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Temporal Trends and Predictors of Salvage Cancer Treatment After Failure Following Radical Prostatectomy or Radiation Therapy
An Analysis From the CaPSURE Registry

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BACKGROUND: Prostate cancer treatment after failure of primary therapy by either radical prostatectomy or radiation therapy can vary greatly. This study sought to determine trends and predictors of salvage treatment after failure of primary treatment in a community cohort over the past 10 years.

METHODS: From the community-based Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database, 6275 patients were identified who initiated a form of primary treatment for prostate cancer; 839 of these were identified as failing treatment by biochemical recurrence or initiation of secondary treatment between 2000 and 2010. Salvage therapy was categorized as either systemic, local, or none. Patient characteristics were tested for association with salvage therapy using analysis of variance, Pearson chi-square tests, and multinomial logistic regression analysis.

RESULTS: Of the 839 patients identified as failing therapy, 390 (47%), 146 (17%), and 303 (36%) received systemic, local, or no salvage therapy, respectively. Type of primary treatment received was associated with type of salvage therapy (P < .01). There has been an increasing trend in the use of local salvage therapy over the past 10 years (P = .04). Primary treatment type and biopsy Gleason score were significantly associated with type of salvage therapy.

CONCLUSIONS: The use of local salvage therapy has increased over the past decade, whereas the use of systemic salvage therapy has declined. Primary treatment is an important factor in determining which type of salvage therapy a patient will receive.

INTRODUCTION
Prostate cancer continues to be the most commonly diagnosed visceral cancer in United States men, with 238,590 incident cases expected in 2013, accounting for 28% of all incident cancers in men this year.1 The most common forms of primary therapy for clinically localized prostate cancer are various forms of surgery and radiation. Despite primary treatment, approximately 15% to 42% of men who undergo surgery and 22% to 69% of men who receive external beam radiation (EBRT), depending on dose delivered, will experience a biochemical recurrence (BCR).2-5

When clinicians are confronted with the decision to offer salvage treatment following recurrence of disease, they are tasked with identifying the most likely location of recurrence: locoregional versus distant. Because no existing guidelines specifically address indications for salvage therapy, variations in practice patterns are expected. The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database has previously been used to explore secondary prostate cancer treatment use after failure of local therapy.6,7 The aims of the current study were to determine contemporary patterns of salvage therapy in patients who previously failed local primary therapy over time, and to identify risk factors predictive of the specific type of salvage therapy.

MATERIALS AND METHODS
Data were reviewed from CaPSURE, a longitudinal disease registry database of patients with biopsy-proven prostate cancer. Patients were recruited through urologists at more than 40 community and/or academic practice sites distributed
throughout the United States, under supervision of the institutional review board at University of California San Francisco. Patients were treated according to their clinicians’ usual practice patterns and followed until time of death or withdrawal from the study. Details of additional methodology regarding CaPSURE have been reported.8,9

As of 2007, 6275 patients underwent either primary radical prostatectomy (RP) or radiation therapy for localized (stage ≤ T3aN0M0) prostate cancer. Between 2000 and 2010, 839 patients experienced a biochemical failure and/or began secondary therapy at least 6 months after completion of primary therapy (earlier treatment was considered to be adjuvant). Biochemical failure was defined as 2 consecutive prostate-specific antigen (PSA) levels ≥ 0.2 ng/mL following RP or 3 consecutive PSA rises after the nadir following radiation therapy. We chose to use the American Society for Radiation Oncology (ASTRO) definition of BCR rather than the Phoenix definition, because for most of the study period, clinicians would still be referring to the ASTRO definition to make salvage treatment decisions. Salvage treatments were defined as none, RP, EBRT, brachytherapy (BT), cryosurgery, hormonal therapy, or chemotherapy. Patients were categorized by type of salvage therapy in the following manner: systemic (medical or surgical androgen deprivation therapy [ADT], or chemotherapy), local (RP, EBRT, BT, cryosurgery), or none. In order to ensure accurate assignment of patients to the salvage treatment category of “none,” patients were required to have at least 6 months follow-up beyond biochemical failure. Patients who underwent adjuvant radiation (n = 31) following prostatectomy but subsequently experienced a BCR and began salvage therapy were included in the analysis. Baseline sociodemographic and clinical characteristics were assessed, including age, race, level of education, household income, number of comorbidities, PSA at diagnosis, biopsy Gleason score, clinical tumor stage, primary treatment received, and Cancer of the Prostate Risk Assessment (CAPRA) score.10 Pearson chi-square tests and analysis of variance were used as tests of association. The Mantel-Haenszel chi-square test for trend was used to determine significant trends in types of salvage therapy across time and trends in clinical CAPRA risk at presentation across time.

