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Surgery confounds biology: the predictive value of stage, grade and prostate-specific antigen for recurrence after radical prostatectomy as a function of surgeon experience

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Abstract

Statistical models predicting cancer recurrence after surgery are based on biologic variables. We have previously shown that prostate cancer recurrence is related both to tumor biology and to surgical technique. Here we evaluate the association between several biological predictors and biochemical recurrence across varying surgical experience. The study included two separate cohorts: 6091 patients treated by open radical prostatectomy and an independent replication set of 2298 patients treated laparoscopically. We calculated the odds ratios for biological predictors of biochemical recurrence—stage, Gleason grade and prostate-specific antigen (PSA)—and also the predictive accuracy (AUC) of a multivariable model, for subgroups of patients defined by the experience of their surgeon. In the open cohort, the odds ratio for Gleason score 8+ and advanced pathologic stage, though not PSA or Gleason score 7, increased dramatically when patients treated by surgeons with lower levels of experience were excluded (Gleason 8+: odds ratios 5.6 overall vs. 13.0 for patients treated by surgeons with 1000+ prior cases; locally advanced disease: odds ratios of 6.6 vs. 12.2 respectively). The AUC of the multivariable model was 0.750 for patients treated by surgeons with 50 or fewer cases compared to 0.849 for patients treated by surgeons with 500 or more. Although predictiveness was overall lower for the independent replication set cohort, the main findings were replicated. Surgery confounds biology. Although our findings have no direct clinical implications, studies investigating biological variables as predictors of outcome after curative resection of cancer should consider the impact of surgeon specific factors.

Keywords

prostate cancer; prediction; molecular markers; outcome studies; surgeon

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Novelty and Impact of paper: We show that estimates of the effects of biological variables – cancer stage, Gleason grade and PSA – on cancer recurrence after radical prostatectomy depend on the experience of the treating surgeon. Our findings suggest that statistical models attempting to predict recurrence after surgery may be dramatically affected by surgeon-specific variables.

Introduction

An increasing focus of cancer research concerns prediction of disease course. This includes multivariable prediction models based on standard clinical variables^{1–2} as well as molecular markers from serum^{1, 3} or tissue⁴. The aim of such research includes both improved prognostication but, perhaps more critically, also superior risk stratification: for example, the Oncotype model⁵ is said to allow clinicians to identify which patients do and do not require adjuvant chemotherapy for breast cancer.

Oncotype is typical of many prediction models in that the prediction concerns the likelihood of tumor recurrence after curative surgery. Published models predicting recurrence after surgery include those for cancers of the prostate⁶, ovaries⁷, colon⁸ and breast.⁹ Such models typically involve predictors such as stage, grade, hormone receptor status, nodes, and thus predominately reflect tumor biology at the time of surgery. Yet the very point of surgery is to circumvent biology. For example, a localized tumor may well have an aggressive phenotype - with markers associated with metastasis, angiogenesis and immune evasion - but this is likely irrelevant if the tumor is totally excised at the time of surgery, before these properties become manifest.

We recently investigated the association between surgeon experience and recurrence after radical prostatectomy¹⁰, a relationship we described in terms of a “learning curve”. In our initial publication, we reported that the learning curve plateaued after a surgeon had completed approximately 250 – 350 operations. Subsequently, we analyzed the learning curve separately for patients with organ-confined and locally advanced disease. We found a plateau in the learning curve only for the latter group; for those with organ-confined cancer, recurrence rates fell towards zero with increasing surgeon experience. We concluded that recurrence in organ-confined disease was primarily a function of surgical technique; conversely, after the surgeon has reached a certain level of experience, recurrence in locally advanced disease appears to be determined solely by biology¹¹. Recently we published a replication of these findings in an independent cohort of patients treated laparoscopically¹².

From these two premises – first, that statistical models predicting cancer recurrence after curative surgery are based on biologic variables and second, that recurrence is related both to tumor biology and surgical experience – we derive a hypothesis: the predictive value of biologic variables and thus recurrence models is influenced by surgeon experience. We set out to test this hypothesis using a large, multi-institutional data set of biochemical recurrence in prostate cancer patients following open retropubic radical prostatectomy. A cohort of patients treated with laparoscopic radical prostatectomy served as a replication set.

