Influence of statin use on clinicopathological characteristics of localized prostate cancer and outcomes obtained after radical prostatectomy: a single center study

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Introduction: *To assess the impact of statin use on biochemical recurrence (BCR) of prostate cancer after radical prostatectomy (RP).*

Materials and methods: *Data from all men treated with robot-assisted laparoscopic RP (RALRP) for localized prostate cancer between 2009 and 2014 at our institution were prospectively collected: age, body mass index (BMI), statin-use status, preoperative prostate-specific antigen (PSA) level, clinical T stage, biopsy Gleason score (bGS), D'Amico risk group, pathological T stage, specimen Gleason score (sGS), multifocality, peri neural invasion, positive surgical margins and time to BCR. Univariate and multivariate analysis were performed to test associations between statin use and prognostic factors of prostate cancer and/or BCR.*

Results: *Overall, 591 patients with a median follow up of 42.3 months [25.8-59.9] were included in the current study and split in two cohorts: statin users (n = 156) and statin non-users (n = 435). When comparing statin user and non-users, no significant difference was found in terms of clinical, biochemical and pathological characteristics except for BMI (median 29 versus 26, respectively; p = 0.04). Regarding BCR, there was no significant difference between men using statin versus those not using them (4.5% versus 4.6%, p = 0.65). In univariate analysis, statin use was not significantly correlated to any prognostic factors of prostate cancer recurrence. Furthermore, there was no significant difference in the 5 years biochemical-free survival rates between statin users and non-users (75% versus 73%; p = 0.7).*

Conclusions: *From the current study, statin daily intake was not significantly associated with any prognostic factors of prostate cancer and with BCR after RARLP.*

Key Words: hydroxymethylglutaryl-CoA reductase inhibitors, prostatic neoplasm, prostate-specific antigen, recurrence, survival

Introduction

Prostate cancer is a widespread male neoplasm that has recently been recognized to account for 27% (233,000) of newly diagnosed cases of cancer and 10% (29,480) of cancer related deaths in 2014 in the United States.[1] Despite ongoing debates regarding both overdiagnosis and overtreatment of prostate cancer, patients presenting with decent life expectancy are still candidates for curative treatment such as radical prostatectomy (RP) that remains one of the gold standard treatment in men between 50 and 70 years.[2] However, up to 40% of patients will experience biochemical recurrence (BCR) after first-line surgical treatment of prostate cancer.[3]

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Interestingly, a specific concern has been recently raised regarding a possible correlation between statin use in these men and the risk of BCR after definitive local therapy of prostate cancer. Statins are 3-hydroxy-3-methyl-glutaryl coenzyme A (HMGCoA) inhibitors that have been increasingly used over the past few years giving their indisputable ability to significantly improve survival by decreasing deaths from cardiovascular disease.[4,5] However, there is also growing evidence suggesting that statins might have a secondary chemoprotective effect against many cancers.[6] Indeed, several authors have demonstrated that statins are able to stop cell-cycle progression, induce apoptosis, reduce inflammation and impede angiogenesis.[7-10] In addition to their lowering cholesterol effect resulting in steroid biosynthesis inhibition rationally involved in hormone dependent cancer progression, statins target the melavonate pathway that is intimately related to well-known signaling routes of carcinogenesis such as p53.[11]

The impact of statin use on the natural history of prostate cancer has been previously investigated in many studies but its real impact still remains controversial.[12,13] Indeed, conflicting results have been reported regarding the propensity of statins to prevent carcinogenesis of aggressive diseases and also to increase the risk of BCR after RP for localized prostate cancer.[14-17]

Thus, our purpose was to assess the impact of statin use on BCR after RP in localized prostate cancer.

Materials and methods

Population

Data from all consecutive men treated with robot-assisted laparoscopic radical prostatectomy (RALRP) for localized prostate cancer between 2009 and 2014 at our institution were prospectively collected in a digital database. Only patients with following available data were included in this observational cohort study: age, body mass index (BMI), statin-use status, preoperative prostate-specific antigen (PSA) level, clinical T stage (cT stage), biopsy Gleason score (bGS), D'Amico risk group, pathological T stage (pT stage), specimen Gleason score (sGS), tumor multifocality (TM), peri neural invasion (PNI), positive surgical margins (PSM), BCR status, time to BCR and follow up. Missing preoperative and/or follow up data in 186 men were consequently exclusion criteria. No patient received preoperative radiotherapy or hormonal treatment. Statin use at the time of diagnosis, regardless of statin dose and type was recorded for each patient. Only men who had taken statin for at least 1 year before surgery were included in the current study. The Ethics Committee of the Assistance Publique-Hôpitaux de Paris (AP-HP) (i.e., IRB approval) approved of the study and the Principles of the Declaration of Helsinki were respected.