The outcome of salvage therapy, categorized as systemic, local, or none, was determined for each patient. A multinomial logistic regression model was created, using a forward stepwise approach, with salvage therapy “none” as the referent group to determine baseline factors associated with type of salvage therapy. To ensure any baseline clinical differences between primary treatment modalities were accounted for in the multivariable analysis, we performed a separate multinomial regression model as a sensitivity analysis adjusting for CAPRA risk.

RESULTS

Overall, 839 of 6275 (13.3%) patients who underwent primary treatment had a BCR and/or received salvage treatment. Baseline characteristics of those patients who failed primary therapy are described in Table 1. Of the 839 patients who failed initial therapy, 390 (47%), 146 (17%), and 303 (36%) received systemic, local, or no salvage therapy, respectively. The type of primary treatment was significantly associated with type of salvage therapy received (P < .01). Patients receiving local salvage therapy were significantly younger compared to those receiving either systemic or no salvage therapy (P < .01). Biopsy Gleason score was associated with type of salvage therapy (P < .01). Patients with Gleason scores of 8 to 10 were more likely to receive systemic salvage therapy. This same pattern was noted with CAPRA risk and type of salvage therapy, with those exhibiting higher risk more likely to receive systemic therapy (P < .01). Patients with PSA > 20 ng/mL at the time of diagnosis of prostate cancer received systemic salvage therapy at a higher proportion compared to those with lower PSA (P < .01). In addition, higher PSA values at failure were associated with receipt of systemic salvage therapy (P < .01).

The type of salvage treatment received varied by primary treatment. The most common form of salvage therapy was ADT. Of those men primarily treated with prostatectomy, EBRT, or BT, 158 (33%), 113 (72%), and 116 (55%) received ADT as salvage therapy, respectively. A total of 135 (29%) men who were treated with prostatectomy had salvage radiation therapy. Following BT, only 3 men (2%) underwent salvage prostatectomy. No patient underwent salvage RP following EBRT (Table 2).

The median time between primary and salvage treatment was 18 months (range, 6-124 months). Figure 1 shows the trends of salvage treatment over time among the 536 men who received local or systemic salvage therapy. There were 77, 310, 138, and 11 men who received salvage therapy in 2000 to 2001, 2002 to 2004, 2005 to 2007, and 2008 to 2010, respectively. A significant trend in the use of salvage therapy over time was observed (P = .04). The use of local salvage therapy increased over time from 22% in the early 2000s to 55% by the end of the decade. Conversely, the use of systemic salvage therapy decreased over this period. Figure 2 demonstrates trends
of salvage treatment stratified by primary therapy. For those 121 patients treated primarily with EBRT, a significant increase in the use of local salvage therapy was observed, although these numbers were small ($P = .01$).

No discernable trend was observed in primary BT patients ($n = 120$); primary RP patients ($n = 295$) had a nonsignificant trend toward increasing use of local salvage therapy ($P = .91$).

A multinomial logistic regression model was fit to determine the effect of clinical characteristics on type of salvage treatment received (Table 3). Type of primary treatment and biopsy Gleason score were significant predictors of the type of salvage treatment. Patients who were treated with primary radiation demonstrated higher odds of receiving systemic salvage therapy compared to men treated with primary RP. The odds of men initially treated with BT receiving systemic salvage therapy were 4-fold higher compared with men initially treated with RP (odd ratio [OR] = 4.04; 95% confidence interval [CI] = 2.55-6.40). Conversely, the odds of receiving local salvage therapy were significantly less in men receiving primary BT (OR = 0.24; 95% CI = 0.10-0.58) or primary EBRT (OR = 0.08; 95% CI = 0.03-0.20) compared to men.
initially treated with RP. Biopsy Gleason score was associated with systemic salvage therapy, but not local salvage therapy. The odds of receiving systemic salvage therapy was higher in men with Gleason 7 (OR = 2.07; 95% CI = 1.44-2.99) or Gleason 8 to 10 (OR = 3.89; 95% CI = 2.37-6.36) disease compared to men with Gleason ≤ 6, even after adjusting for primary treatment. The odds of systemic salvage therapy in men with clinical stage T3 disease were 4.13 times higher than men with clinical stage T1 disease (OR = 4.13; 95% CI = 1.34-12.7). At presentation, patients undergoing primary EBRT were at higher risk as indicated by CAPRA score. However, after adjusting for risk differences between primary treatment groups in a sensitivity analysis, the results were unchanged.

