LM, Ornstein RM, Saunders BD, Hollenbeak CS. Incidence and survival differences of differentiated thyroid cancer among younger women.

Forthcoming in Clinical Oncology in Adolescents and Young Adults, 2013

In addition, this project enhanced the skills of Mr. Schaefer, our statistician, in working with SEER-Medicare data. He continues to leverage this knowledge and is working on other studies using SEER-Medicare data to study head and neck cancer and other cancer sites.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No_____X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Objectives: Over the past 20 years the incidence of thyroid cancer has doubled to approximately 24,000 new cases diagnosed yearly. Despite the excellent prognosis of thyroid cancer in which the proportion of deaths has remained relatively constant over time, recurrence of thyroid carcinomas is not unusual. The objective of this project is to address deficiencies in the knowledge base about treatment outcomes for recurrent thyroid cancers. The research will lead to an understanding of the factors associated with variation in treatment, the costs of different treatments, the clinical outcomes of different treatments, and the relative value of alternative interventions.

Specific Aims: *1)* To identify factors associated with variation in treatment for thyroid cancers in the Medicare population, *2)* To estimate the impact of different treatments on cost of medical care for patients with recurrent thyroid carcinomas, controlling for tumor features, demographic characteristics, and co-morbid conditions, and *3)* To estimate the impact of different treatments on overall and disease-free survival for patients with recurrent carcinomas.

Research Design: All information obtained and analyses performed will utilize the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, which has collected standardized data, covering approximately 14% of the U.S. population, from a number of population-based registries since 1973. The data that will be used include thyroid cancer diagnoses from 1986-2005 and their associated billing records that are available from 1986 to 2008. To achieve *Specific Aim 1* the univariate associations between thyroid cancer treatment and candidate predictor variables such as age categories, gender, stage, and co-morbidities will be analyzed. In *Specific Aim 2* we will first compute one-, two-, and five-year total costs for each patient. Costs will be defined as total Medicare

payments. To estimate one-, two- and five-year costs a consistent estimator of the survivor function is obtained. This will be done using the Kaplan-Meier product limit method. Second, the average costs incurred on each day is estimated for patients who are at risk (that is, not censored). Finally, the sum of the product of these terms yields a consistent estimate of average cumulative costs. In *Specific Aim 3* we will perform survival analyses of patient survival and tumor free survival among patients with recurrent disease using the Kaplan-Meier method. Survivor functions will be stratified by treatment and comparisons will be made using the log rank test. We will then estimate survivor functions using the Cox proportional hazard model to control for demographic characteristics, tumor features, and co-morbidities.

Progress

The focus of this research was recurrence of thyroid cancer in the elderly. We recognize that Specific Aim 1 is a slight departure from the initial statement of aims. Specific Aim 1 was to study variation in treatment for thyroid cancer, which was not done as part of this study. The amount of effort required to identify and code recurrence was substantial and the research team felt that the contribution of recurrent was greater than treatment variation. Specific Aim 2 was to estimate the cost of thyroid cancer. This was achieved and one of our two publications focuses on this aim. The main internal focus for the analysis was the additional costs attributable to recurrence. However, when we submitted our paper for peer review, the reviewers felt that the recurrence piece was less important than the overall cost of thyroid cancer and asked that we remove it. So the first of our two papers, which achieved Specific Aim 2, estimated the attributable cost of thyroid cancer in the elderly. Specific Aim 3 was to estimate the effect of recurrence on survival for elderly patients with thyroid cancer. This aim was achieved and our second paper was accepted for publication.

Publication 1:

Attributable costs of differentiated thyroid cancer in the elderly Medicare population

Introduction

The incidence of thyroid cancer in the United States has more than doubled since the early 1970s. The yearly incidence has increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002. Although the incidence is rising steadily, thyroid cancer is still relatively uncommon as there were only 56,460 cases diagnosed in 2012. The majority of disease is differentiated thyroid cancer (DTC), which includes papillary and follicular cancers, and comprises approximately 90% of all thyroid cancers.[1]

In addition, thyroid cancer incidence also increases with age. Elderly patients often present with more aggressive forms of thyroid cancer, larger tumors, more extensive local growth, or distant metastases.[3-5] However, the literature for outcomes in this age group remains scarce.

Treatment of low-risk differentiated thyroid cancer is controversial despite the management guidelines recommended by the American Thyroid Association, which were first developed in 1996, and most recently updated in 2009.[1] Given the long-term survival of DTC, the rising cost of healthcare, and the need for cost-containment, treatment strategies have become

increasingly conservative. Follow-up and treatment of well differentiated thyroid cancer extends for years beyond the initial surgical procedure.

Although long-term survival of patients with differentiated thyroid cancer is common, little is known about the cost attributable to the disease and follow-up care. The objective of this study was to use data from the Surveillance Epidemiology and End Results (SEER) and Medicare linked databases[6] to study the costs attributed to the stage of disease, treatment options, and recurrence of differentiated thyroid cancer in the elderly, as well as the cumulative cost of the disease over 5 years.

Methods

Data

Data for this study were from the SEER-Medicare linked data from the National Cancer Institute.[7] The SEER program is a national tumor registry that collects data on approximately 26% of the US population, and reports cancer incidence and survival in the United States.[8] SEER-Medicare linked data contains the subset of Medicare enrollees in the SEER registry. It then links these patients to all Medicare claims records. Thus, using the Medicare billing claims data it is possible to identify specific types of resource utilization in the combined SEER-Medicare data. We exploited this feature of the data in order to identify recurrent thyroid cancer based on utilization of specific procedures commonly used to treat recurrent disease.[9] The SEER-Medicare database also includes a group of patients without cancer that can be used for comparison purposes.[7]

Study Population

Our analysis was limited to elderly adult Medicare enrollees (66 years and older) diagnosed with a single primary thyroid cancer (papillary or follicular). Claims data were only available for certain types of services since 1994. Therefore, we limited our sample to patients who were first diagnosed between 1995 and 2005. In addition, patients enrolled in a health maintenance organization (HMO) at or after the cancer diagnosis were excluded as these patients do not have any Medicare billing records. The final analysis data set contained 2,761 patients.

A comparison group sample of Medicare patients without cancer was selected from the Medicare 5% sample. To control for potentially different distributions of patient characteristics, propensity score matching was used to select a comparison sample that had a similar distribution of background characteristics as the thyroid cancer patients. We chose a propensity score matching approach since there was a large number of characteristics on which to match, including age, gender, race/ethnicity, and several comorbidities. An additional advantage of this technique is that the statistical analysis does not require adjustment for pairing as do exact matching techniques.

The propensity score was the estimated probability in a logistic regression of case status (N = 2,761) versus comparison group status (N = 422,259). Covariates included year of birth (<1900, 5-year increments 1900-1934, ≥1935), sex, and race/ethnicity (White, Black, Asian, Other). An interaction between sex and race was also included, as it was the only interaction that was statistically significant. The predicted probability of being a case was computed for

each subject and used as a propensity score. Two controls were matched to each case with the exact propensity score. Hence, each case was matched to two controls with the same sex and race, and born within the same 5-year window. With these criteria the final sample included 2,761 patients with papillary or follicular thyroid cancer, and 5,522 matched non-cancer comparison group cases.

Costs

The cost analyses took the perspective of Medicare as payer and represented actual payments made by Medicare for all-cause treatment of patients. All costs were adjusted for inflation to year 2005 dollars. Billing files were used to create monthly costs for 5 years after the primary thyroid cancer diagnosis. All billing records, regardless of whether the bills were directly for treating cancer, were accumulated in each of the 60 months. For the month of diagnosis, bills from one month prior to diagnosis and the diagnosis month were included. For the month of death, bills from the month of death and two months after death were included in order to account for lags in reporting.

Covariates

We studied the impact of demographic and disease characteristics, comorbidities, and treatment choice on 1-year and 5-year costs. Data from the SEER registry included the demographic variables age, gender, race/ethnicity, and urbanicity. Disease variables included stage at diagnosis (in-situ/local, regional, distant, unstaged). Treatment indicators were identified as no treatment, surgical intervention, surgery with radiation, and other treatment. An indicator was also included for chemotherapy, which may have been used in combination with the other treatments.

Recurrent thyroid cancer was defined using a combination of International Classification of Diseases 9th Version, Clinical Modification (ICD9-CM) and Current Procedural Terminology (CPT) codes as there is no specific classification or code for recurrent thyroid cancer.10 Patients undergoing injection of I-131 (ICD9 92.28), thyroid carcinoma imaging for metastasis (CPT 78015), had thyroid carcinoma metastasis uptake (CPT 78020), total or complete thyroidectomy (CPT 60240), subtotal or partial thyroidectomy (CPT 60271), or subtotal or total thyroidectomy for malignancy with limited dissection (CPT 60252) more than six months after their initial diagnosis date and procedure (total or hemi-thyroidectomy and/or I-131 therapy) were classified as having recurrent thyroid cancer. While we recognize that this algorithm will not perfectly capture recurrent disease, it has been previously reported and it may be adequate in the absence of a clinical assessment since these are procedures that are very infrequently received among thyroid cancer patients except in the case of recurrent disease.[9]

Statistical Analysis

Patients in the SEER-Medicare data have variable follow-up. Therefore, the approach to estimating costs at one year and five years was a method proposed by Bang and Tsiatis, which accounts for variable follow-up and patient censoring.[11] This approach estimates costs for each patient at regular time intervals (monthly costs) and weights those estimates by the inverse of the probability that the patient is not censored. Bang and Tsiatis recommend a nonparametric estimator of the inverse probability. This was obtained from a Kaplan-Meier

estimator of time to censoring. Using 60 monthly observation periods we weighted the monthly costs for each patient that was uncensored by the inverse probability, and then summed the weighted costs up to twelve months to estimate one-year average cumulative costs, and up to 60 months to estimate five-year average cumulative costs. This was done separately for thyroid cancer cases and comparison group patients.

Multivariate analysis was performed using the approach suggested by Lin.[12] Using this approach, each of the 60 monthly costs were fit to a linear model, where covariates included patient, disease, treatment, and recurrence variables. Coefficients for months one through twelve were summed to give marginal effects of covariates on one-year costs; coefficients for months one through sixty were summed to give marginal effects on five-year costs. Ninety-five percent confidence intervals were obtained from 1,000 bootstrap replicates. All analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC) and R (2.13.0), open source software available at: http://www.r-project.org/.

Results

Characteristics of the 2,761 patients with papillary or follicular thyroid cancer are presented in Table I. The majority of patients (30.5%) were first diagnosed between the ages of 66 years and 69 years, were female (72.7%), white (79.3%), and married (54.3%). The comorbidity burden was relatively low, with most patients (84.8%) having no comorbidities. Most thyroid cancer patients lived in a metropolitan area (85.7%) and had local disease (54.1%) as opposed to regional (32.6%) or distant (10.2%) disease. In addition, 52.9% of thyroid cancer patients did not receive radiation, but of those who did, 76% underwent I-131 therapy. Surgical therapy alone was the primary treatment modality (84.3%), followed by a combination of surgery and radiation therapy (6.6%). Not surprisingly 33.1% of the patients developed recurrent disease.