Materials and Methods

Patients and outcomes

The study cohort and endpoints have been previously described^{10,12}. In brief, the open surgery cohort consisted of 7,765 eligible patients with clinically localized prostate cancer who were treated by open radical retropubic prostatectomy 1987 – 2003 by one of 72 surgeons at four US academic institutions. The laparoscopic cohort included 4,702 patients treated by one of 29 surgeons from seven institutions in Europe and North America 1998 – June 2007. All information was obtained with appropriate Institutional Review Board waivers, and data were de-identified prior to analysis.

For each patient, surgeon experience was coded as the number of radical prostatectomies performed by the surgeon prior to the patient’s operation. This number reflects the surgeon’s total prior experience, including operations that the surgeon performed at nonstudy

institutions and operations involving patients who were ineligible for this analysis. In the open cohort cancer recurrence was defined as a serum PSA of more than 0.4 ng/mL that was corroborated by a subsequent higher PSA level (i.e., biochemical recurrence)¹³ and either a rising PSA level > 0.2 ng/ml (four institutions) or > 0.1 ng/ml (three institutions) for the laparoscopic cohort. Differences in recurrence definitions would not affect our results because surgeons practice in a single institution and serve as their own control: this is not a comparison of more vs. less experienced surgeons, but of individual surgeons' results later vs. earlier in their careers. In rare cases (e.g., <1% in the Memorial Sloan-Kettering Cancer Center data set), secondary treatment was initiated for patients who did not meet the criteria for recurrence: such treatment was counted as an event.

Statistical methods

Biochemical recurrence after open radical prostatectomy is a time-to-event variable. The typical approach for prediction models is therefore to use Cox proportional hazards regression, reporting hazard ratios for predictors, and the concordance index as a measure of predictive accuracy. However, we posited that a statistical artifact might be associated with use of these statistics to address hypotheses about the effects of experience on predictive accuracy. It is generally easier to predict events that happen a short time after a prediction is made than those that occur many years subsequently. As surgeons become more experienced over time, surgeon experience is correlated with date of surgery and so patients treated by more experienced surgeons have been followed for a shorter period of time. Accordingly, the only events recorded for patients treated by the most experienced surgeons are those which occur shortly after surgery, and which are therefore easier to predict. As a result, we might expect surgical experience to be associated with the concordance index of a predictive model irrespective of any causal relationship.

To investigate the association between concordance index and length of follow-up, we examined extraprostatic extension (EPE) in patients treated 2000–2003. There is no reason to believe that either stage shift or change in pathology evaluation would have an important impact on the value of this predictor over a brief span of recent years. The results are shown in table 1. There is a strong association between predictive accuracy and length of follow-up that is difficult to explain in terms of changes in tumor biology over a short period of time. This suggests it would be unsound to use the concordance index or hazard ratio in comparisons between different levels of experience.

In order to adjust for a possible association between concordance index and length of follow-up, we used a previously published statistical methodology¹⁴ that involves converting recurrence to a binary event of recurrence by two years. In this analysis, patients who recur before two years are coded as having an event; patients who recur after two years or who were recurrence-free at a follow-up time greater than two years are coded as event-free; patients censored before two years are excluded. Predictive accuracy is then assessed by calculating the area-under-the-curve (AUC) of a logistic regression model, with the coefficients of predictors given as odds ratios. Although conversion of time-to-event data to binary data affects the prevalence of the event, it does not influence AUC as this is calculated separately from sensitivity and specificity. Repeating this analysis on the EPE data showed, as anticipated, no trends over time.

Prediction models for biochemical recurrence after radical prostatectomy most usually include prostate specific antigen (PSA) level; pathologic Gleason grade and pathologic stage defined as extraprostatic extension (EPE), seminal vesicle invasion (SVI) and lymph node invasion (LNI). As there were limited numbers of events in some of analysis, we used a simplified model: PSA (without non-linear terms), Gleason score of the pathologic specimen ≤6, 7 or ≥8 and pathologic stage (organ-confined or locally advanced, defined as any of

EPE, SVI or LNI). The odds ratio for each predictor was calculated based on patients treated by surgeons with at least x prior radical prostatectomies, where x varied from 0 – 1500 for the open cohort and 0 – 700 for the laparoscopic cohort. In order that the odds ratios for PSA was on a similar scale as for stage and grade, it was given as that for a PSA >10 ng/ml compared to 10 ng/ml or less. To test whether the odds ratio for each predictor was independent of surgeon experience we used a permutation test. Surgeon experience was randomly permuted - under the null hypothesis that experience values are exchangeable – on

an iterative basis to obtain a distribution for $\sum_{x=1}^{1500} OR_x - OR_0$, where OR_x is the odds ratio for predictor when analysis is restricted to patients treated by surgeons with at least x prior cases.