DISCUSSION
The initiation of salvage therapy following failure of primary prostate cancer therapy can be a complex decision process, for multiple reasons. For instance, many definitions of what constitutes a biochemical failure following both radiation and surgery have been proposed. Furthermore, many variables must be considered, such as pathologic findings at RP (seminal vesicle or margin positivity), PSA doubling time, PSA value at beginning of salvage radiation or prostatectomy, and Gleason grade.\(^{11,12}\) Despite this information, the decision to offer local versus systemic salvage therapy can remain challenging.

In this analysis of a community-based cohort, we identified trends in the use of salvage therapy and pretreatment predictors of the type of salvage therapy received. The use of local salvage therapy has significantly increased during the past decade, whereas systemic salvage therapy use has diminished. Primary treatment type and biopsy Gleason score were significantly associated with the type of salvage therapy received. Men receiving primary radiation therapy were more likely to receive systemic salvage therapy than were men treated initially with RP. In addition, higher Gleason scores were associated with increased odds of systemic salvage therapy, but not with local salvage therapy. Others have found Gleason score to be associated with systemic therapy. Moreira et al, using the SEARCH database, demonstrated that patients with Gleason score 8 to 10 had a 4-fold higher risk of receiving hormonal therapy compared to men with Gleason score 6 disease following RP. Additional factors predictive of receiving hormonal therapy included time from RP to recurrence, tumor stage, hospital site, and year of recurrence.\(^{13}\)

The timing and type of salvage treatment remains controversial. This is evident in that more than a third (303 of 839) of patients who had failed their primary prostate cancer therapy had not received any salvage form of therapy. This finding suggests that clinicians may be monitoring disease progression to better define the natural history of failure and distinguish between local versus distant disease recurrence before initiating a salvage treatment. This finding was also seen in previous CaPSURE analyses regarding the use of secondary treatments.\(^{6,14,15}\)

Furthermore, Freedland et al demonstrated that men with low-risk recurrences (ie, Gleason score ≤ 7) face a lower risk of cancer-specific mortality compared to higher risk men.\(^{6}\)

TABLE 3. Multivariable Multinomial Logistic Regression Model to Evaluate Factors Associated With Type of Salvage Therapy\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Secondary Salvage Therapy</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Treatment</td>
<td>Brachytherapy vs RP</td>
<td>Systemic</td>
<td>4.04 (2.55-6.40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local</td>
<td>0.24 (0.10-0.58)</td>
</tr>
<tr>
<td></td>
<td>EBRT vs RP</td>
<td>Systemic</td>
<td>1.23 (0.85-1.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local</td>
<td>0.08 (0.03-0.20)</td>
</tr>
<tr>
<td>Biopsy Gleason score</td>
<td>7 vs 6</td>
<td>Systemic</td>
<td>2.07 (1.44-2.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local</td>
<td>0.78 (0.48-1.26)</td>
</tr>
<tr>
<td></td>
<td>8-10 vs 6</td>
<td>Systemic</td>
<td>3.89 (2.37-6.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local</td>
<td>1.28 (0.67-2.47)</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td>T2 vs T1</td>
<td>Systemic</td>
<td>1.29 (0.92-1.80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local</td>
<td>1.21 (0.79-1.87)</td>
</tr>
<tr>
<td></td>
<td>T3 vs T1</td>
<td>Systemic</td>
<td>4.13 (1.34-12.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local</td>
<td>0.01 (0.01-999)</td>
</tr>
</tbody>
</table>

