

Role of HMG-CoA reductase inhibitors with curative radiotherapy in men with prostate cancer

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Abstract: Brachytherapy and external beam radiotherapy are effective and commonly used treatment modalities in men with localized prostate cancer. In this review, we explore the role of radiation therapy in the curative management of prostate cancer, including the use of conformal therapeutic techniques to allow for the escalation of radiation doses to tumor, along with the use of combined radiation and hormonal therapy to enhance disease outcomes in men with aggressive disease. We also review the possible anticancer role of HMG-CoA reductase inhibiting agents (statins) in men with prostate cancer. Laboratory evidence suggests that statins may have antineoplastic effects when used alone and may sensitize cells to radiation therapy when given in combination. We explore the biologic basis for an anticancer effect and the clinical evidence suggesting statins may aid in improving outcomes with radiation therapy for localized prostate cancer.

Keywords: HMG-CoA reductase inhibitors, statins, radiotherapy, prostate cancer

Introduction

Prostate cancer is the most commonly diagnosed malignancy in elderly men. Approximately 217,730 patients in the USA are estimated to have been diagnosed with prostate cancer in 2010, and 32,050 will die of the disease.¹ The optimal management of prostate cancer is nuanced and specific to any given patient's clinical presentation, comorbid medical conditions, and predicted disease course. Active surveillance, radical prostatectomy, and radiotherapy (including external beam radiotherapy [EBRT] and brachytherapy), are the primary management options for localized prostate cancer. Since the implementation of widespread prostate-specific antigen (PSA) screening, there has been a shift in the pattern of initial presentation in men diagnosed with prostate cancer. Over the last 30 years, there has been a shift from clinically palpable disease on digital rectal examination toward diagnosis via screening PSA elevation in nearly 50% of patients.² With this in mind, the key consideration in the approach to the patient with newly diagnosed prostate cancer involves the estimation of whether a cancer may create clinically significant morbidity and mortality. Multiple parameters have been used to help differentiate those who may have clinically significant disease and may benefit from aggressive local therapy. These include the presence of a palpable nodule on digital rectal examination, Gleason score on biopsy, pretreatment PSA, and the percentage of biopsy cores which contain disease. These factors are used to categorize patients as having low-risk, intermediate-risk, or high-risk disease, and consequently help guide decision-making.³⁻⁸ In this review, we aim to introduce the radiotherapeutic issues in the treatment of localized prostate cancer, and present the biologic rationale

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and clinical data for the possible anticancer effect of HMG-CoA reductase inhibitors (statins) with radiotherapy in the treatment of prostate cancer.

Local therapy for prostate cancer

In men undergoing treatment for prostate cancer, there are few randomized studies comparing the different treatment modalities, and no clearly superior treatment exists.^{9–12} Thus the decision for surgery or radiotherapy is influenced by patient comorbidity, age, a tolerable side effect profile, and patient preference.¹³ Retrospective data suggest that both treatment modalities offer similar biochemical control. A retrospective analysis of 1682 men with cT1–2 disease treated at the Cleveland Clinic with prostatectomy or high-dose EBRT revealed similar biochemical control in both cohorts with long-term follow-up.¹⁴ Potters et al performed a retrospective study of 1819 patients with cT1–2 disease treated with either radical prostatectomy, EBRT, or seed implant, and also showed similar freedom from biochemical recurrence at seven years, with 74% (seed implant), 77% (EBRT), and 79% (radical prostatectomy) for the three groups ($P=0.09$).¹⁵ Nearly 40% of men with prostate cancer ultimately pursue radiotherapeutic modalities for treatment.¹⁶