The average inverse probability weighted costs through 60 months is presented in Figure 1. A significant portion of the costs attributed to thyroid cancer over five years occurred in the first 7 months of diagnosis. During those first 7 months the average cost attributed to the disease was $7,000 to $10,000. At 10 months after diagnosis the costs leveled out over the remaining 60 month follow-up.

Figure 2 presents the average cumulative cost curves from diagnosis up to 5 years following diagnosis for DTC patients and comparison group patients. The costs were calculated under the assumption that the patient survived up to the time period specified on the x-axis. At one year following diagnosis DTC patients had accumulated approximately $25,000 while comparison group patients had accumulated an average of $7,000. By five years, accumulated costs were approximately $100,000 for DTC patients and $70,000 for comparison patients. The difference between the curves is $30,000, meaning approximately $30,000 per patient is attributable to thyroid cancer over the 60 months post-diagnosis.

In the multivariable models of one-year costs, several patient, disease, and treatment factors were significantly associated with accumulated costs at one year (Table II). At one year, patients age 70-74 had $4,140 (95% CI: $321-8,496) higher costs and patients greater than 79 years had $4,510 (95% CI: $717-8,656) higher costs than younger patients age 66-70. The

higher costs incurred by males and black patients were not statistically significant. Disease stage was a significant determinant of cost. Patients with regional disease incurred $9,612 (95% CI: $6,703-12,725) and patients with distant disease incurred $28,059 (95% CI: $20,357-36,345) in additional costs. Comorbidities were the most substantial driver of costs where 1-2 comorbidities added $12,966 (95% CI: $6,398-20,686) and greater than 3 comorbidities added $36,011(95% CI: $25,289-47,623) in costs. Treatment also significantly affected 1-year costs. Compared to surgery alone, patients undergoing both surgery and radiation incurred $13,380 (95% CI: $6,817-20,138) higher cost, and patients undergoing other treatment including chemotherapy incurred $21,575 (95% CI: $10,617-34,374) higher costs.

Similar effects were observed for costs accumulated at five years following diagnosis (Table III). Patients aged 70-74 incurred on average $9,168 (95% CI: $1,870-16,563) in higher costs, patients age 74-78 incurred on average $8,045 (95% CI: $1,459-14,846), and patients age 79 or older incurred on average $14,038 (95% CI: $6,512-22,430) compared to younger patients (reference age 66-69). In contrast to one-year cumulative costs, the higher costs of approximately $7,342 (95% CI: $827-13,847) in male patients was statistically significant. Disease stage was also a significant determinant of costs as patients with regional disease accumulated $9,521 (95% CI: $3,670-$15,437) and patients with distant metastases incurred on average $21,264 (95% CI: $9,615-32,130) in additional costs, which was similar to one-year costs. Comorbidities were a substantial driver of five-year costs where patients having 1-2 comorbidities incurred $26,470 (95% CI: $16,653-36,381) in additional costs at five years and greater than 3 comorbidities resulted in $51,812 (95% CI: $37,012-67,599) in additional cumulative costs. Treatment choice was significantly associated with five-year costs. Compared to patients who received surgery alone, patients who received surgery and radiation therapy had $21,495 (95% CI: $10,359-33,886) higher costs and patients who underwent other treatments which included chemotherapy had $21,876 (95% CI: $2,601-43,950) higher costs. While patients with recurrence incurred $4,417 in additional costs, it was not statistically significant (95% CI: -$1,417-10,353).

Discussion

The rapid and dramatic increase in the incidence of differentiated thyroid cancer carries with it the corresponding escalating economic burden of thyroid cancer care. The long-term disease-specific survival from this relatively indolent malignancy is excellent. However, close and ongoing surveillance is necessary to detect and treat potential cancer recurrence for years after the initial diagnosis of a differentiated thyroid cancer. In this era of rising public and private health care expenditures, as well as the recognized need for cost-containment, it is vital to have valid data on the true monetary cost attributable to disease management.

The costs associated with the increasing incidence of thyroid cancer are not well-understood. There is currently no literature on the overall costs related to non-metastatic thyroid cancer, the long term management, or repeat I-131 therapy for refractory disease. Given that most thyroid cancer is non-metastatic and the number of these cases is on the rise, the costs related to therapy will almost inevitably rise.[13]

A study by Shrime et al. sought to compare the 20 year cost-effectiveness of an initial

hemithyroidectomy versus total thyroidectomy in the management of small papillary thyroid cancer. They used pooled data of 31 studies from the published literature to determine key statistics for decision analysis such as rates of recurrence, rates of complications for all interventions undertaken, and rates of death. The authors found that during 20 years the cost estimates including initial surgery, follow-up, and treatment of recurrence were between $13,897 and $14,242 for total thyroidectomy and between $15,038 and $15,064 for hemithyroidectomy.[14]

Another study by Berger et al. performed a retrospective longitudinal cohort study using a US health insurance claims database and analyzed the costs of health related interventions in 183 patients with newly metastatic thyroid cancer between 2003 and 2005. Inpatient care was the main driver of the total healthcare expenditure, representing 43% of all costs. I-131 therapy was used in 19%, thyroid surgery in 13%, and chemotherapy in 11% of patients. The costs were substantial and totaled $60,200 per patient during the first year and $35,200 during the second year of follow-up.[15]

The present study sought to identify the total cumulative costs of medical care for differentiated thyroid cancer in a well-defined, and at-risk, population of patients. The Medicare-linked SEER database is a powerful, well-validated and large cross-sectional sample of elderly cancer patients in the United States. The billing files associated with this database represent actual payments by Medicare such that a meaningful measure of costs for differentiated thyroid cancer care at one and five years from diagnosis could be obtained.

We have identified that the one year incremental increase in cost for a patient with differentiated thyroid cancer is in excess of $15,000. Much of this cost is incurred within the first seven months of a new diagnosis and initial treatment of the thyroid malignancy. This time frame appears logical in that the up-front costs associated with initial surgical extirpation, hospitalization, and, if used, radioactive iodine remnant ablation, is anticipated to be clustered in the several months surrounding a diagnosis. From month ten after initial diagnosis through to sixty months after the diagnosis, the incremental cost is present over a control patient without malignancy, but remains relatively stable. The sum total excess expenditure attributable to differentiated thyroid cancer over a five year period nears $40,000 per patient.

Multivariate analysis of the one- and five-year costs revealed numerous factors that significantly influence the costs attributable to the care of differentiated thyroid cancer patients. Advancing age of the individual patient plays the largest demographic role in the cost of care. This is despite treatment and surveillance guidelines that do not differentiate between age groupings in their recommendations. Further, all patients included in this Medicare-based study would be included in the high risk category based on any number of the thyroid cancer risk scores. Male gender and black race statistically significantly increased the cost of care for this disease process, notably at the five year mark. Finally, more medically fragile patients as measured by their recorded number of co-morbid diagnoses had a great impact on and higher costs for care of differentiated thyroid cancer.

As might be expected due to higher disease burden, patients with more advanced disease had

a stepwise increment in costs associated with thyroid cancer care. Differentiated thyroid cancer metastatic to regional lymph nodes added over $9,500 of cost at one and five years. Disease classed as metastatic added in excess of $28,000 and $21,000 at one and five years, respectively. Somewhat surprising in our data was the fact that disease recurrence did not alone account for a significant increase in the costs encountered during the care of a patient with differentiated thyroid cancer.

The addition of multimodal treatment for differentiated thyroid cancer is often the standard pathway for the care of these patients. While this has been shown to offer decreases in disease recurrence, it does come with an associated economic cost. The use of radioisotope therapy in an adjuvant setting does increase the one and five year costs by an average of $13,000 and $21,000, respectively.

This study is limited by the granularity of the data available in the SEER-Medicare database. There was a clear clinical limitation to the broad descriptors of disease stage. Further, the details of surgery and adjuvant therapies were limited as well. Finally, this data set did not have clear coding for cancer recurrence, and thus we employed a proxy by capturing procedures typically used in the treatment of recurrent differentiated thyroid cancer. While certainly not perfect, the rate of cancer recurrence identified in this study, 33%, is in-line with historical estimates of cancer recurrence in the elderly population.

The strength of this data is the capture of actual payments made by Medicare for the care of these thyroid cancer patients. The excess cost encumbered as a result of differentiated thyroid cancer is a real contributor to health care costs, and is likely to increase as the rate of this diagnosis rises, and patients survive longer. The costs were largely accounted for via immutable variables such as necessary upfront treatments and disease stage-specific variables. However, these monetary data can be included in cost effectiveness analyses as future iterations of treatment and surveillance guidelines are researched.

These data show too that there were apparent disparities in the cost of care by gender, race/ethnicity, and urbanicity. While there is likely a complex interplay amongst all these factors, and with disease-specific factors, further investigation into this will be necessary to ensure that costs are contained as much as possible. These data may ultimately suggest that regionalization of care yields the most cost effective care for a diverse and growing population of patients.

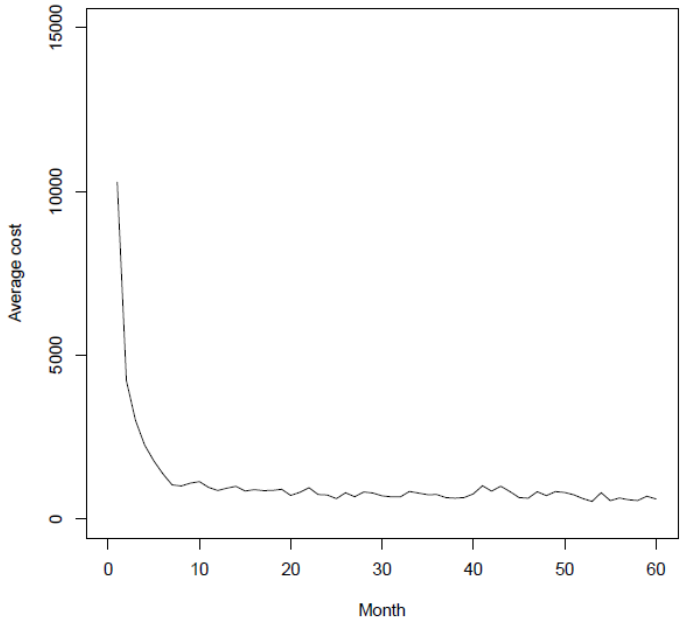

Fig. 1. Average inverse probability weighted (IPW) costs through 60 months

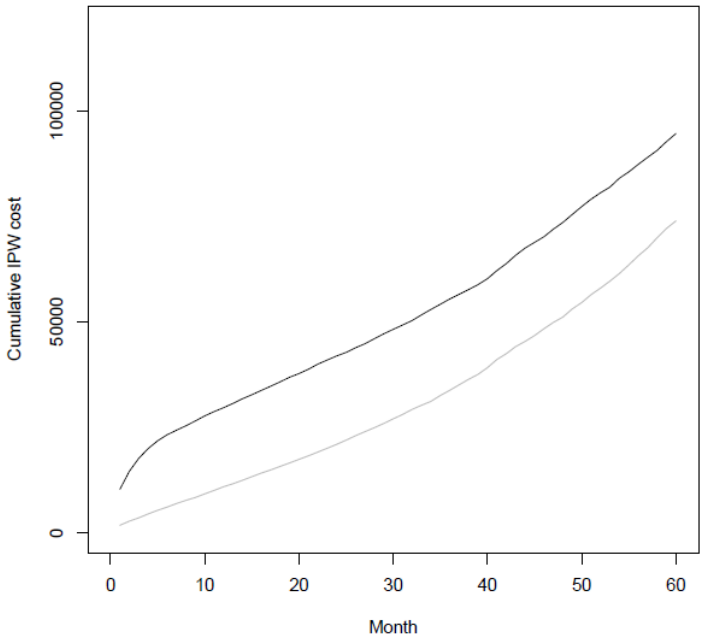

Fig. 2. Cumulative inverse probability weighted (IPW) unadjusted costs for patients with differentiated thyroid cancer (black line) and matched disease-free comparison group cases (gray line)