Intervention

The da Vinci surgical system was used by two referent surgeons at our institution to perform RARLP, as described previously.[18]

Pathological evaluation

All surgical specimens were analyzed by a single referent uropathologist. They were first fixed in a 10% neutral buffered formalin and were then cut transversally at regular intervals. Pathological stage was defined using the 2009 TNM classification. Tumor differentiation was given according to the surgical Gleason score based on the ISUP 2005 criteria. During the macroscopic examination (orientation, weight, size, description) of the surgical specimen, the entire surface of the RP specimen was covered with ink for an accurate evaluation of surgical margins. Positive surgical margins on pathologic evaluation were defined as cancer cells touching the inked surgical margins of the RP specimen.

Follow up

All patients were seen at 3 and 6 months after surgery and at least once a year thereafter to assess functional outcomes (i.e. potency, urinary continence) and to screen for BCR using PSA testing. Survival was evaluated from the date of surgery to the last follow up visit or death. According to the current guidelines, BCR was defined as two consecutive measures of PSA > 0.2 ng/mL with a 3 month delay.[2] Consequently, recurrence-free survival rate was defined as the time from RALRP to BCR.

Statistical analysis

The Shapiro-Wilk test was used to assess the normal distribution of variables. Then, Student's t-test and Mann Whitney U-test were used to compare normally and non-normally distributed continuous variables, respectively. The chi-square test was used to compare non-normally categorical variables. Associations between statin daily intake and prognostic factors commonly used to assess prostate cancer outcomes: cT stage, bGS, D'Amico risk group, pT stage, sGS, TM, PNI, PSM were tested in univariate analysis. Then, univariate and multivariate Cox regression analysis including statin use were performed to determine potential independent predictors of BCR and estimate their hazard ratios (HR) with 95% IC. Kaplan Meier method and log rank statistics were used to calculate biochemical-free survival rates (BFSR). Statistical values were considered significant for a p value < 0.05. All tests were carried out using SPSS, version 12 (Chicago, IL, USA).

Results

Population

Overall, 591 patients with a median age of 62.8 years [IQR 49.1-69.2] were included in the current study and split in two different cohorts: statin users (n = 156) and statin non users (n = 435). Demographic characteristics of study population are listed in Table 1. Median preoperative PSA level was 8.3 ng/mL [IQR 4.1-12.4] and RALRP was performed on patient with a median BMI of 26.8 [IQR 21.9-34.3]. According to the D'Amico classification, 316 (53.5%), 201 (34.0%) and 74 (12.5%) patients were ranked into preoperative low, intermediate and high risk groups of prostate cancer,

TABLE 1. **Main characteristics of the study population**

Characteristics	**Overall**	**Statin non users**	**Statin users**	**p value**
No. patients (%)	591 (100)	435 (73.6)	156 (26.4)	
Median age (yrs) [IQR]	62.8 [49.1-69.2]	62.4 [49.1-69.2]	63.8 [50.2-69.8]	0.11
Median BMI (kg/m^2) [IQR]	26.8 [21.9-34.3]	26.0 [21.1-33.5]	29.0 [23.4-36.0]	0.04
Median preoperative PSA (ng/mL) [IQR]	8.3 [4.1-12.4]	8.4 [4.3-13.7]	7.9 [3.9-11.8]	0.31
No. clinical T stage				0.18
cT1c	362 (61.2)	265 (60.9)	97 (62.2)	
cT2a	68 (11.5)	49 (11.3)	19 (12.1)	
cT2b	50 (8.5)	36 (8.3)	14 (8.8)	
cT2c	44 (7.5)	33 (7.6)	11 (7.0)	
cT3a	67 (11.3)	52 (11.9)	15 (9.9)	
cT3b	0 (0%)	0 (0%)	0 (0%)	
No. biopsy Gleason score (%)				0.47
≤ 6	351 (59.4)	258 (59.3)	93 (59.5)	
7	185 (31.3)	136 (31.3)	49 (31.3)	
≥ 8	55 (9.3)	41 (9.4)	14 (9.2)	
No. D'Amico risk group (%)				0.41
Low	316 (53.5)	232 (53.3)	84 (53.8)	
Intermediate	201 (34.0)	148 (34.0)	53 (34.0)	
High	74 (12.5)	55 (12.7)	19 (12.2)	
Median blood loss (mL)	347.5 [324.8-370.1]	352.2 [324.6-379.7]	334.1 [296.1-372.2]	0.75
No. specimen Gleason score (%)				0.10
≤ 6	206 (34.9)	147 (33.8)	59 (37.8)	
7	313 (52.9)	233 (53.6)	80 (51.3)	
≥ 8	72 (12.2)	55 (12.6)	17 (10.9)	
No. pathological T stage (%)				0.35
pT2a	27 (4.6)	20 (4.6)	7 (4.7)	
pT2b	19 (3.2)	13 (3.0)	6 (4.2)	
pT2c	381 (64.5)	281 (64.6)	100 (63.9)	
pT3a	133 (64.5)	98 (22.5)	35 (22.1)	
pT3b	31 (5.2)	23 (5.3)	8 (5.1)	
No. tumor multifocality (%)	556 (94)	409 (94.1)	147 (94.1)	0.94
No. peri neural invasion (%)	508 (85.9)	374 (86.0)	134 (85.7)	0.84
No. positive surgical margins (%)	87 (14.7)	64 (14.7)	23 (14.7)	0.96
No. biochemical recurrence (%)	27 (4.6)	20 (4.6)	7 (4.5)	0.65
Median time to BCR (months)	18.5 [12.3-25.1]	18.1 [11.6-25.9]	18.9 [13.1-26.2]	0.23
Median follow up (months) [IQR]	42.3 [25.8-59.9]	41.5 [24.1-57.8]	43.7 [26.4-60.2]	0.19