Radiation therapy for prostate cancer

Radiotherapy is used in the curative treatment of multiple malignancies, and can also play an important role in palliation. EBRT uses X-rays created by a linear accelerator to damage the DNA of malignant cells. This is accomplished via direct damage to DNA strands as well as by the creation of oxygen radicals, which contribute a relatively larger proportion of the damage to DNA. Although X-ray radiation is not cell-specific, its greatest impact is in rapidly dividing cells, because the damage to DNA manifests in apoptosis and senescence during cellular mitosis/meiosis. Actively dividing normal tissue cells are also at risk for damage from radiotherapy, leading to the toxicities of treatment. In men undergoing radiotherapy for prostate cancer, the rectum and bladder are the primary normal tissues at risk for radiation damage. Thus, the most successful delivery of radiation necessitates a balance between acute and long-term toxicity to normal tissues and maximal tumor cell kill. Small daily doses of radiotherapy (fractionation) over several sessions (eg, 8–9 weeks for prostate cancer) are frequently prescribed to take advantage of the differential sensitivity of normal tissues and malignant cells to radiotherapy. Advances in planning (intensity-modulated radiotherapy) and onboard

imaging have significantly improved the ability to deliver high doses of radiation therapy safely, resulting in improved cure rates. Alternatively, agents that sensitize tissues to radiation damage (radiosensitizing agents) can also contribute to increased cell kill, and could widen the therapeutic window by increasing the lethality of radiotherapeutic effects.

EBRT dose escalation

In men who select EBRT, there is evidence to indicate that doses greater than 70 Gy provide improved prostate cancer control. Multiple randomized trials have demonstrated the benefit of dose escalation in the definitive management of prostate cancer. Pollack et al randomized 301 men with cT1–T3 disease to 70 Gy and 78 Gy.^{17,18} Ten-year freedom from biochemical or clinical failure was 73% in the 78 Gy group and 50% in the 70 Gy group ($P=0.004$). A Dutch randomized study by Peeters et al also showed a benefit in biochemical or clinical progression-free survival with 78 Gy over 68 Gy in 664 men.^{19,20} Seven-year freedom from failure was 56% for 78 Gy and 45% for 68 Gy. Zietman et al randomized 393 men with cT1b–T2b disease to 70.2 Gy or 79.2 Gy using combined photon and proton EBRT.^{21,22} Those receiving 79.2 Gy had significantly improved ten-year biochemical progression-free survival (83% versus 68%). The Medical Research Council assessed whether the benefit of dose escalation was maintained with the use of neoadjuvant and concurrent hormonal therapy. The Medical Research Council RT01 trial randomized men with T1b–T3a disease to 3–5 months of neoadjuvant and concurrent hormonal therapy with either 64 Gy or 74 Gy.²³ Five-year biochemical progression-free survival was 71% in the dose-escalated group and 60% for the lower-dose group (hazard ratio [HR] 0.67 [0.53–0.85], $P=0.007$). There was a trend toward improved clinical progression-free survival and freedom from salvage androgen suppression therapy.²³

Brachytherapy

Radioactive seed implant (brachytherapy) is an effective and convenient alternative to traditional EBRT, and can provide similar outcomes when performed properly. In this procedure, seeds formed of a radioactive isotope, commonly iodine-125 or palladium-103, are placed within the prostate gland. These seeds emit high-energy gamma irradiation over a small distance, allowing for a very conformal treatment modality. Patients electing for brachytherapy undergo a volume study to plan an optimal seed arrangement to deliver a tumoricidal dose to the prostate, while limiting excessively high doses to the urethra. The implant procedure is usually performed over

1–2 hours on an outpatient basis. Candidacy for brachytherapy is based on prostate volume, disease risk category, history of transurethral resection of the prostate, and ability to tolerate spinal or general anesthesia. Prostate volumes smaller than 15–20 mL may have an increased radiation dose to the urethra. Additionally, seed implantation in men with gland volumes greater than 60 mL may be technically difficult or even impossible due to pubic arch interference, making these groups poor candidates. Brachytherapy as monotherapy is used mostly in those with low-risk disease, although combined EBRT and brachytherapy has been shown to provide disease control in higher-risk patients.^{24,25} Radiation dosimetry appears to be a key factor in biochemical control. Stock et al found that doses greater than 140 Gy to 90% of the prostate volume allowed for 96% six-year freedom from biochemical failure compared with 60% in those with lower doses.²⁶