Table I. Demographic and disease characteristics of SEER-Medicare patients with well-differentiated thyroid cancer

	Total (N=2761)
Year of diagnosis	
1995	113 (4.1%)
1996	119 (4.3%)
1997	130 (4.7%)
1998	117 (4.2%)
1999	115 (4.2%)
2000	273 (9.9%)
2001	304 (11%)
2002	372 (13.5%)
2003	362 (13.1%)
2004	415 (15%)
2005	441 (16%)
Age	
66-69	842 (30.5%)
70-73	633 (22.9%)
74-78	666 (24.1%)
79+	620 (22.5%)
Sex	
Male	754 (27.3%)
Female	2007 (72.7%)
Race	
White	2190 (79.3%)
Black	151 (5.5%)
Asian	232 (8.4%)
Hispanic	90 (3.3%)
Other	98 (3.5%)
Marital status	
Single	203 (7.4%)
Married	1500 (54.3%)
Separated	17 (0.6%)
Divorced	151 (5.5%)
Widowed	779 (28.2%)
Unknown	111 (4%)
Urban/rural code	
Big Metro	1630 (59%)
Metro	736 (26.7%)
Urban	146 (5.3%)
Less Urban	201 (7.3%)
Rural	48 (1.7%)
Stage	
Localized	1495 (54.1%)
Regional	899 (32.6%)
Distant	281 (10.2%)
Unstaged	86 (3.1%)
Number of comorbidities	

0	2340 (84.8%)
1-2	252 (9.1%)
≥3	169 (6.1%)
Radiation	
None	1460 (52.9%)
Beam radiation	141 (5.1%)
Radioactive implants	38 (1.4%)
Radioisotopes	985 (35.7%)
Combination of beam with implants/isotopes	50 (1.8%)
Radiation, NOS	17 (0.6%)
Refused/Unknown	70 (2.5%)
Treatment	
None	173 (6.3%)
Surgery alone	2328 (84.3%)
Radiation alone	39 (1.4%)
Surgery + Radiation only	182 (6.6%)
Chemo (± Surgery/Radiation)	39 (1.4%)
Recurrence	
No	1847 (66.9%)
Yes	914 (33.1%)

Table II. Multivariate regression results for 1-year costs

		95% Confidence	
Variable	Parameter Estimate, $	*Lower*	*Upper*
Intercept	15,048	12,271	17,728
Age 66-69	Reference		
Age 70-73	4,140	321	8,496
Age 74-78	2,864	-979	6,736
Age 79+	4,510	717	8,656
Female	Reference		
Male	2,760	-836	6,664
White	Reference		
Black	8,217	-957	18,482
Asian	-2,544	-7,374	2,338
Race, Other	-3,379	-7,837	1,737
Married	Reference		
Single	7,163	-793	17,709
Separated/Divorced	374	-4,740	6,193
Widowed	3,325	165	6,658
Marital status unknown	725	-7,018	10,066
Big Metro	Reference		
Metro	-6,045	-8,770	-3,198
Urban	-4,822	-1,105	1,400
Less urban/Rural	-8,337	-12,784	-3,587
Localized	Reference		
Regional	9,612	6,703	12,725
Distant	28,059	20,357	36,345
Unstaged	-10,104	-17,346	-2,509
No comorbidities	Reference		
1-2 comorbidities	12,966	6,398	20,686
3+ comorbidities	36,011	25,289	47,623
Surgery alone	Reference		
No treatment	6,641	-3,173	16,850
Surgery and radiation	13,380	6,817	20,138
Other treatment	21,575	10,617	34,374
No recurrence	Reference		
Recurrence	1,833	-879	4,719

Table III. Multivariate regression results for 5-year costs

		95% Confidence	
Variable	Parameter Estimate, $	*Lower*	*Upper*
Intercept	41,373	35,598	47,575
Age 66-69	Reference		
Age 70-73	9,168	1,870	16,563
Age 74-78	8,045	1,459	14,846
Age 79+	14,038	6,512	22,430
Female	Reference		
Male	7,342	827	13,847
White	Reference		
Black	11,543	-4,219	28,566
Asian	-3,128	-13,177	7,156
Race, Other	-7,497	-17,333	2,544
Married	Reference		
Single	15,854	2,776	29,148
Separated/Divorced	3,420	-6,130	13,525
Widowed	8,988	2,429	16,012
Marital status unknown	2,246	-11,965	17,784
Big Metro	Reference		
Metro	-9,689	-15,042	-3,954
Urban	-3,637	-14,762	8,584
Less urban/Rural	-14,913	-22,766	-6,734
Localized	Reference		
Regional	9,521	3,670	15,437
Distant	21,264	9,615	32,130
Unstaged	-10,271	-25,204	4,231
No comorbidities	Reference		
1-2 comorbidities	26,470	16,653	36,381
3+ comorbidities	51,812	37,012	67,599
Surgery alone	Reference		
No treatment	7,121	-6,768	22,372
Surgery and radiation	21,495	10,359	33,886
Other treatment	21,876	2,601	43,950
No recurrence	Reference		
Recurrence	4,417	-1,417	10,353

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Publication 2:

Recurrence of Differentiated Thyroid Cancer in the Elderly

Introduction

The incidence of well-differentiated thyroid cancer in the United States has more than doubled since the early 1970s. Between 1996 and 2005, the incidence rose annually by 5.8% among men and 7.1% among women, a more rapid increase than any other cancer site. Although the incidence is rising steadily, thyroid cancer is still relatively uncommon as only 45,000 cases are diagnosed per year.[1]

Prognosis for well-differentiated thyroid cancer remains excellent, and its associated mortality has not changed in years. In the 1990's well-differentiated (papillary and follicular) thyroid cancer had an expected 10-year survival of 90% or greater. Even patients with distant metastatic disease live many years before succumbing to their disease or dying of other causes. The literature suggests that approximately 55% of patients who present with pulmonary metastases and thyroid cancer survive at least 10 years.[2]

Recurrence of thyroid cancer is not unusual, and the literature suggests that it has an impact on mortality. Coburn et al. suggests that patients who develop recurrent disease after curative treatment do not fare as well as those with no recurrence, with 50-60% eventually dying of the disease.[2] The ability to detect recurrent disease has improved in recent years. In the past, surveillance to detect persistent or recurrent differentiated thyroid carcinoma did not include sensitive serum thyroglobulin assays or neck ultrasonography by experienced technicians. Therefore, many patients appeared to be cured by initial therapy of total thyroidectomy with or without lymph node dissection and radioactive iodine (I-131) ablation therapy to the remnant tissue only to have recurrent disease found years later.[3]

Although most cases of thyroid cancer are diagnosed before age 55[4], it does occur frequently among patients over age 65. Furthermore, the implications for recurrent disease may be very different in the elderly population than among younger patients. Older patients are at greater risk of other health conditions to which they may succumb, lessening the health burden of the recurrent thyroid cancer. Assessing the rate of recurrence of thyroid cancer and the impact of thyroid cancer recurrence on mortality is made more challenging by the fact that recurrence and mortality are competing risks. Patients who die will not recur, and a recurrence suggests that patients survived long enough for the event to happen. This must be accounted for in any analysis of thyroid cancer recurrence and its impact. The objective of this study was to use data from the Surveillance Epidemiology and End Results (SEER)[5] Medicare-linked database to study recurrent well-differentiated thyroid cancer in the elderly. We identified risk factors associated with recurrent thyroid cancer of well-differentiated histology among elderly Medicare patients, and assessed the impact of recurrence on five-year survival after controlling for patient, disease, and treatment related variables, as well as competing risks with mortality.

METHOD

Data

Data for this study were from the SEER-Medicare linked data of the National Cancer Institute (NCI).[5] The SEER program is a national tumor registry that collects data on approximately 26% of the US population, and reports cancer incidence and survival in the United States.[6] The SEER-Medicare linked data contains the subset of Medicare enrollees in the SEER registry. It then links these patients to all Medicare claims records. Thus, using the Medicare billing claims data it is possible to identify specific types of resource utilization in the combined SEER-Medicare data. We exploit this feature of the data in order to identify recurrent thyroid cancer based on utilization of specific procedures commonly used to diagnose and treat recurrent disease.

Our analysis was limited to elderly adult Medicare enrollees (65 years and older) diagnosed with a single, unifocal primary thyroid cancer (papillary or follicular) between 1995 and 2007. Data from the SEER registry included demographics (age, gender, race/ethnicity, location of residence), stage at diagnosis (local, regional, distant, unstaged), therapy (surgical intervention, radioisotope therapy with surgery, chemotherapy), and survival (duration from diagnosis until death). We also included only patients who survived at least through the first year so that recurrence could be possible. The final analysis data set contained 2,883 patients.

Recurrence Definition

Recurrence of disease is not recorded as such in the SEER registry.[7] Therefore, we identified recurrence through billing records for procedures that are not commonly used except in such cases. Billing codes included a combination of International Classification of Diseases 9th Version, Clinical Modification (ICD9-CM), Current Procedural Terminology (CPT) codes and Healthcare Common procedure Coding System (HCPCS) codes. Patients undergoing injection of I-131 (ICD9-CM 92.28), therapeutic I-131 injection (HCPCS A9530) with thyroid uptake on nuclear imaging (CPT 78000), thyroid carcinoma imaging for metastasis (CPT 78015), had thyroid carcinoma metastases imaging whole body (CPT 78018) or with additional studies (CPT 78016) total or complete thyroidectomy (CPT 60240), thyroid lobectomy (CPT 60220), subtotal or partial thyroidectomy (CPT 60271), subtotal or total thyroidectomy for malignancy with limited neck dissection (CPT 60252), thyroidectomy with radical neck dissection (CPT 60254), thyroidectomy substernal with sternal split (CPT 60270), or modified radical neck dissection (CPT 38724), more than six months after their initial diagnosis date and procedure (total or hemi-thyroidectomy and/or I-131 therapy) were classified as having recurrent thyroid cancer. While we recognize that this algorithm cannot perfectly capture recurrent disease, these are procedures that are very infrequently received among thyroid cancer patients except in the case of recurrent disease.