We also calculated the AUC of a multivariable predictive model for the entire cohort and for subgroups of patients treated by surgeons with varying levels of experience. Predictive accuracy was corrected for overfit (“optimism”) by bootstrap resampling with 200 replications.

Analyses were conducted using Stata 10.1 (Stata Corp., College Station, TX). The analyses for the open cohort were completed in April 2008; the independent replication on the laparoscopic cohort was conducted in April 2009.

Results

Of the initial sample of 7765 and 4702 patients in the open and laparoscopic cohorts, 1674 and 2404 respectively were censored before two years and were therefore excluded from this analysis. Baseline characteristics of included patients (a total of $n=8389$ treated by 93 surgeons) are shown in table 2. Patients included in the analysis have slightly less favorable tumor characteristics than those excluded for insufficient follow-up (e.g. 33% versus 25% rate of locally advanced disease). This might be expected given that patients who recurred early were included in analysis. There was also a strong association between surgeon experience and heterogeneity in tumor characteristics. For example, the difference between the 75th and 25th centile of PSA is 8.8 for patients treated by surgeons who at the time had 10 or fewer prior surgeries, compared to 3.1 for whom surgical experience was 1500 or greater. We have previously explained this effect in terms of a screening-related stage migration¹⁰. In contrast, we did not see an association between surgeon experience and heterogeneity in tumor characteristics in the laparoscopic cohort: the difference between the 75th and 25th centile of PSA was 5.3 and 4.8 for patients treated by surgeons with 10 or fewer cases and more than 750 prior cases, respectively. In neither cohort did we see evidence of case selection by surgeons as they became more experienced^{10,12}. In the laparoscopic cohort, for example, experience was associated with a trivially lower 5-year predicted risk of recurrence (0.1% per 100 surgeries), explained by differences between institutions ($p=0.4$ after adjusting for institution).

The odds ratios of stage, grade and PSA for biochemical recurrence after radical prostatectomy are shown in figure 1A. Excluding patients treated by surgeons with limited prior experience increases the odds ratios of pathologic stage and high Gleason score, (both $p<0.001$) for predicting recurrence. For example, among the patients treated by open radical prostatectomy, the odds ratio for recurrence of a Gleason score of 8+ compared to 7 is 5.6 when including all patients, rising to 13.0 if the only patients included are those treated by highly experienced surgeons (1000 or more prior surgeries at the time of the patient’s case). For locally advanced disease, the odds ratio is 6.6 overall and 12.2 for patients treated by the most experienced surgeons. The predictiveness of PSA was not significantly influenced by

surgeon experience ($p=0.3$) whereas the odds ratio of Gleason score of 7 versus 6 increases slightly with greater experience ($p=0.01$).

Figure 1b shows the results for the independent replication set. There are some clear differences between the laparoscopic and open cohort, in particular, the odds ratios for each variable are lower. This may reflect differences in staging, recurrence definition or surgical technique between the two cohorts. However, the principal findings are replicated: the odds ratio increases significantly for Gleason 8+ ($p=0.018$) and advanced pathologic stage ($p=0.037$), with no statistically significant for increase PSA ($p=0.4$) and at most a moderate effect for Gleason 7, which is not statistically significant in this cohort ($p=0.2$).

It is plausible that the effects of surgeon experience on the predictiveness of biologic variables could be affected by surgical margin status. Accordingly, we conducted a sensitivity analysis excluding patients with positive margins (leaving 4387 open and 1786 laparoscopic patients for analysis). Our findings were very similar (see figures 2a and 2b). We again found increasing odds ratios for Gleason 8+ and pathologic stage, but not for Gleason 7 or PSA. The increase in odds ratio is somewhat larger: in the case of Gleason 8, odds ratios rose from 6.1 to 13.1 and from 3.4 to 21.3 for the open and laparoscopic cohorts respectively.