Radiotherapy + hormonal therapy

Hormonal therapy with gonadotropin-releasing hormonal agents and nonsteroidal antiandrogens has been shown to be an effective, although ultimately temporary, single-treatment modality in prostate cancer.²⁷ One proposed mechanism of hormonal therapy is likely via apoptosis of prostate cancer cells.²⁸ Hormonal therapy has been found to have an additive, and possibly synergistic, effect with radiotherapy on malignant cells in both in vitro and animal studies.^{29–31} This has led to the study of hormonal therapy with radiation to sensitize prostate cancer cells to radiotherapy, allowing for increased cell kill with a similar radiation dose.

The role of combined radiotherapy and neoadjuvant, concurrent, and adjuvant androgen suppression therapy in men with more aggressive prostate cancer has been studied in multiple randomized studies.^{32–43} In patients with high-risk disease, there appears to be a benefit to long-term androgen suppression therapy; men in this cohort often receive 2–3 years of hormonal therapy with radiation therapy.^{35–43} In intermediate-risk patients, randomized studies suggest a benefit for shorter-term androgen suppression.^{32–34} These men typically receive six months of hormonal therapy with radiation therapy. Among those with intermediate-risk disease, men with percent positive cores greater than 50% may benefit more than those with lower volume disease.⁷ However, the benefit of hormonal therapy must be weighed against the potential toxicity, including increased risk of cardiovascular events, metabolic syndrome, hot flashes, and decreased libido and sexual function.⁴⁴ Thus, those with significant medical comorbidity may not be optimal candidates for treatment, and selection of those who would

most benefit from hormonal therapy becomes a more difficult question.

Statins as anticancer agents

Despite advances in technique and technology in both brachytherapy and EBRT, there continues to be a challenge to provide excellent rates of disease control while keeping the risk of toxicity very low. There is growing evidence that HMG-CoA reductase inhibitors (statins) may have a role in patients with prostate cancer. We surveyed the literature regarding the use of statins as anticancer agents using the search phrases “statin + radiotherapy,” “statin + prostate cancer,” and “statin + cancer” via PubMed, the American Society of Therapeutic Radiology and Oncology abstract database, and the American Society of Clinical Oncology abstract database.

Although the effect of statins in overall prostate cancer incidence is unclear, statin users may have a decreased risk of advanced prostate cancer.^{45–47} Shannon et al performed a case-control study evaluating the association between statins and risk of prostate cancer, and found a reduction in risk of development of Gleason score ≥ 7 disease.⁴⁷ Murtola et al similarly found no benefit for overall prostate cancer incidence, but a decreased risk for advanced disease in a non-PSA-screened population in Finland.⁴⁸ Platz et al performed a study in a large cohort of health professionals, and found a decreased risk of metastatic and fatal prostate cancer, but no association with total prostate cancer incidence.⁴⁵

In addition to the hypothesized preventative benefit of statin use, laboratory studies suggest that statins may also have anticancer activity. This opens up the possibility to use statin agents in the treatment of malignancy. Below we discuss the biologic evidence suggesting an anticancer effect of statin agents, as well as clinical studies evaluating the relationship between statin agents and biochemical and clinical outcomes in prostate cancer.

Statins as radiosensitizing agents

Considerable effort has been made to understand the effects of statins on malignancy at the cellular level. HMG-CoA reductase inhibitors have been hypothesized to have anti-neoplastic activity through several mechanisms, including decreasing tissue inflammation, antiangiogenesis, decreased tumor cell adhesion/invasion, and increasing tumor cell apoptosis.^{49–57} Specifically, in prostate cancer, Zhuang et al showed that simvastatin may increase apoptosis in certain prostate cancer cells by modulating membrane lipids.⁵⁸ Multiple studies have implicated possible cellular signaling

pathways involved in anticancer activity.^{59,60} However, in most of these studies, statins have only been shown to exert significant anticancer activity at high doses.