Statistical Analysis

The statistical analysis was designed to identify risk factors for recurrent thyroid cancer in the SEER population, and estimate the impact of recurrence of cancer-specific mortality, controlling for other patient and disease characteristics that may also impact survival. Summary statistics for patient characteristics, cancer stage, histology, and treatment, stratified by recurrence are presented using Chi-squared and Wilcoxon tests to test for differences between groups. Time to recurrence was defined as the time from the date of diagnosis to the date of the first recurrence treatment code at least six months after diagnosis. Patients who were alive and free from recurrence at their last follow-up were censored. Death

prior to recurrence is a competing risk that must be accounted for in the analysis. Traditional Kaplan-Meier survival methods are not appropriate as the method assumes that censored individuals remain at risk for recurrence. This is violated for patients who die prior to recurrence. Therefore, cumulative incidence curves were used to estimate the time to recurrence curves in the presence of the competing risk of death.

As an alternative, we used a landmark Kaplan-Meier analysis at 1 and 2 years. In this analysis, only patients that are alive at the landmark are included in the analysis. Patients who have recurred prior to the landmark are classified as having recurrence, and patients who have not recurred prior to the landmark are classified in a comparison group, even if recurrence occurred after the landmark. Kaplan-Meier curves were created for these groups beginning at the time of the landmark. One limitation to the landmark approach is that we must select a landmark before conducting the data analysis and patient data is explicitly excluded in the estimation of the survival curves. In addition the interpretation is conditional on the time point chosen.

Multivariate analysis of survival was also performed using a Cox proportional hazards model with a time-varying covariate. In this model, all patients are initially grouped as "no recurrence" at baseline. Once a recurrence is observed, the patient group status is changed to "recurrence" at the time (month) of recurrence. Comparisons of recurrence vs. non-recurrence were based only on those time points that have both recurrent and non-recurrent patients. The multivariable model includes adjustments for baseline patient characteristics. All statistical analyses were performed using SAS software (version 9.2, Cary, NC). All tests were two-sided and statistical significance was defined as a P value < 0.05.

Results

Recurrence

Using data from the SEER database 2,883 patients were identified with either primary papillary or follicular thyroid cancer between 1995 and 2007. Of this group 1,117 patients developed recurrence at some point according to our measure (38.7%, average length of follow-up was 5 years). Characteristics of patients stratified by recurrence are presented in Table 1, which shows that these groups were similar in demographic characteristics such as gender ($p = 0.57$), race ($p = 0.33$), and urbanicity ($p = 0.56$). The groups were also similar in terms of histology ($p = 0.19$). There were, however, characteristics that were suggestive of risk factors for recurrence, which include age, stage, and treatment (all $p < 0.0001$). Regional disease was present in 44% of the recurrence group and in only 24% of the control group. In addition, only 32% of the recurrence group received single modality surgery while 61% of patients who did not experience recurrence had single modality surgery. And while 53% of the recurrence group had surgery and radioisotope therapy (I-131) as part of their initial treatment, only 22% of the non-recurrence group had the same treatment, indicating that I-131 is a marker of more aggressive disease.

The overall cumulative incidence for recurrence in the presence of the competing risk of death, as well as cumulative incidence stratified by histology, is presented in Fig. 1. In all three panels a majority of thyroid cancer recurrence occurred within the first two years of

diagnosis. After the first two years of diagnosis the probability of developing recurrent thyroid cancer within ten years never exceeded 45%.

All-Cause Mortality

Of the 2,883 patients diagnosed with thyroid cancer 662 (23%) patients died. Thyroid cancer represented the cause of death in 273 (41.2%) of those patients, or 9% of the patients overall. Fig. 2 (left panel) presents ten-year all-cause mortality stratified by recurrent disease status at a landmark of 1 year. Without controlling for other factors, patients who had a disease recurrence had a higher risk of all-cause mortality within ten years of diagnosis than patients with no recurrence; however this was not statistically significant ($p = 0.65$). A similar trend was observed at a landmark of 2 years (Fig. 2, right panel) ($p = 0.99$).

Fig. 3 presents ten-year all-cause mortality stratified by recurrent disease and histology. Interestingly, patients with follicular cancer and disease recurrence (bottom panels) had a lower risk of all-cause mortality within ten years of diagnosis than patients with no recurrence at both 1 year ($p = 0.61$) and 2 year ($p = 0.09$) landmarks, but this was not statistically significant.

Table 2 presents the results of a Cox proportional hazards regression of all-cause mortality fit separately for papillary and follicular thyroid cancer. Recurrence is estimated as a time-varying covariate. Among patients with papillary thyroid cancer and controlling for other covariates, patients who had thyroid cancer recurrence were more likely to die (HR, 1.13, $p < 0.27$) than patients with no recurrence, but this was not statistically significant. Other factors also contributed to all-cause mortality with the papillary group. For example, older patients (HR, 1.50; $p < 0.001$) with regional (HR, 1.68; $p < 0.001$) or distant (HR, 4.52; $p < 0.001$) thyroid disease had a significantly increased risk of all-cause related death. In addition, patients who had treatment other than surgery or I-131 therapy (HR, 1.99; $p < 0.001$) or no treatment at all (HR, 4.39; $p < 0.001$) had an increased all-cause mortality risk. I-131 therapy in conjunction with surgery was a protective factor (HR, 0.77; $p = 0.024$) when assessing mortality from all causes.

Unlike papillary cancer, recurrence in patients with follicular cancer was protective against all-cause mortality (HR, 0.54; $p = 0.03$). The only significant risks of all-cause mortality in patients with follicular cancer were older age and stage of disease. Distant disease increased mortality by 593% ($p < 0.001$). As with papillary thyroid cancer, patients with follicular thyroid cancer who underwent surgery and I-131 therapy were 31% less likely to die ($p = 0.21$).

Discussion

Thyroid cancer is the most common malignancy of the endocrine system. There were 44,670 cases diagnosed in the U.S. in 2010. Well-differentiated tumors (papillary or follicular) are highly treatable and usually curable. Poorly differentiated tumors (medullary or anaplastic) are much less common, more aggressive, metastasize early, and have a much poorer prognosis. Factors such as age, sex, size of the tumor, stage of disease, presence of extrathyroidal spread, and completeness of resection have been found to significantly influence prognosis and outcomes. [8, 9]

Well-differentiated thyroid carcinoma is associated with good outcomes in the majority of patients. In prior series the recurrence rates for WDTC has been reported to be 20-30% [2, 10]. The overall rate of recurrence for WDTC in our series of elderly Medicare patients was 39%, which is 10 percentage points above the range of prior studies. As with other studies, recurrence in our study had a significantly negative impact on patient outcomes, but only for patients with papillary disease. In one study 50-60% of patients with differentiated thyroid cancer who recurred eventually died of their disease.[2]

Since many studies are based on single institutional series and because papillary thyroid cancer (PTC) is overwhelmingly more common than follicular thyroid cancer (FTC), many studies combine the two types of WDTC together in their findings. Previous reports suggest that the rate of recurrence for PTC is approximately 25% ,[11] while the rate of recurrence for FTC is approximately 18% [12]. Rates of recurrence in this study were not similar. Of the patients who developed a recurrence, 89.3% had PTC and 10.7% had FTC. We found those with FTC had a decreased risk for developing thyroid cancer recurrence when compared those with PTC.

The risks of metastasis and recurrence have been summarized by the American Joint Committee on Cancer (AJCC) and the National Comprehensive Cancer Network (NCCN)[13] and are related to both patient and tumor related factors. Sex is considered an independent risk factor in well-differentiated thyroid cancer, with males typically having a more aggressive disease course. In our study 71.6% of females as opposed to 28.4% of males developed recurrent disease, which was not a statistically significant difference. Age has also been considered an important factor for well-differentiated thyroid cancer. For patients below the age of 40, mortality rate at the time of diagnosis is low and increases progressively after the age of 40. Patients, who are older than 65 years as compared to patients younger than 40 years, often develop locally aggressive tumors and have clinical recurrences.[14] We, too, found similar evidence that older age significantly impacts outcome for WDTC.

Racial disparities in thyroid cancer have been reported. The incidence of thyroid cancer in African-Americans is significantly lower than in white Americans. In fact, thyroid cancer is half as common in the African-American population as in the white population. [15] A number of studies have investigated racial disparities in incidence and outcome in thyroid cancer. [16] Mitchell et al. found that although African-American patients were more likely to harbor larger neoplasms, the mortality and survival was not significantly different. [17] Recently Yu et al. concluded that African-American patients had a lower 5 year survival from PTC than other racial or ethnic groups, but not from other thyroid cancer histology.[18] In the current study, only 20.3% of non-white patients developed recurrence compared to 79.7% of whites, but was not statistically significant.

Regional disease was present in 44% of the recurrence group and in only 24% of patients without recurrence ($p < 0.0001$). This may suggest that regional metastasis at diagnosis puts patients at higher risk for recurrence.

Postoperative iodine-131 therapy for well-differentiated thyroid cancer has been advocated for several reasons, which include treatment of possible residual disease, and ablation of

residual thyroid tissue to allow more accurate follow-up of the patient with whole-body I-131 scans and serum thyroglobulin measurements. Radio-iodine therapy in patients with differentiated thyroid cancer has resulted in decreased recurrences, regardless of whether patients had known residual disease [11] or no known residual disease.[19] In our study 53% of the recurrence group had received radioisotope therapy (I-131), while only 22% of the control (non recurrent) group ($p < 0.0001$) had undergone I-131 treatment. It is not clear whether this difference represents actual practice in the elderly Medicare population or whether it represents a limitation of the data. In addition, use of radioactive iodine therapy may indicate more advanced disease.

The most important departure from the literature in our findings was that patients who had follicular thyroid cancer with recurrence were less likely to die from all-causes than patients without a recurrence. There are several possible explanations for this finding. First, it may call into question the use of billing data to identify recurrence. However, the specific procedure codes we used to identify recurrence are rarely used outside the context of a recurrence. Furthermore, the fact that the rate of recurrence in the aggregate histologies was similar to previous studies, lends face validity to our billing code proxy. The most likely explanation is that recurrence and mortality are competing risks that are more important in an older population. Some time is required for micrometastases to grow into full-blown recurrence. In a younger population where thyroid cancer is seen most often, it would be rare for a patient not to outlive the recurrence. However, in a study population whose average age is 73, this may not be the case. We suspect that many elderly patients in our population are not living long enough for recurrence to become a reality. Recurrence, then, in the elderly population becomes an indicator that a patient has survived longer. The longer survival observed among the population who recurred does not suggest that recurrence contributed to survival, but rather it is an indicator of a patient who would or who has survived longer independent of the recurrence.

The primary limitation of this study is the lack of a clinical variable in the SEER registry to indicate recurrence. We therefore relied on evidence from billing data of iodine-131, imaging for metastatic thyroid carcinoma, additional thyroid operations, or lymph node dissection beyond six months of diagnosis to suggest recurrence. While our proxy measure has face validity, as mentioned previously, there is still the chance that this measure missed patients who did not receive iodine treatment or who underwent no treatment or non-conventional treatment for their thyroid cancer. It may also have erroneously counted patients who underwent treatment for their primary cancer in a delayed fashion and did not actually have a recurrence. In addition, our analysis is unable to account for persistent disease beyond six months of diagnosis. However, given that thyroid cancer is a surgically treated disease the likelihood of having persistent disease is low. Another limitation is that because our population is the elderly Medicare population, our results do not generalize to a younger population where thyroid cancer is more prevalent.