With respect to Gleason score, one possible explanation for the change in odds ratio with surgeon experience is that grading practices have changed over time¹⁵, and time is, of course, correlated with experience. We therefore repeated the multivariate analyses adjusting for year. Our results were not importantly different; the odds ratio for Gleason score 8+ was not affected by more than 0.1 for any analysis. Our results were also unaffected if we used different timepoints for recurrence.

Table 3 gives predictive accuracy of the multivariable model for subgroups defined by surgeon experience. The AUC of the complete sample for the open cohort is 0.817. This is similar to that of the concordance index (0.791) providing support for our statistical methodology. Predictive accuracy is clearly dependent on surgeon experience, rising from 0.750 for patients treated by the least experienced surgeons to 0.849 for those treated by surgeons who at the time had a surgical experience of 500 or more prior cases. Statistical optimism, which is subtracted from the AUC to calculate a corrected AUC, was always less than 0.01, suggesting that our results are not an effect of overfit or correction for overfit. Results were unchanged if analysis was restricted to patients treated after 1995 (data not shown). Very similar results were found for the independent replication set: although there is a higher than expected predictive accuracy for patients treated by the least experienced surgeons – perhaps explained by sampling variation associated with the relatively small number of cases – the overall trend remains the same, with increasing predictive accuracy for surgeons with greater experience.

To examine the possibility that our results might be affected by surgeons who never developed a significant caseload, we repeated all analyses restricting the sample to patients treated by surgeons who developed a lifetime experience of at least 100 cases. Our results were not importantly affected. For example, table 3 shows that AUC increased by 0.099 in the open cohort comparing the <50 with those who had 500+ prior operations; this changed to 0.098 for the sensitivity analysis.

Discussion

We have shown that predictions of recurrence based on typically used biological variables of tumor grade, stage and serum PSA after radical prostatectomy are modified by surgeon experience. Many of the statistics we looked at - odds ratios for individual predictors, AUCs

for multivariable models – changed depending on whether the patients included were treated by surgeons with minimal or extensive experience. Some of the findings we reported are dramatic, such as a doubling of the predictive value of Gleason 8+. Our results are independently replicated in two separate cohorts, with the analysis of the first cohort completed before the data for the second cohort were available. Moreover, our replication cohort includes patients accrued after the stage shift. We have previously found no evidence of patient selection by more experienced surgeons^{10,12}, however, if it were the case the more experienced surgeons were selecting lower risk patients – in some manner that was not statistically detectable – it would have the opposite effect to that reported here, with an attenuation of the effect of pathologic stage and high Gleason grade with higher levels of experience.

Experience is correlated with time, and it is worth considering whether some aspects of our results might be explained by temporal trends. First, there have been clear changes in the presentation of prostate cancer due to the introduction of the PSA test (“stage migration”)¹⁶. Predictiveness of a multivariable model depends, in part, upon the heterogeneity of the predictors. Stage migration has led to lowered heterogeneity in the presentation of prostate cancer over time: for example, the rate of locally advanced disease decreased from 40% in patients treated up to 1995 to 27% in patients treated in 1996 and after; the interquartile range for PSA for these two time periods was 9.7 and 4.1 respectively. We would expect this lower heterogeneity to lead to lower predictiveness, the opposite of the effect we saw here. Moreover, we found very similar results in the laparoscopic cohort, which was treated largely after the stage migration. Second, grading practices have changed over time¹⁷. Yet adjusting for year in our analyses did not seem to affect the change in odds ratio for Gleason score with experience. Moreover, the change in grading has been predominately from Gleason score 4 and 5 to score 6/7, and would therefore not explain the very large change in the impact of Gleason score 8+ depending on surgeon experience. Differences in staging or grading practices between institutions are unlikely to explain our findings because, in a learning curve study, surgeons serve as their own control.

We claim that the results of the laparoscopic cohort constitute an independent replication because our main findings were replicated: large changes in odds ratios for pathologic stage and Gleason 8, but not Gleason 7 or PSA, and increasing AUC with greater surgeon experience. However, there were some disparate findings: overall, predictiveness was higher in the open surgery group, and the relative effect of experience on pathologic stage and Gleason 8 was different in each cohort. If anything, these differences would strengthen our conclusion that the effects of biological variables on cancer outcome are mediated by surgical technique.