The evaluation of statins to potentiate other established antineoplastic therapeutic modalities, such as radiotherapy, may yield more implications for clinical management. In prostate cancer, several laboratory studies have evaluated the ability of statin agents to act as radiosensitizing agents, ie, to make tumor cells more sensitive to radiotherapy. However, the data suggest that statins may have a more complex relationship with radiotherapy than being mere sensitizers. Nubel et al found that lovastatin and simvastatin decreased E-selectin gene activation in human umbilical vein endothelial cells and EA.hy-926 cells treated with radiation.⁵³ E-selectin has been shown to increase tumor cell adhesion to endothelial cells, thus facilitating extravasation, and potentially promoting metastasis.⁶¹ Thus by modulating E-selectin gene activation, lovastatin may play a role in decreasing the likelihood of tumor spread.⁶² It may do so through inhibition of nuclear factor kappa beta activation, which is necessary for E-selectin expression. However, this only seems to hold true at high doses. Nubel et al found that at lower doses, lovastatin may decrease apoptosis in human umbilical vein endothelial cells undergoing radiation, thus suggesting a radioprotective effect in endothelial cells.⁶³ Seemingly, at lower doses (closer to physiologic intracellular and intravascular doses), statins may have a radioprotective effect, while at higher doses ($>10 \mu\text{mol/L}$), they may have a radiosensitizing effect. Since many of the toxic side effects of radiotherapy have their roots in endothelial dysfunction, improving endothelial stability could potentially allow for more tolerable toxicity profiles, leading to closer adherence to therapy and reduced late toxicity.^{64–66}

Fritz et al⁶⁷ studied the effect of pretreatment with lovastatin on cellular apoptosis and cytotoxicity after radiation with gamma rays in multiple human cancer cell lines, and found that lovastatin acted as a radiosensitizer in a cell-specific and dose-dependent manner. In this study, while sensitizing HeLa cervical cancer and MeWo human melanoma cell lines, there was no effect on DLD1 colon cancer, T47D and MCF-7 breast cancer, and Chinese hamster ovary K1 cell lines. Specifically, lovastatin pretreatment in HeLa cells was not associated with changes in double-strand DNA breaks or subsequent repair, but did appear to decrease the fraction of cells in the G2 phase of the cellular cycle from 50% to 25% at 24–72 hours after radiation.⁶⁷ Because increases in cellular G2 arrest following radiation have

been associated with increased resistance to radiation,^{68–70} the authors suggested that the radiosensitizing effects of lovastatin may be at least in part due to this phenomenon.⁶⁷ Additionally, statins have been found to be radiosensitizers by decreasing isoprenylation of the oncogenes, ras and rho, in cells with increased activity of the *ras* oncogene, which is important in patients undergoing radiation therapy, because increased ras activity has also been associated with radiation resistance.^{71,72}

Statin use and outcomes with radiotherapy

To assess the clinical significance of these laboratory studies, several groups have investigated the effect of combined statin use with radiotherapy. In addition to the prevention of aggressive prostate cancer, statins may play a role in the treatment of other malignancies. For example, in a cohort of patients treated with preoperative concurrent chemoradiotherapy for rectal carcinoma, statin use was associated with an improved pathologic complete response at the time of surgery.⁷³

In men with prostate cancer, the results of retrospective studies in men undergoing EBRT and/or brachytherapy show inconsistent changes in biochemical, survival, and clinical progression in statin users. Table 1 depicts the results of several recent studies comparing outcomes after radiotherapy in statin users and statin nonusers undergoing treatment for prostate cancer.