To our knowledge, this study represents the largest series of recurrent well differentiated thyroid cancer in the elderly Medicare population. We found an overall recurrence risk of 39% of the 2,883 patients in the cohort. In this population patients with regional disease and distant metastases were at greater risk for developing recurrent disease. Those with PTC were

at greater risk for recurrence than those with FTC. Sex and racial difference impacted the chance of recurrence but were not statistically significant. Patients with follicular thyroid cancer and recurrent disease had significantly longer survival, most likely suggesting a competing risk between recurrence and mortality. This may be important when considering treatment strategies for recurrent follicular thyroid cancer in the elderly population. Additional research is needed in order to study the economic implications of recurrent thyroid cancer in the elderly.

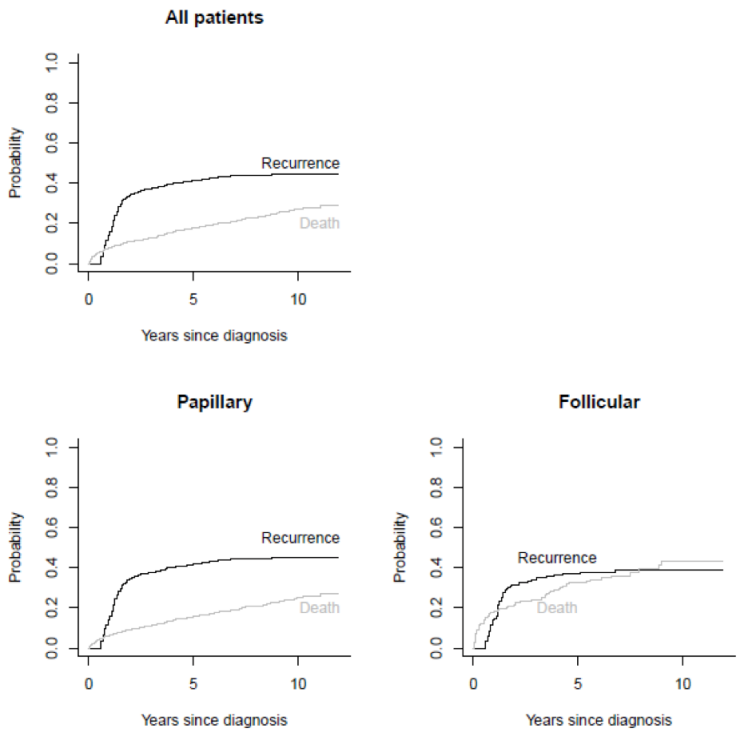

Fig. 1. Univariable cumulative incidence curve for recurrence in the presence of competing risk of death and cumulative incidence curves stratified by histology.

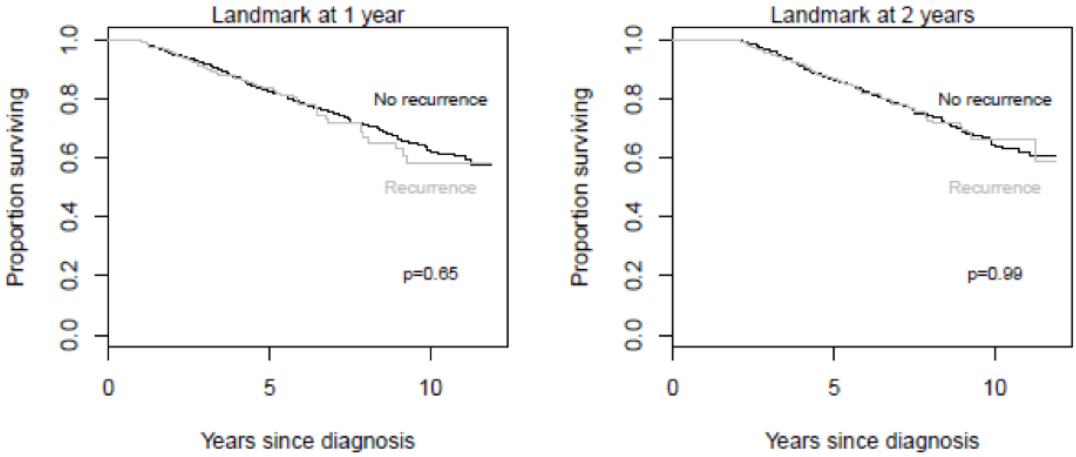

Fig. 2. Kaplan-Meier curves for recurrence status at landmarks of 1 and 2 years.

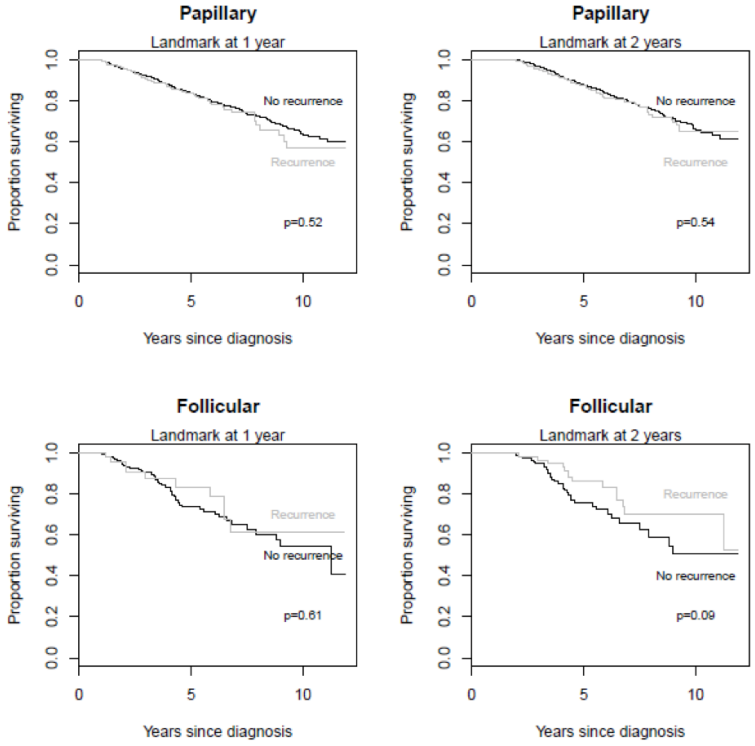

Fig. 3. Kaplan-Meier curves for recurrence status for each histology at landmarks of 1 and 2 years.

TABLE 1 Characteristics of patient cohort stratified by recurrence

Variable	No Recurrence N=1766	Recurrence N=1117	P value
Age at diagnosis, years			<0.0001
Mean (SD)	74.6 (6.43)	72.8 (5.43)	
Median	74	72	
Range	66.0-99.0	66.0-94.0	
Age at diagnosis (group)			<0.0001
66-69 years	496 (2.18%)	394 (35.3%)	
70-74 years	469 (26.6%)	334 (29.9%)	
75-79 years	405 (22.9%)	237 (21.2%)	
80+ years	396 (22.3%)	152 (13.6%)	
Sex			0.5699
Female	1282 (72.6%)	800 (71.6%)	
Male	484 (27.4%)	317 (28.4%)	
Race			0.3264
White	1380 (78.1%)	890 (79.7%)	
Non-white	386 (21.9%)	227 (20.3%)	
Urban/rural code			0.5564
Big metro	1056 (59.8%)	653 (58.5%)	
Metro/urban	562 (31.8%)	358 (32.1%)	
Less urban/rural	148 (8.4%)	106 (9.5%)	
Historic stage			<0.0001
Localized	1077 (61%)	493 (43.8%)	
Regional	428 (24.2%)	496 (44.4%)	
Distant	196 (11.1%)	103 (9.2%)	
Unstaged	65 (3.7%)	29 (2.6%)	
Histology			0.1929
Papillary	1548 (87.7%)	997 (89.3%)	
Follicular	218 (12.3%)	120 (10.7%)	
Treatment			<0.0001
None	161 (9.1%)	24 (2.1%)	
Surgery only	1069 (60.5%)	361 (32.3%)	
Surgery and radioisotopes	385 (21.8%)	596 (53.4%)	
Other (Chemo, non-radioisotope radiation)	151 (8.6%)	136 (12.2%)	

TABLE 2 Multivariable Cox models fit separately for papillary and follicular thyroid cancer

	Papillary		Follicular	
	HR* (95% CI)	**P-value**	**HR* (95% CI)**	**P-value**
Age, 5 year increase	1.50 (1.41-1.60)	<0.001	1.39 (1.19-1.61)	<0.001
Sex				
Male	1.30 (1.08-1.56)	0.005	1.28 (0.86-1.91)	0.22
Female	Reference		Reference	
Race				
White	Reference		Reference	
Non-white	1.01 (0.82-1.24)	0.96	0.92 (0.60-1.41)	0.69
Urban/Rural code				
Big metro	Reference		Reference	
Urban/metro	0.88 (0.73-1.07)	0.21	0.81 (0.53-1.24)	0.33
Rural	1.03 (0.77-1.39)	0.83	1.45 (0.80-2.65)	0.22
Historic stage				
Localized	Reference		Reference	
Regional	1.68 (1.36-2.08)	<0.001	1.75 (0.97-3.14)	0.06
Distant	4.52 (3.47-5.87)	<0.001	6.93 (3.89-12.4)	<0.001
Unstaged	0.57 (0.36-0.91)	0.018	2.27 (0.79-6.49)	0.13
Number comorbidities				
0	Reference		Reference	
≥1	1.79 (1.46-2.19)	<0.001	1.18 (0.75-1.85)	0.47
Treatment				
Surgery	Reference		Reference	
Surgery and radioisotopes	0.77 (0.61-0.97)	0.024	0.69 (0.38-1.24)	0.21
Other	1.99 (1.54-2.58)	<0.001	1.09 (0.63-1.88)	0.76
None	4.39 (3.26-5.91)	<0.001	1.72 (0.96-3.09)	0.07
Recurrence				
Yes	1.13 (0.91-1.41)	0.27	0.54 (0.31-0.93)	0.028
No	Reference		Reference	

*HR=Hazard Ratio

Abstracts Presented

Podium Presentations

Boltz MM, Hollenbeak CS, Saunders BD, Schaefer, E, Goldenberg D. Attributable Costs of Differentiated Thyroid Cancer in the Elderly Medicare Population. *American Association of Endocrine Surgeons*, April 2013, Chicago, IL.

Hollenbeak CS, Boltz MM, Schaefer E, Saunders B, Goldenberg D. Recurrence of Differentiated Thyroid Cancer in the Elderly. *American College of Surgeons 97th Annual*

Clinical Congress – Surgical Forum, October 2011, San Francisco, CA.

Poster Presentations
Boltz MM, Hollenbeak CS, Saunders BD, Schaefer, E, Goldenberg D. Attributable Costs of Differentiated Thyroid Cancer in the Elderly Medicare Population. *Penn State Hershey Medical Center Resident Research Day*, May 2013, Hershey, PA.