In conclusion, we find support for our hypothesis that the predictive value of biologic variables, and thus multivariable models based on biological variables, is influenced by surgeon experience: prediction was enhanced in patients treated by the most experienced surgeons. To state that surgery confounds biology is perhaps platitudinous; nonetheless, this may inform analysis and interpretation of the very large number of studies that use biological variables to predict outcome after curative surgery for cancer. While our findings do not have obvious clinical implications, we recommend that investigators examine whether prediction models for other cancers, such as colon, breast, ovarian or bladder, are influenced by surgeon characteristics such as experience.

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Figure 1. Univariate odds ratio for predictors of biochemical recurrence, by surgical experience for patients treated by (a) open or (b) laparoscopic radical prostatectomy PSA (≤ 10 vs. > 10 ng/ml) (dashed line), Gleason 8+ vs. Gleason 7 (black solid line), Gleason 7 vs. Gleason 6 (dark gray solid line), and organ confined versus locally advanced (light gray solid line). The odds ratios on the y axis correspond to analysis of the cohort excluding patients treated by surgeons with fewer than x prior cases. Curves are smoothed by locally weighted regression.

Figure 2. Univariate odds ratio for predictors of biochemical recurrence by surgical experience, restricted to patients with negative surgical margins who treated by (a) open or (b) laparoscopic radical prostatectomy

PSA (≤ 10 vs. >10 ng/ml) (dashed line), Gleason 8+ vs. Gleason 7 (black solid line), Gleason 7 vs. Gleason 6 (dark gray solid line), and organ confined versus locally advanced (light gray solid line). The odds ratios on the y axis corresponds to analysis of the cohort excluding patients treated by surgeons with fewer than x prior cases. Curves are smoothed by locally weighted regression.

Table 1

Univariate concordance index and hazard ratio of extra prostatic extension 2000–2003

Year	Patients	Median (IQR) Length of follow-up (months)	Hazard ratio for EPE	Concordance index for EPE
2000	704	37 (19, 49)	4.0	0.659
2001	737	32 (17, 41)	8.0	0.729
2002	692	25 (15, 31)	8.4	0.756
2003	661	14 (6, 20)	13.1	0.790

Table 2

Characteristics of patients who underwent open RP, separately for patients who were censored before two years, and by subgroups of surgeon experience at time of patient's surgery. All values are median (IQR) or proportion (frequency).

	Open Radical Prostatectomy		Laparoscopic Radical Prostatectomy	
Variable	Patients censored before two years N = 1674	Included in analysis N = 6091	Patients censored before two years N = 2404	Included in analysis N = 2298
Age at surgery (years)	60 (55, 65)	62 (56, 66)	62 (56, 66)	63 (59, 67)
PSA (ng/ml)	6.0 (4.6, 8)	7.0 (5, 11)	5.8 (4.4, 8.3)	7.0 (5.0, 10)
Clinical stage $\geq$ T2	611 (38%)	3401 (56%)	670 (29%)	1180 (52%)
Pathologic Gleason Grade				
≤ 6	739 (44%)	2726 (45%)	971 (40%)	1112 (48%)
7	862 (51%)	2938 (48%)	1284 (53%)	1005 (44%)
≥ 8	73 (4%)	427 (7%)	149 (6%)	181 (8%)
Extraprostatic extension	368 (22%)	1893 (31%)	608 (25%)	722 (31%)
Seminal vesical invasion	77 (5%)	618 (10%)	143 (6%)	245 (11%)
Positive surgical margins	355 (21%)	1704 (28%)	498 (21%)	512 (22%)
Lymph node involvement	23 (1%)	268 (4%)	45 (2%)	36 (2%)
Non Organ Confined Disease	386 (23%)	2037 (33%)	622 (26%)	746 (32%)

Table 3

AUC of 2 year biochemical recurrence for patients treated by open RP, by surgeon experience.

Number of prior cases	Open cohort			Laparoscopic cohort		
	No. Patients	No. Events	Corrected AUC	No. Patients	No. Events	Corrected AUC
Any	6091	1256	0.817	2298	385	0.672
<=50	1137	355	0.750	498	100	0.712
<250	3006	789	0.791	1286	258	0.653
<500	4281	1031	0.803	1761	338	0.658
250+	3085	467	0.844	1012	127	0.717
500+	1810	225	0.849	537	47	0.739