Statin use and biochemical control

Moyad et al studied a cohort of 512 patients with cT1–T3a localized disease undergoing brachytherapy, of whom 65 were statin users.⁷⁴ With a median follow-up of 5.3 years, eight-year biochemical progression-free survival, defined as $\text{PSA} \leq 0.4 \text{ ng/mL}$, was higher in statin users, although this difference was not statistically significant (97% versus 94%, $P = 0.398$). However, statin users in this study had a more favorable clinical presentation. This group had significantly more T1b–T2b stage patients (92% versus 77%, $P = 0.006$), lower pretreatment PSA (median 5.7 versus 6.9, $P = 0.012$), and a shorter follow-up (median 4.4 versus 5.5 years, $P = 0.002$). When divided into risk subgroups, no subset had a statistically significant improvement in progression-free survival. Multivariate analysis of the data showed that statin use was not a significant predictor of biochemical progression-free survival.⁷⁴

In a follow-up study, Moyad et al published nine-year outcomes data of an expanded cohort of 938 patients, with 191 statin users.⁷⁵ Although length of follow-up, pretreatment

Table I Selection of studies evaluating statin use and outcomes with radiotherapy in men with prostate cancer

Study	Type of RT	Patients (n)	Number of statin users (% total patients)	Median pretreatment PSA	Pretreatment risk grouping	Androgen deprivation therapy	Median follow-up (years)	Biochemical progression-/relapse-free survival			P value
								Time point	Statin user	Statin nonuser	
Moyad et al ⁷⁴	Brachytherapy	512	65 (13%)	6.7	LR 33% IR 41%	NR	5.3	8 years	97%	94%	0.398
Moyad et al ⁷⁵	Brachytherapy	938	191 (20%)	7	HR 24% LR 35% IR 45%	NR	5.4	9 years	98%	95%	0.062
Soto et al ⁷⁸	3DCRT or IMRT	968	220 (23%)	7.9	HR 20% LR 28% IR 42%	36%	4.1	5 years	67%	57%	0.03
Gutt et al ⁷⁶	EBRT ± brachytherapy or brachytherapy alone	691	189 (27%)	8.4	HR 30% LR 39% IR 39%	47%	50 months	4 years	93%	80%	<0.001
Kollmeier et al ⁷⁷	3DCRT or IMRT	1681	382 (29%)	Statin group: < 10: 73% 10–20: 19% > 20: 8%	HR 22% FR 35% IR 45% HR 20%	49%	5.9	5/8 years	89%/80%	83%/74%	0.002

Abbreviations: RT, radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; EBRT, external beam radiotherapy; LR, low risk; IR, intermediate risk; HR, high risk; FR, favorable risk; PSA, prostate specific antigen.

PSA, prostate volume, and percent positive biopsies were still statistically more favorable in statin users, nine-year biochemical progression-free survival trended to be better in statin users. Despite this, statin use was not significantly associated with improved biochemical outcome on multivariate analysis.⁷⁵

Gutt et al⁷⁶ studied 691 men with prostate cancer, of whom 61 (9%) had brachytherapy only, 584 (84%) men had EBRT, and 46 men had a combination of the two (7%). Forty-one percent of the men received neoadjuvant, concurrent, or adjuvant androgen deprivation therapy (ADT), with a median duration of four months. In this cohort, 189 men were statin users (27%). With a median follow-up of 50 months, four-year freedom from biochemical failure was 93% in statin users, compared with 80% in statin nonusers. This benefit was seen in all National Comprehensive Cancer Network risk groups, and was independent of hormonal use and radiotherapy dose. Additionally, statin dose and type of statin did not impact freedom from biochemical failure. Statin use was associated with freedom from biochemical failure, as well as relapse-free survival, on both univariate and multivariate analysis (HR 0.43 for freedom from biochemical failure, 95% confidence interval 0.25–0.73).⁷⁶ A subset analysis of men with lipid panels available ($n = 293$) at the start of radiation therapy demonstrated that men with lower low-density lipoprotein levels also had improved outcome, independent of statin use. Although the numbers of patients in this subset analysis were too limited to make firm conclusions, the results suggest that the potential anticancer effect of statins may be, at least in part, mediated through the lipid pathway.