REFERENCES

1. Surveillance Epidemiology and End Results program 2010 US Mortality data 1969-2007. National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released June 2010.
2. Coburn M, Teates D, Wanebo HJ. Recurrent thyroid cancer. Role of surgery versus radioactive iodine (I131). *Ann Surg*. 1994;219:587-593; discussion 593-585.
3. Kloos R. Thyroid cancer recurrence in patients clinically free of disease with undetectable or very low serum thyroglobulin values. *J Clin Endocrinol Metab*. 2010;95:1-8.
4. American Cancer Society. Thyroid cancer. Available from URL: http://www.cancer.org/Cancer/ThyroidCancer/DetailedGuide/thyroid-cancer-key-statistics. Accessed April 29, 2011.
5. Surveillance Epidemiology and End Results program 2010 SEER Medicare research data 1986-2007. National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released June 2010.
6. National Cancer Institute. Surveillance Epidemiology and End Results. Available from URL: http://seer.cancer.gov/. Accessed April 29, 2011.
7. American Thyroid Association. ICD-9 codes recommended to Medicare by the ATA. Available from URL: http://www.thyroid.org/professionals/advocacy/icd9.html. Accessed April 1, 2010.
8. Sautter-Bihl ML, Raub J, Hetzel-Sesterheim M, Heinze HG. Differentiated thyroid cancer: prognostic factors and influence of treatment on the outcome in 441 patients. *Strahlenther Onkol*. 2001;177:125-131.
9. Leung AM, Dave S, Lee SL, Campion FX, Garber JR, Pearce EN. Factors determining the persistence or recurrence of well-differentiated thyroid cancer treated by thyroidectomy and/or radioiodine in the Boston, Massachusetts area: a retrospective chart review. *Thyroid Res*. 2011;4:9.
10. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med*. 1994;97:418-428.
11. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 1990;71:414-424.
12. DeGroot LJ, Kaplan EL, Shukla MS, Salti G, Straus FH. Morbidity and mortality in follicular thyroid cancer. *J Clin Endocrinol Metab*. 1995;80:2946-2953.
13. NCCN and AJCC/IUCC thyroid carcinoma practice guidelines. Available from URL: http://www.nccn.org/physician_gls/fguidelines.html 2003). Accessed November 5, 2011.
14. Cunningham MP, Duda RB, Recant W, Chmiel JS, Sylvester JA, Fremgen A. Survival discriminants for differentiated thyroid cancer. *Am J Surg*. 1990;160:344-347.

15. Miller BA, Scoppa SM, Feuer EJ. Racial/ethnic patterns in lifetime and age-conditional risk estimates for selected cancers. *Cancer*. 2006;106:670-682.
16. Hollenbeak C, Wang L, Schneider P, Goldenberg D. Outcomes of thyroid cancer in African Americans. *Ethn Dis*. 2011;21:210-215.
17. Mitchell I, Livingston EH, Chang AY, Holt S, Snyder WH, 3rd, Lingvay I, et al. Trends in thyroid cancer demographics and surgical therapy in the United States. *Surgery*. 2007;142:823-828; discussion 828 e821.
18. Yu GP, Li JC, Branovan D, McCormick S, Schantz SP. Thyroid cancer incidence and survival in the national cancer institute surveillance, epidemiology, and end results race/ethnicity groups. *Thyroid*. 2010;20:465-473.
19. Mazzaferri EL. Treating differentiated thyroid carcinoma: where do we draw the line? *Mayo Clin Proc*. 1991;66:105-111.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X__No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving

Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____ Yes
__X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
____ Yes
____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Recurrence of differentiated thyroid cancer in the elderly	Hollenbeak CS, Boltz MM, Schaefer EW, Saunders BD, Goldenberg D	European Journal of Endocrinology	Sept 2012	☐Submitted ☐Accepted ☑Published
2. Attributable costs of differentiated thyroid cancer in the elderly Medicare population.	Boltz MM, Hollenbeak CS, Schaefer E, Goldenberg D, Saunders BD.	Surgery	June 2013	☐Submitted ☐Accepted ☑Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____ No_____X_____

If yes, please describe your plans:

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None. This study was designed to reflect outcomes rather than to change them.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes__ No___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Hollenbeak, Christopher S.	Professor of Surgery and Public Health Sciences
eRA COMMONS USER NAME CHOLLENBEAK	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Brigham Young University, Provo, UT	B.A.	05/94	Economics
Washington University, St. Louis, MO	M.A.	05/95	Economics
Washington University, St. Louis, MO	Ph.D.	05/00	Economics

A. Positions and Honors.

Positions and Employment

1998-2000 Research Associate, Graduate Program in Health Administration, Washington University School of Medicine, St. Louis, MO
2000-2004 Senior Scientist in Health Economics, Community Health and Health Studies, Lehigh Valley Hospital, Allentown, PA
2000-2006 Assistant Professor of Surgery and Health Evaluation Sciences, Penn State College of Medicine, Hershey, PA
2006-2012 Associate Professor of Surgery and Public Health Sciences (formerly Health Evaluation Sciences), Penn State College of Medicine, Hershey, PA
2007-2010 Director, Graduate Education, Department of Public Health Sciences
2008-Present Chief, Division of Outcomes Research and Quality, Department of Surgery, Penn State College of Medicine, Hershey, PA
2011–Present Director, Discovery and Dissemination, Center for Quality Innovation, Penn State Milton S. Hershey Medical Center, Hershey, PA
2012-Present Professor of Surgery and Public Health Sciences, Penn State College of Medicine, Hershey, PA

B. Selected peer-reviewed publications (in chronological order since 2002).From a total of 134.

1. **Hollenbeak CS**, Lowe VJ, Stack BC Jr. The cost-effectiveness of fluorodeoxyglucose 18-F positron emission tomography in the N0 neck. Nov 1 Cancer. 2001;92(9):2341-2348.
2. Vora AC, Saleem TM, Polomano RC, Eddinger VL, **Hollenbeak CS**, Girdharry DT, Joshi R, Martin D, Gabbay RA. Improved perioperative glycemic control by continuous insulin infusion under supervision of an endocrinologist does not increase costs in patients with diabetes. Endocr Pract. 2004; 10(2): 112-8.
3. Ruda JM, Stack BC Jr., **Hollenbeak CS**. The cost-effectiveness of sestamibi scanning compared to bilateral neck exploration for the treatment of primary hyperparathyroidism. Otolaryngol Clin North Amer. 2004;37(4):855-870.
4. Scurry WC Jr, Beus KS, **Hollenbeak CS**, Stack BC Jr. Perioperative parathyroid hormone assay for diagnosis and management of postthyroidectomy hypocalcemia. Laryngoscope. 2005 Aug;115(8):1362-6.
5. **Hollenbeak CS**. Functional form and risk adjusting hospital costs: Bayesian analysis of a Box-Cox random coefficients model. Statist Med. 2005;24(19):3005-3018.
6. Ruda JM, Stack BC Jr, **Hollenbeak CS**. The cost-effectiveness of additional preoperative

ultrasonography or sestamibi-SPECT in patients with primary hyperparathyroidism and negative findings on sestamibi scans. Arch Otolaryngol Head Neck Surg. 2006;132(1):46-53.

7. Khalid AN, **Hollenbeak CS**, Quraishi SA, Fan CY, Stack BC Jr. The cost-effectiveness of iodine 131 scintigraphy, ultrasonography, and fine-needle aspiration biopsy in the initial diagnosis of solitary thyroid nodules. Arch Otolaryngol Head Neck Surg. 2006;132(3):244-250.
8. **Hollenbeak CS**, Stack BC Jr, Daley SM, Piccirillo JF. Using comorbidity indexes to predict costs for head and neck cancer. Arch Otolaryngol Head Neck Surg. 2007;133(1):24-27.
9. **Hollenbeak CS**, Lendel I, Beus KS, Ruda JM, Stack BC Jr. The cost of screening for synchronous thyroid disease in patients presenting with primary hyperparathyroidism. Arch Otolaryngol Head Neck Surg. 2007;133(10):1013-1021.
10. Khalid AN, Quraishi SA, **Hollenbeak CS**, Stack BC Jr. Fine-needle aspiration biopsy versus ultrasound-guided fine-needle aspiration biopsy: cost-effectiveness as a frontline diagnostic modality for solitary thyroid nodules. Head Neck. 2008;30(8):1035-1039.
11. Choby G, **Hollenbeak CS**, Johnson S, Goldenberg D. Surface electrode recurrent laryngeal nerve monitoring during thyroid surgery: normative values. J Clin Neurophysiol. 2010 Feb;27(1):34-7.
12. Sekhar DL, Wang L, **Hollenbeak CS**, Widome MD, Paul IM. A cost-effectiveness analysis of screening urine dipsticks in well-child care. Pediatrics. 2010 Apr;125(4):660-3.
13. Hollenbeak CS, Wang L, Schneider P, Goldenberg D. Outcomes of thyroid cancer in African Americans. Ethn Dis. 2011 Spring;21(2):210-5.
14. Boltz MM, **Hollenbeak CS**, Schaefer E, Goldenberg D, Saunders BD. Attributable costs of differentiated thyroid cancer in the elderly Medicare population. Surgery. 2013 Aug 22.
15. **Hollenbeak CS**, Boltz MM, Schaefer EW, Saunders BD, Goldenberg D. Recurrence of differentiated thyroid cancer in the elderly. Eur J Endocrinol. 2013 Mar 15;168(4):549-56.

C. Research Support

Ongoing Research Support

No number Gabbay (PI) 07/01/2010 – 06/30/2015
AHRQ
Title: Assessing a Statewide Multi-stakeholder Chronic Care Model Implementation
Project goal: This proposal is to evaluate the impact of the PA Chronic Care Initiative on patient outcomes and cost-of-care for diabetes.
Role: Co-Investigator

ACRIN 6685 Lowe (PI) 04/01/2010 – 03/31/2014
American College of Radiology Imaging Network
Title: A Multicenter Trial of FDG-PET/CT Staging of Head and Neck Cancer and its Impact on the N0 Neck Surgical Treatment in Head and Neck Cancer Patients
Project goal: To determine through a prospective randomized trial the negative predictive value of PET/CT for the N0 neck based upon pathologic sampling of the neck lymph nodes and determine PET/CT's potential to change treatment of the N0 neck in patients with newly diagnosed head and neck squamous cell carcinoma being considered for surgical resection.
Role: Co-Investigator

No number Hollenbeak (PI) 07/01/2013 – 12/31/2013
NIH/American College of Radiology
Title: Quality of Life and Cost Effectiveness Analysis
Project goal: to perform a prospective clinical trial to determine the negative predictive value of PET/CT for the NO neck based upon pathologic sampling of the neck lymph nodes and determine PET/CT's potential to change treatment of the NO neck.
Role: PI

No number Hollenbeak (PI) 09/01/2013 – 04/30/2014
Prima Health Analytics (Amgen)
Title: Prevalence of Case Mix Factors for Payments under the ESRD Prospective Payment System
Project goal: 1) to provide population-level estimates of prevalence of case mix factors applied to payments under the ESRD prospective payment system (PPS), and other demographic variables such as race and ethnicity, as of the time period used to set the PPS adjusters, and 2) to understand whether there are differences in case mix prevalence by dialysis industry segments based on dialysis organization size and type.
Role: PI

Completed Research Support

5 R18 DK 067495-05 Gabbay (PI) 09/15/2005 - 08/31/2011
NIH/NIDDK
Title: Impact of Nurse Case Management on Diabetes Co-Morbidity
Project goal: The goal of this study is to determine the effectiveness of a nurse case manager in increasing compliance of diabetes patients through increased education and follow-up.
Role: Co-Investigator