Abbreviations: EBRT, external beam radiotherapy; RP, radical prostatectomy.
\(^a\)Referent salvage outcome group is “none.” A total of 801 patients were included in final multivariable model.
Overall, the use of systemic salvage therapy demonstrated a significant decline over time, reflective of the increasing trend in local salvage therapy. This decreasing trend is unlikely to be related to lack of follow-up time in the more recent time periods, because the decline was noted in the early 2000s and persisted. When stratified by primary treatment type, patients initially treated with RP also showed a similar pattern. A potential explanation of this trend could be the increasing evidence suggesting hormonal therapy is associated with an increased risk of cardiovascular (CV)-related morbidity. Recently, SEER-Medicare linked data have shown an increased risk of CV-related deaths in those treated with ADT compared to those men not receiving ADT.16 To be sure, this association is controversial, because others have not found an increased risk of CV-related deaths in those treated with ADT.17,18 In addition, patients were not presenting with increased risk of CV-related deaths in those treated with ADT compared to those men not receiving ADT.16 To be sure, this association is controversial, because others have not found an increased risk of CV-related deaths in those treated with ADT.17,18 In addition, patients were not presenting with earlier stage disease in the latter time periods to account for this decreasing trend in systemic salvage therapy, as evidenced by no significant change in clinical CAPRA risk at initial diagnosis over time (P = .52).

In those patients initially treated with EBRT, there was a significant increase in the use of local salvage therapy. This increase in local salvage and subsequent decrease in systemic therapy may also be related to advances in radiation technology (ie, intensity-modulated radiation therapy)19 and promising results of salvage RP data.20,21 Kaffenberger et al reported a contemporary series of robotic-assisted salvage prostatectomy with favorable outcomes regarding minimal blood loss, low incidence of bladder neck contracture, and short hospital stays (ie, 94% with 1-day length of stay). In addition, the short-term oncologic outcomes at 16 months were promising with only 18% showing a biochemical failure. Recent data have informed the success of salvage BT and cryotherapy following primary EBRT or BT: the 2- and 4-year BCR-free survival rates were reportedly 89% and 70% following salvage high-dose-rate BT and salvage MRI-guided BT, respectively.22,23 In addition, Williams et al reported a 5-year disease-free survival of 47% in 187 patients who underwent salvage cryotherapy following primary radiation therapy.24

There were several limitations to our study. New enrollment into CaPSURE was reduced in the latter years (after 2007) due to limitations in funding. This could have introduced selection bias as to how those who were enrolled were identified for participation, but did not affect follow-up of existing patients. Furthermore, there were no consistent indications for salvage treatment use or knowledge behind the rationale of salvage treatment choice. CaPSURE data do not represent a statistically random sample of US patients. However, previous comparisons to SEER have found relatively minor differences in terms of demographics and risk characteristics.25 Also, the comparison of use of salvage therapies over time may be confounded by follow-up time and smaller sample size, especially in the most recent years. Often, the decision to offer salvage therapy is based on many factors including posttreatment PSA trends, which take time to accumulate. CaPSURE does not collect radiation dose information, and thus we could not account for these potential changes over time in men whose primary therapy was radiation. Finally, there were only a small number of patients receiving salvage RP following radiation therapy during the study time period. Although recent years have seen growing interest in this strategy in published literature from academic centers,26 it remains relatively uncommon, particularly in the community setting.27

Conclusions
Of the 839 patients who failed primary therapy in this study, 46%, 17%, and 36% received systemic salvage, local salvage, and no salvage therapy, respectively. On multivariable analysis, primary treatment type and biopsy Gleason score were associated with type of salvage therapy received. Over the past decade, there has been an increasing trend in the use of local salvage therapy and subsequent decrease in systemic salvage therapy. This trend is most prominent in patients receiving either primary EBRT or RP.

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CONFLICT OF INTEREST DISCLOSURE
Dr. Carroll has been an investigator for Myriad Genetics, Genomic Health, and Abbott Laboratories, and has received grants from the Department of Defense and the National Cancer Institute, outside the submitted work. Dr. Fuldeore is an employee of and owns stock in Abbvie. Dr. Cooperberg has been a consultant for Myriad Genetics, Genomic Health, GenomeDx, Dendreon, Eli Lilly, Abbott Laboratories, Amgen, and Janssen Pharmaceuticals, outside the submitted work. All other authors made no disclosure.

REFERENCES