IQR = interquartile range; BMI = body mass index; PSA = prostate-specific antigen; BCR = biochemical recurrence

TABLE 2. **Univariate analysis testing associations between statin use and clinical, pathological or biochemical characteristics commonly used to assess disease course of localized prostate cancer after robot-assisted laparoscopic radical prostatectomy**

Characteristics	Statin users versus non users	
	HR (95% IC)	p value
Preoperative PSA level	0.98 (0.95-1.02)	0.31
Clinical T stage	0.93 (0.82-1.04)	0.26
Biopsy Gleason score	0.94 (0.74-1.19)	0.57
D'Amico risk group	0.91 (0.79-1.07)	0.31
Specimen Gleason score	0.73 (0.54-1.02)	0.08
Pathological T stage	0.89 (0.79-1.08)	0.36
Extra capsular invasion	0.96 (0.62-1.49)	0.85
Seminal vesicles invasion	0.92 (0.84-1.02)	0.17
Multifocality	0.90 (0.51-1.61)	0.73
Peri neural invasion	1.00 (0.62-1.60)	0.99
Positive surgical margins	0.99 (0.59-1.64)	0.96

respectively. In the statin users group, the median length of statin intake before surgery was 28.2 months [IQR 22.5-36.7]. When comparing statin users with non-users, no significant difference was found in terms of clinical, biochemical and pathological characteristics except for BMI (median 29 versus 26, respectively; p = 0.04). Notably, TM (94.1%; p = 0.94) PSM (14.7%, p = 0.96) rates were exactly the same in both groups. However, there was no significant difference between statins users and non-users according to: preoperative stratification in low risk group of prostate cancer risks (53.8% versus 53.3% respectively; p = 0.41), or pT2 stage diseases on pathologic specimen (73.1% versus 72.2% respectively; p = 0.35).

Statin use and prognostic factors

There was no significant association between statin daily intake and clinicopathological features of aggressive prostate cancer, see Table 2.

Statin use and BCR

After a median follow up of 42.3 [25.8-59.9] months, BCR occurred in 27 (4.6%) patients, Table 1. Again there was no significant difference among statin users compared to statin non-users in BCR (4.5% versus 4.6%, respectively; p = 0.65). Median time to BCR was 18.5 [12.3-25.1] months without any significant difference between statin users and non-users (18.9 versus 18.1, respectively; p = 0.23).

In univariate analysis, statin intake was not significantly associated with a decreased risk of BCR compared to the non-user group (HR = 0.84; 95% IC = [0.36-2.00]; p = 0.70), see Table 3. When performing multivariate analysis, only bGS (HR = 1.60; 95% IC = [1.02-2.51]; p = 0.04), D'Amico risk group (HR = 1.51; 95% IC = [1.24-1.78]; p = 0.01), sGS (HR = 1.94 95% IC = [1.08-3.01]; p = 0.02) and positive surgical margins (HR = 2.82; 95% IC = [1.06-7.05]; p = 0.04) were independent predictors of BCR after RARLP, Table 3.

TABLE 3. **Univariate and multivariate analysis of biochemical recurrence predictors after robot-assisted laparoscopic radical prostatectomy for treating localized prostate cancer**

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95% IC)	p value	HR (95% IC)	p value
Body mass index	0.99 (0.98-1.02)	0.98	-	-
Statin use	0.84 (0.36-2.00)	0.70	-	-
Preoperative PSA level	1.03 (0.98-1.09)	0.21	-	-
Clinical T stage	1.06 (0.95-1.18)	0.37	-	-
Biopsy Gleason score	1.82 (1.34-2.48)	< 0.001	1.60 (1.02-2.51)	0.04
D'Amico risk group	1.78 (1.21-2.35)	0.02	1.51 (1.24-1.78)	0.01
Specimen Gleason score	2.43 (1.53-3.87)	< 0.001	1.94 (1.08-3.01)	0.02
Pathological T stage	2.09 (1.34-3.28)	< 0.001	1.79 (0.93-3.43)	0.08
Multifocality	1.86 (0.55-6.32)	0.32	-	-
Peri neural invasion	2.25 (0.66-7.57)	0.19	-	-
Positive surgical margins	2.53 (1.14-5.66)	0.02	2.82 (1.06-7.05)	0.04

According to Kaplan Meier survival curves, there was no significant difference in the 5 year BFSR between statin users and non-users (75% versus 73%, respectively; p = 0.7). The statistical power of the study was 0.5 .