5 R03 DEOOO019511-02 Hollenbeak (PI) 9/8/2009 – 08/31/2012
NIH/ NIDCR
Title: Clinical and Financial Impact of Treatment for Oral and Pharyngeal Cancer
Project Goal: To assess the financial and clinical impact of different treatment approaches for oral and pharyngeal cancers.
Role: Co-PI

No number Hollenbeak (PI) 7/1/2010 – 6/30/2012
Dean's Feasibility Grant, PSU, COM
Title: Outcomes for Recurrent Thyroid Cancer in the Elderly
Project goal: to identify factors associated with variation in treatment for thyroid cancers in the Medicare population. To estimate the impact of different treatments on cost of medical care for patients with recurrent thyroid carcinomas, controlling for tumor features, demographic characteristics, and comorbid conditions.
Role: PI

No number Hollenbeak (PI) 11/01/2011 – 05/31/2012
United BioSource
Title: Optimizing the Economic Benefits of Induction Immunosuppression using Thymoglobulin
Project goal: to identify the independent and dependent variables that predict the cost of care of a kidney transplant patient over time and by patient and donor risk type.
Role: PI

5 R01NR011874-03 Loeb (PI) 09/29/2009 – 07/31/2013
NIH
Title: Infusing End-of-Life Care into Complex Organizations: The Prison Study
Project goal: The goal of this project is to examine the feasibility of using Participatory Action Research for instilling generalist end-of-life strategies into the complex organizational system of a state Department of Corrections.
Role: PI

5U49/CE001274-05 Dias (PI) 09/30/2007 – 09/29/2013
Centers for Disease Control & Prevention

Title: Pennsylvania Abusive Head Trauma Prevention Program
Project goal: The objective of this research is to test two simple, low cost interventions that have a high probability of reducing abusive head trauma (AHT) in Pennsylvania. Our long-term goal is to find interventions that can prevent the majority of AHT.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
David Goldenberg, M.D.	**Professor of Surgery and Medicine**
eRA COMMONS USER NAME (credential, e.g., agency login) DGOLDENBERG	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Ben Gurion University of the Negev, Beersheva, Israel	B.Sc.	02/92	Medical Sciences
Ben Gurion University of the Negev, Beersheva, Israel	M.D.	02/95	Medicine
Soroka Medical Center, Beersheva, Israel		03/96	Internship
Rambam Medical Center, Haifa, Israel		03/02	Residency
Johns Hopkins Medical Institution and University School of Medicine, Baltimore, MD		06/05	Fellowship

A. Positions and Honors

Positions and Employment

1995-1996 Internship, Soroka Medical Center-Ben Gurion University of the Negev Beer Sheva Israel

1996-2002 Residency Otolaryngology-Head and Neck Surgery Dept of Otolaryngology- Head and Neck Surgery- Rambam Medical Center, Haifa Israel

1999-2002 Instructor of Otolaryngology Bruce Rappaport Faculty of Medicine Technion, Israel Institute of Technology

2000-2002 Coordinator - Galil Center for Telemedicine and Medical Informatics Faculty of Medicine, Technion – Israel Institute of Technology

2002-2005 Fellow in Head and Neck Surgery- Dept of Otolaryngology- Head and Neck Surgery, Johns Hopkins University School of Medicine

2005-present Professor of Surgery and Medicine- Pennsylvania State University, The M.S. Hershey Medical Center, The Pennsylvania State University, College of Medicine, Hershey, PA

Honors and Other Professional Activities

1999 Outstanding Clinical Lecturer Award - Otolaryngology Bruce Rappaport Faculty of Medicine-Award

1999 Citation of Special Merit - Outstanding work as a physician and teacher American Physicians Fellowship for Medicine in Israel Boston, Mass.

2000 Residents Award and Grant - Israel Society of Surgical Oncology of the Head and Neck

2000 Outstanding Lecturer Award – Anatomy; University Award - Technion Israel Institute of Technology

2000 Outstanding Preclinical Lecturer Award -Head and Neck Anatomy, Bruce Rappaport Faculty of Medicine Award

2000 Outstanding Clinical Lecturer Award – Otolaryngology, Bruce Rappaport Faculty of Medicine Award

2001 Outstanding Preclinical Lecturer Award - Head and Neck Anatomy, Bruce Rappaport Faculty of Medicine Award

2002 Post doctoral scholarship - Israel Cancer Society
2002 Post doctoral scholarship- Galil Center for Telemedicine and Medical Informatics, Bruce Rappaport Faculty of Medicine Award
2003 Basic Science Research Award- American Head and Neck Society
2004 Daiichi Clinical Scholar -Clinical Research and Biostatistics -American Academy of Otolaryngology- Head and Neck surgery
2005 Honor Award- American Academy of Otolaryngology- Head and Neck Surgery
2009 Alpha Omega Alpha Medical Honor Society

B. Selected Peer-reviewed Publications (Selected from 120 original manuscripts)

Most relevant to the current application

1. **Goldenberg D**, Begum S, Westra W, Khan Z, Sciubba J, Pai S, Califano JA, Tufano RP, Koch WM: Cystic lymph node metastasis in patients with head and neck cancer: An HPV-associated phenomenon. *Head Neck*. 2008 Jul; 30(7):898-903.
2. **Goldenberg D**, Zagon IS, Fedok F, Crist HS, McLaughlin PJ: Expression of opioid growth factor (OGF) – OGF receptor (OGFr) axis in human non-medullary thyroid cancer *Thyroid*. 2008 Nov; 18(11):1165-70.
3. Ort S, **Goldenberg D**: Management of regional metastasis in well-differentiated thyroid cancer. *Otolaryngol Clin North Am*. 2008 Dec; 41(6):1207-18, xi.
4. Carvalho AL, Jeronimo C, Kim MM, Henrique R, Ahang Z, Hoque MO, Chang S, Brait M, Nayak CS, Jiang WW, Claybourne Q, Tokumaru Y, Lee J, **Goldenberg D**, Garrett-Mayer E, Goodman S, Moon CS, Koch W, Westra W, Sidransky D, Califano JA. Evaluation of promoter hypermethylation detection in body fluids as a screening/diagnostic tool for head and neck squamous cell carcinoma. *Clin Cancer Res*. 2008 Jan1; 14(1):97-107.
5. **Goldenberg D**, Park SS, Carr, M. Percutaneous tracheotomy in otolaryngology - head and neck surgery residency training programs. *Laryngoscope.* Feb 2009;119(2):289-292.
6. **Adil E, Adil T, Fedok F, Kauffman G, Goldenberg D.** Minimally invasive radioguided parathyroidectomies performed for primary hyperparathyroidism. *Otolaryngol Head Neck Surg*. Jul 2009;141(1):34-38.
7. **Goldenberg** D, Brooksby, C, Hollenbeak CS. Age as a determinant of outcomes for patients with oral cancer. *Oral Oncol*. Aug 2009;45(8):e57-61. Epub 2009 Apr 9.
8. Ondik M, Dezfoli S, Lipinski L, Ruggiero F, **Goldenberg D**. Secondary central compartment surgery for thyroid cancers. *Laryngoscope.* Oct 2009;119(10):1947-1950.
9. McLaughlin P, Zagon IS Park S, Conway A, Donahue RN, **Goldenberg D**. Growth inhibition of thyroid follicular cell-derived cancers by the opioid growth factor (OGF) - opioid growth factor receptor (OGFr) axis. *BMC Cancer.* Oct 18 2009;9:369.
10. Poeta L, Manola J, **Goldenberg D**, Forastiere A, Califano J, Ridge J, Goodwin J, Kenady D, Saunders J, Westra W, Sidransky D, Koch WM. The Ligamp TP53 assay for detection of minimal residual disease in head and neck squamous cell carcinoma surgical margins. *Clin Cancer Res.* Dec 15 2009;15(24):7658-7665.11. Choby G, Hollenbeak CS, Johnson S, **Goldenberg D.** Surface electrode recurrent laryngeal nerve monitoring during thyroid surgery: normative values. *J Clin Neurophysiol.* Feb 2010;27(1):34-37.
12. **Goldenberg D**. Response: Minimally invasive radioguided parathyroidectomy performed for primary hyperparathyroidism. *Otolaryngol Head Neck Surg.* Mar 2010;142(3):462; author reply 462-3.
13. Hollenbeak CS, Wang L, Schneider P, Goldenberg D. Outcomes of thyroid cancer in African Americans. *Ethnicity Dis*. 2011;21(2):210-5.
14. Carvalho AL, Henrique R, Jeronimo C, Nayak CS, Reddy AN, Hoque MO, Chang S, Brait M, Jiang WW, Kim MM, Claybourne Q, **Goldenberg D**, Khan Z, Khan T, Westra WH, Sidransky D, Koch W, Califano JA. Detection of promoter hypermethylation in salivary rinses as a biomarker for head and

neck squamous cell carcinoma surveillance. *Clin Cancer Res*. 2011 Jul 15;17(14):4782-9. PMCID: PMC3215270

15. Tashima L. Mitzner R, Durvesh S, **Goldenberg D**. Dyspnea as a prognostic factor in anaplastic thyroid carcinoma*. Eur Arch Otorhinolaryngol*. 2012 Apr;269(4):1251-5.
16. Goyal N. Camacho F, Mangano J, **Goldenberg D**. Thyroid cancer characteristics in the population surrounding Three Mile Island. *Laryngoscope*. 2012 Jan;122(6):1415-21. Epub 2012 May 7.

C. Research Support

Ongoing Research Support

No number Goldenberg (PI) 05/01/2012– 04/30/2014 NCE
George L. Laverty Foundation Grant
Title: Environmental Causes for the Souring Rates of Thyroid Cancer in Pennsylvania
Project goal: To try and ascertain environmental risk factors to explain the rising rates of Thyroid Cancer in the Harrisburg Area
Role: PI

No number Goldenberg PI 4/4/2012 – 04/30/2014 NCE
Woodward Endowment for Medical Sciences Education
Title: Transoral Surgical Anatomy using the daVinci Robot: Creation of an Anatomic and Surgical Atlas and its Impact on Trainee Education
Project goal: to provide an educational reference for residents, as well as to demonstrate the importance of a spatially oriented atlas from the point of view used in robotic approaches.
Role: PI

Completed Research Support

No number Goldenberg & Robertson (PI) 4/1/2009 – 6/30/2011
PSU/Collaborative Dean's Feasibility Grant
Title: P16 Alteration and BRAF Mutation and Patient Outcomes in Papillary Thyroid Cancer
Project goal: This project aims to link p16 alteration and BRAF mutation with poor outcomes
Role: PI

No number Goldenberg (PI) 7/1/2006 – 6/30/2011 NCE
PSU, COM, Department of Surgery- Surgery Feasibility Grant
Title: Upload Growth factor in Differentiated and Undifferentiated Thyroid Cancer Cell Lines
Project goal: This project aims to link the upload growth factor axis with thyroid cancer cell lines.
Role: PI