Kollmeier et al performed a retrospective review of 1681 men with prostate cancer undergoing EBRT.⁷⁷ Fifty-six percent of men received neoadjuvant and concurrent hormonal therapy. In total, 382 men (23%) were statin users. With a median follow-up of 5.9 years, statin users had an improved eight-year PSA relapse-free survival compared with nonusers. Eight-year PSA relapse-free survival was 80% in statin users, and 74% in nonusers ($P = 0.002$). Univariate and multivariate analysis revealed statin use was associated with improved PSA relapse-free survival. Analysis by National Comprehensive Cancer Network risk category revealed that this association was limited to men in the high-risk group. Men with high-risk prostate cancer had eight-year PSA relapse-free survival of 75% in men treated with a statin, compared with 58% in men not on a statin.⁷⁷

Conversely, Soto et al found that statin use did not correlate with differences in biochemical failure in a cohort of 968 patients undergoing EBRT. Although statin users had better 5-year progression-free survival (67% versus

57%) on univariate analysis, when limiting the cohort to patients treated during 1996–2006, statin users failed to have improved biochemical progression-free survival on multivariate analysis, because the statin group had fewer high-risk patients than the nonstatin group.⁷⁸ Sharma et al reviewed 983 patients receiving EBRT in a cohort of men with mostly T1–T2 stage disease, excluding those having ADT prior to radiation therapy, and compared outcomes with respect to statin use.⁷⁹ With a median follow-up of 58.1 months, there was no difference in biochemical progression-free survival among statin users and statin nonusers.⁷⁹

Interestingly, statin use has been correlated with improved rates of biochemical control in men undergoing radical prostatectomy. Hamilton et al studied 1319 men treated with radical prostatectomy at four Veterans Administration hospitals with clinical data available in the SEARCH (Shared Equal Access Regional Cancer Hospital) database.⁸⁰ At the time of prostatectomy, 236 men (18%) were statin users. Statin use was documented and dose was normalized to an equivalent dose. A total of 260 men (20%) received radiation therapy, 158 (12%) received hormonal therapy, and 84 (6%) received both following surgery. There was no significant difference in adjuvant treatment between statin users and nonusers. After controlling for multiple clinical and pathologic factors, statin use was associated with a decreased risk of PSA recurrence (HR 0.70, $P = 0.03$). This held true only in men with a statin dose of at least one dose equivalent (46% reduced risk of biochemical recurrence). Duration of statin use prior to surgery was not associated with biochemical outcome.⁸⁰

Statin use and clinical endpoints

Changes in survival outcomes in statin users undergoing radiotherapy have been evaluated in several studies. Moyad et al found that statin users undergoing brachytherapy for prostate cancer trended toward better nine-year overall survival and cancer-specific survival.⁷⁵ In this study, atorvastatin users had a trend for improved overall survival compared with men taking other statin drugs (94% versus 81.3%, $P = 0.12$). Additionally, patients being treated with ADT who were statin users trended toward better cancer-specific survival, overall survival, and biochemical progression-free survival than statin nonusers.⁷⁵ Participants in the CaPSURE trial undergoing statin therapy did not have any improved prostate cancer-specific mortality.⁸¹ Gutt et al, Sharma et al, and Kollmeier et al found no statistically significant difference in cancer-specific survival or overall survival between statin users and statin nonusers.^{76,77,79} Additionally, no difference in the development of metastatic

disease was found, although follow-up duration may not have been long enough to detect any such difference in all of these studies.^{76,77,79}