Discussion

Because statins decrease the level of cholesterol, they have been known for many years to reduce the incidence of major vascular events such as myocardial infarction, coronary accidents and strokes but their impact on prostate carcinogenesis remains controversial. There are biological theories based on experimental data that support a potential preventive effect of cholesterol lowering treatments against hormone dependent cancer progression given that cholesterol is a necessary precursor of steroid biosynthesis.[19] Furthermore, statins might alter prostate cancer cell proliferation considering that cholesterol is the major component of lipid rafts involved in signaling pathways. Likewise, the ability of statins to induce pro-apoptotic, anti-inflammatory and anti-angiogenic effects has also been previously well-described in experimental studies.[14] Despite these encouraging premises, we found that statin use was only correlated to pre-operative BMI, which was significantly higher among statin users. Logically, statin users are more likely to have diabetes or metabolic syndrome both usually linked with an elevated BMI.

Although BCR rate was slightly lower in the statin user group in our study, we failed to demonstrate any significant difference with the statin non-user group. Furthermore, we did not observe any association between prognostic factors of prostate cancer and statin intake, which suggests that statin medication did not influence prostate cancer outcomes after RALRP. Our findings are also highlighted by the similar 5 year BFSR when comparing statin users and non users. One other flaw could also be the lack of power due to the limited number of patients included in each group.

Nevertheless, our findings are consistent with several studies in the recent literature. Recent meta-analysis have shown that the overall risk of prostate cancer was not reduced by statin use[20,21] and several studies have reported that cholesterol lowering treatments intake had no impact on BCR after radical treatment of prostate cancer.[14,22] Based on the analysis of data from 6729 patients included in the REDUCE study, Freedland et al observed that men taking statins on a daily basis had lower PSA levels, higher BMI and lower serum testosterone levels, although differences were low.[23] In this study, the population was stratified according to the D'Amico classification statin use was not associated with aggressive pattern of prostate cancer.

However, some studies have also reported conflicting data. Indeed, Platsz et al demonstrated that statin use was correlated to a significant reduced risk of advanced prostate cancer.[24] These findings were also supported in other large studies.[25,26] Furthermore, Hamilton et al reported a 30% reduction of the risk of BCR among statin users but the results were only significant after adjustments for drug dosage. [27] Indeed, only a daily intake of over 20 mg of simvastatin was associated with a reduced risk of BCR after RP. In our study, we did not record these data considering that only statin use regardless of statin dose and type was recorded in our database. However it remains a moot point according to a recent report.[28] Surprisingly, Misrai et al concluded that statin use was associated with high risk prostate cancer features at diagnosis but with an increased BFSR.[15] In addition, Allott et al reported a reduced risk of BCR with postoperative daily intake of statin, after adjusting for clinical and pathological characteristics.[29] However these data came out from retrospective database and must be taken with caution. In addition, some authors have recently suggested that BCR might only be delayed by statin intake given that cholesterol lowering treatments appear to also lower PSA values.[27] Indeed, Hamilton et al concluded that PSA levels significantly decreased after statin initiation but changes in PSA concentrations were strongly correlated to statin dose and LDL level.[30] Overall, statin use appeared to lower PSA values by only 4% which is more likely to alter initial prostate cancer detection than observed time to BCR after surgery (i.e.; considering a cut-off value of 0.2 ng/mL as a definition of BCR). Further prospective studies with robust methodology are needed to evaluate the clinical significance of this effect given that we did not find any association between statin use and PSA level.

Conclusions

We acknowledge limitations in our study. The follow up was limited (42.3 months) considering the natural history of prostate cancer and a further evaluation with a longer follow ups would be interesting to better assess the risk of BCR after RALRP. Lastly, we did not take into consideration the type of statin and dosage.

In the light of our experience, we would not support the hypothesis that statins influence the risk of BCR in the absence of other meaningful data. In our study, we found no influence of statin medication on clinicopathological features of aggressiveness on the specimen and outcomes of localized prostate cancer after radical surgery. Only a robust randomized clinical trial would help to make a final statement on the impact of statin drugs on prostate cancer recurrence after first-line treatment. □

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