No number Goldenberg (Co-PI) 7/1/2010 – 6/30/2011
PSU, COM, Department of Surgery – Dean's Feasibility Grant
Title: Outcomes for Recurrent Thyroid Cancer in the Elderly
Project goal: To identify factors associated with variation in treatment for thyroid cancers in the Medicare population. To estimate the impact of different treatments on cost of medical care for patients with recurrent thyroid carcinomas, controlling for tumor features, demographic characteristics, and co-morbid conditions.
Role: Co-PI

5 R03 DEOOO019511-02 Goldenberg/Hollenbeak (Co-PI) 09/01/2010 – 08/31/2012
NIH/ NIDCR
Title: Clinical and Financial Impact of Treatment for Oral and Pharyngeal Cancer
Project Goal: To assess the financial and clinical impact of different treatment approaches for oral and pharyngeal cancers.
Role: Co-PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Schaefer, Eric	Biostatistician
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Wisconsin – River Falls	B.S.	05/03	Mathematics
University of Wisconsin – River Falls	B.S.	05/03	Computer Science
University of Iowa	M.S.	05/05	Biostatistics

A. Positions and Honors

Positions and Employment

2003-2004 Graduate Teaching Assistant, College of Public Health, University of Iowa
2004-2007 Graduate Research Assistant, Center for Public Health Statistics, University of Iowa
2007-2008 Statistician I, Mayo Clinic Cancer Center
2009-present Biostatistician/Scientific Coordinator, Penn State College of Medicine

B. Selected Peer-reviewed Publications

1. Schaefer EW, Loaiza-Bonilla A, Juckett M, DiPersio JF, Roy V, Slack J, Wu W, Laumann K, Espinoza-Delgado I, Gore SD. A phase 2 study of vorinostat in acute myeloid leukemia. *Haemotologica*. 2009;94(10):1375-1382. PMCID: PMC2754953
2. Schaefer EW, Kumar S, Dispenzieri A, Allred J, Gertz MA, Lacy MQ, Rajkumar SV, Mandrekar SJ. (2010) Residual serum monoclonal protein predicts for progression-free survival in patients with previously untreated multiple myeloma. *Cancer*. 2010;116(3):640-646. PMCID: PMC2905541
3. Kapoor P, Greipp PT, Schaefer EW, Mandrekar SJ, Kamal AH, Gonzalez-Paz NC, Kumar S, Greipp PR. Idiopathic systemic capillary leak syndrome (Clarkson's Disease): the Mayo clinic experience. *Mayo Clin Proc*. 2010;85(10):905-921. Epub 2010 Jul 15. PMCID: PMC2947962
4. Matsushima K, Peng M, Schaefer EW, Pruitt JH, Kashuk JL, Frankel HL. Post traumatic contrast induced acute kidney injury: minimal consequences or significant threat? *J Trauma.* 2011;70(2):415-419; discussion 419-420.
5. Curry WJ, Lengerich EJ, Kluhsman BC, Graybill M, Liao J, Schaefer EW, Spleen A, Dignan MB. Academic detailing to increase colorectal cancer screening by primary care practices in Appalachain Pennsylvania. *BMC Health Serv Res.* 2011;11:112. PMCID: PMC3128846
6. Budge MD, Lewis GS, Schaefer EW, Coquia S, Flemming DJ, Armstrong A. Comparison of two-dimensional and three-dimensional corrected glenoid version measurements. *J Shoulder Elbow Surg.* 2011;20(4):577-583. Epub 2011 Feb 16.
7. Uemura T, Schaefer E, Hollenbeak CS, Khan A, Kadry Z. Outcome of induction immunosuppression for liver transplantation comparing anti-thymocyte globulin, daclizumab and corticosteroid. *Transplant Int.* 2011;24(7):640-650. Epub 2011 Mar 23.
8. Moore MK, Schaefer E. A comprehensive regression tree to estimate body weight from the skeleton. *J Forensic Sci.* 2011;56(5):1115-1122. doi: 10.1111/j.1556-4029.2011.01819.x. Epub 2011 Jun 3.

9. Hollenbeak CS, Boltz MM, Nikkel LE, Schaefer E, Ortenzi G, Dillon PW. Electronic measures of surgical site infections: implication for estimating risks and costs. *Infect Control Hosp Epidemiol.* 2011;32(8):784-790.
10. Hollenbeak CS, Nikkel L, Schaefer E, Alemao E, Ghahramani N, Raman JD. Determinants of Medicare all-cause costs among elderly patients with renal cell carcinoma. *J Manag Care Pharm.* 2011;17(8):610-620. PMCID: PMC3350946
11. Camacho FT, Weisman CS, Anderson RT, Millemeier MM, Schaefer EW, Paul IM. Development and validation of a scale measuring satisfaction with maternal and newborn health care following child birth. *Matern Child Health J.* 2012;16(5):997-1007.
12. Paul IM, Beiler JS, Schaefer EW, Hollenbeak CS, Alleman N, Sturgis SA, Yu SM, Camacho FT, Weisman CS. A randomized trial of single home nurse visits vs. office-based care after nursery/maternity discharge. *Arch Pediatr Adolesc Med.* 2012;166(3):263-70. Epub 2011 Nov 7.
13. Kadry Z, Schaefer EW, Uemura T, Shah AR, Schreibman I, Riley TR. Impact of geographic disparity on liver allocation for hepatocellular cancer in the United States. *J Hepatol.* 2012;56(3):618-25. Epub 2011 Oct 23.
14. Matsushima K, Peng M, Velasco C, Schaefer E, Diaz-Arrastia R, Frankel H. Glucose variability negatively impacts long-term functional outcome in traumatic brain injury patients. *J Crit Care.* 2012;27(2):125-31. Epub 2011 Oct 26.

C. Research Support

Ongoing Research Support

No number Hollenbeak (PI) 9/1/2013 – 04/30/2014
Prima Health Analytics
Title: Prevalence of Case Mix Factors for Payments under the ESRD Prospective Payment System (PPS)
Project goal: 1) to provide population-level estimates of prevalence of case mix factors applied to payments under the ESRD prospective payment system (PPS), and other demographic variables such as race and ethnicity, as of the time period used to set the PPS adjusters, and 2) to understand whether there are differences in case mix prevalence by dialysis industry segments based on dialysis organization size and type.
Role: Biostatistician

Completed Research Support

No Number Assigned Hollenbeak (PI) 07/1/2010 – 06/30/2012
Dean's Feasibility Grant, PSU, COM
Title: Outcomes for Recurrent Thyroid Cancer in the Elderly
Project goal: to identify factors associated with variation in treatment for thyroid cancers in the Medicare population. To estimate the impact of different treatments on cost of medical care for patients with recurrent thyroid carcinomas, controlling for tumor features, demographic characteristics, and comorbid conditions.
Role: Biostatistician

5 R03 DEO19511-02 Hollenbeak (PI) 09/08/2009 – 08/31/2012
NIH/NIDCR
Title: Clinical and Financial Impact of Treatment for Oral and Pharyngeal Cancer
Project goal: To assess the financial and clinical impact of different treatment approaches for oral and pharyngeal cancers.
Role: Biostatistician

5 R18 HS19150-02 Gabbay (PI) 09/01/2010 – 07/31/2013
NIH/AHRQ
Title: A Multi-payer Patient Centered Medical Home Initiative in Pennsylvania
Project goal: This proposal is to evaluate the impact of the PA Chronic Care Initiative on patient outcomes and cost-of-care for diabetes.
Role: Biostatistician

1R01NR011874-01 Loeb (PI) 09/29/2009 – 07/31/2013
NIH/NINR
Title: Enhancing End-of-Life Care in Complex Organizations: The Prison Study
Project Goals: (1) To compare and contrast the current status of end-of-life (EOL) care in contextually diverse prison communities across the Pennsylvania Department of Corrections (PA DOC) system; (2) to evaluate the infusion of modified approaches to EOL care using an intervention toolkit to meet the prioritized needs identified by stakeholders in diverse correctional facilities of the PA DOC; and (3) to identify resource utilization data that are most appropriate for determining cost-effectiveness of modified approaches to EOL care and perform cost-effectiveness analysis of EOL interventions.
Role: Statistical Analyst

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Melissa Boltz, DO	General Surgery Resident
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Nova Southeastern University	BS	06/01	Life Science
Philadelphia College of Osteopathic Medicine	DO	06/06	Medicine
St. Luke's Hospital, Bethlehem, PA		06/07	Medicine Internship
Penn State Hershey Medical Center			General Surgery
Penn State World Campus, MBA program	MBA	08/11	Business

A. Positions and Honors

2006 – 2007 Traditional Rotating Intern. St. Luke's Hospital, Bethlehem, PA.
2007 – present General Surgery Resident. Penn State Milton S Hershey Medical Center, Hershey, PA.
2011 Penn State Milton S. Hershey Medical Center Department of Surgery Education Award
2012 Surgical Intensive Care Unit Collaborative Practice Award

B. Publications/manuscripts

1. Keith E, **Boltz M**, Gadh R, Ghorsriz R, Mangatt D, Janoff L. Adhesion of tear proteins to contact lenses and vials. *Appl Biochem.* 2001;34,5-12.
2. **Boltz M**, Hollenbeak C, Julian K, Ortenzi G, Dillon P. Hospital costs associated with surgical site infections in general and vascular surgery patients*. Surgery.* 2011 Nov;150(5):934-942.
3. Stewart DB, Hollenbeak CS, **Boltz MM**. Laparoscopic versus open abdominoperineal resection for rectal cancer: how patient selection and short-term complication rates differ by surgical approach. *J Gastrointest Surg.* 2011 Nov;15(11):1928-38.
4. Hollenbeak C, **Boltz M**, Wang L, Schubart J, Ortenzi G, Zhu J, Dillon P. Cost-effectiveness of the National Surgical Quality Improvement Program. *Ann Surg.* 2011 Oct;254(4): 619-624.
5. **Boltz M**, Hollenbeak C, Nikkel L, Schaefer E, Ortenzi G, Dillon P. Electronic measures of surgical site infection: implications for estimating risks and costs. *Infect Control Hosp Epidemiol*. 2011 Aug;32(8):784-790.
6. Stewart DB, Hollenbeak CS, **Boltz MM**. Renal transplant status in patients undergoing colorectal surgery: is immunosuppression safer than kidney disease? *Surgery.* 2012 Oct;152(4):537-47.
7. **Boltz MM**, Hollenbeak CS, Ortenzi G, Dillon PW. Synergistic implications of multiple postoperative events. *Am J Med Qual.* 2012 Sep-Oct;27(5):383-90.
8. **Boltz MM**, Enomoto LM, Ornstein RM, Saunders BD, Hollenbeak CS. Incidence and survival differences of differentiated thyroid cancer among younger women. *Clin Oncol Adolescents Young Adults.* 2013 Nov;3:79-88.
9. **Boltz MM**, Hollenbeak CS, Saunders BD, Schaefer, E, Goldenberg D. Attributable costs of differentiated thyroid cancer in the elderly Medicare population. *Surgery.* 2013 Aug 22. [Epub ahead of print]

10. Hollenbeak CS, **Boltz MM**, Schaefer E, Saunders BD, Goldenberg D. Recurrence of differentiated thyroid cancer in the elderly. *Eur J Endocrinol.* 2013 Mar;168:549-56.

C. Research Support

Ongoing Research Support

None

Completed Research Support

None