One of the challenges in interpreting the results of many of these studies is that statin users tend to present with more favorable prognostic factors, such as Gleason score and pretreatment PSA, as well as differences in radiation treatment parameters. In retrospective cohort studies it is unclear how much of this imbalance in disease presentation is attributable to more aggressive PSA screening and earlier presentation by nature of more health-conscious patients. Comparative analysis becomes even more complex when patients undergo multiple treatment modalities such as ADT in addition to EBRT, because most radiation therapy studies had some proportion of patients undergoing ADT. Additionally, it is unclear whether the statins are merely suppressing PSA values or actually suppressing disease growth, because statins have been shown to decrease PSA levels in healthy individuals.^{82,83} The effect of cholesterol levels and obesity on prostate cancer has also been controversial, and may obscure the true benefit of statins in these studies.^{58,84,85} As noted earlier, Gutt et al had pretreatment lipid panel information available for a subset of men. Pretreatment high-density lipoprotein and triglyceride levels were not associated with improved freedom from biochemical progression (FFBP) but lower total cholesterol and low-density lipoprotein values were correlated with improved FFBP.⁷⁶

Statin tolerability

Overall, statin agents have a relatively low risk of significant adverse reactions. The two most common dangerous side effects are hepatic dysfunction and myopathy. A meta-analysis of 35 randomized trials (74,102 subjects) found a significantly increased risk of transaminase elevation of 4.2 cases per 1000 versus placebo. There was no significant increase in the risk of myalgia, creatine kinase elevation, or rhabdomyolysis. However, older patients, those with renal insufficiency or chronic active disease, and those using combined therapy are often excluded in these trials.⁸⁶ A study of 23,000 patients in a large health maintenance organization found that statin users had a 0.1% rate of developing alanine aminotransferase elevation higher than 10 times the upper limit of normal, with most of these due to drug interactions. In nearly all these cases, elevation resolved upon discontinuation of the statin agent.^{87,88}

The presentation of myopathy in statin users encompasses a spectrum from myalgias to rhabdomyolysis that could potentially result in renal damage. The incidence of

overall myopathy is 1.2 per 10,000 person-years in statin users, which is similar to that in the general population.⁸⁷ The incidence of rhabdomyolysis was 0.05% in patients receiving simvastatin in the Heart Protection Study.^{89,90} Although randomized data fail to show significantly increased risks for myopathy, it continues to be a common cause for discontinuation of statin therapy in clinics.

Other complications of statin use have not clearly been elucidated. There may be a small increase in the risk for diabetes in patients using statins. A meta-analysis of 13 trials found a small increase in risk for diabetes (odds ratio 1.09).^{91,92} Additionally, benign proteinuria has also been seen in statin users.^{92,93} Meanwhile, the association of statin use with an increased risk for cataracts, neuropathy, and memory loss has been suggested, but remains unclear.^{94–99}

Conclusion

Although the results of several studies investigating the role of statins in improving the outcomes of radiotherapy in men with prostate cancer are encouraging, it is difficult to draw firm conclusions regarding the efficacy of statins to improve cancer control. Without a randomized prospective study testing the biochemical and clinical outcomes in men with prostate cancer treated with radiotherapy with or without statin therapy, the exact impact of statin use cannot be assessed. Additionally, the optimal dose and timing of statin administration is unclear. Due to the retrospective nature of the existing data, the relatively short follow-up, and heterogeneous populations in these studies, we cannot make a clear judgment regarding the efficacy of statins in addition to radiotherapy in men with prostate cancer. However, the possibility exists for these relatively safe and inexpensive agents to augment radiotherapy outcomes to have a potential impact on improving prostate cancer cure rates, and to decrease the need for relatively toxic adjuvant therapies, such as hormonal therapy. Further dose escalation of statin therapy, and ultimately a randomized controlled trial, would be warranted to elucidate the optimal role of statins in the treatment of prostate cancer.

Disclosure

The authors report no conflicts of interest in this work.

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