JSCP Visiting Fellow Paper
Oncological outcomes of laparoscopic total mesorectal excision with extended lateral pelvic lymph node dissection for advanced lower rectal cancer after preoperative chemoradiotherapy


This abstract has been previously published.

ASCRS Visiting Fellow Paper
Simvastatin enhances radiation sensitivity of colorectal cancer cells by targeting the EGFR-RAS-ERK axis

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Aim: Preoperative chemoradiation is recommended for locally advanced rectal cancer. However, response is variable among patients, and greater response is associated with improved survival and reduced local recurrence rates. We have shown that taking HMG-CoA reductase inhibitors, commonly known as statins, during chemoradiation is associated with improved response, suggesting a potential radiation-sensitizing role for these drugs. The purpose of this study was to investigate the effects of simvastatin on colorectal (CRC) cancer cells in vitro and explore the underlying mechanisms.

Method: The sensitivity of CRC cell lines HRT18 and SW480 to simvastatin, radiation or combination therapy was assessed using colony formation and ATP-based cell viability assays. To test the dependence of any effects on isoprenylation pathways downstream of HMG-CoA, a rescue arm was added wherein the prenoid geranylgeranyl diphosphate (GGPP) was included in the media. Protein lysates were obtained and tested for expression and phosphorylation status of proteins downstream of Epidermal Growth Factor Receptor (AKT, Ras, MEK, ERK1/2), since these have been reported as a potential target of statins. The effects of simvastatin on cell growth were rescued by the addition of GGPP to the media, and the combination dose necessary to achieve comparable inhibition (Figure). These effects of simvastatin compared to control cells demonstrated a significant decrease in ERK1/2 phosphorylation, while AKT phosphorylation levels remained constant. Two different patient-derived CRC stem cells established from surgical specimens, a subpopulation of tumor cells characterized by radiation resistance.

Results: CRC cell lines (HRT18 and SW480) were sensitive to clinically relevant doses of simvastatin (Inhibitory Concentration [IC] 50: 1.8 and 2 μM, respectively). The combination of radiation and simvastatin yielded decreased cell growth and viability compared to either treatment alone in both lines, in effect halving the radiation dose necessary to achieve comparable inhibition (Figure). These effects of simvastatin on cell growth were rescued by the addition of GGPP to the media, suggesting its depletion drives these effects. Protein analysis of cells treated with simvastatin compared to control cells demonstrated a significant decrease in ERK1/2 phosphorylation, while AKT phosphorylation levels remained constant. Two different patient-derived CRC stem cell lines were radiation-resistant at baseline, but resistance was overcome by simvastatin treatment (IC50: 0.06–0.2 μM), and by combination treatment of simvastatin and radiation.

Conclusion: In accordance with our prior clinical observations, treatment with simvastatin enhanced the sensitivity of CRC cells to radiation in vitro. The dependence of these effects on GGPP depletion and the associated decrease in ERK1/2 phosphorylation suggest a prominent role for the EGFR-RAS-ERK1/2 axis. In addition, simvastatin effectively targets and kills the radioreistant subpopulation of CRC stem cells which are known to contribute to tumor resistance and recurrence. Mechanistic and in vivo studies are under development, laying the foundation for the ultimate goal of a clinical trial.

KSCP Visiting Fellow Paper
Multidimensional analysis of the learning curve for robotic total mesorectal excision for rectal cancer: lessons from a single surgeon’s experience

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Aim: To provide a multidimensional analysis of the learning curve in robotic total mesorectal excision (TME) for rectal cancer.

The robotic approach was expected to overcome the technical limitations and long learning periods associated with the laparoscopic approach in the treatment of rectal cancer. However, there have been few studies on the learning curve associated with robotic TME.

Method: This is a single surgeon’s experience of 167 patients undergoing robotic TME between December 2007 and August 2012. Operative time, conversion, perioperative morbidity, and circumferential margins were hypothesized as the most relevant factors in evaluating the comprehensive learning process, and were used to generate a single hybrid variable to measure the success of the procedure. A moving average for operative time and a risk-adjusted Cumulative Sum (CUSUM) model were used to fit the learning curve.

Results: Overall conversion occurred in 2 cases (1.2%). The risk-adjusted CUSUM plot demonstrated that the composite event was more frequent at the beginning of the series, and began to decrease after 32 cases, the cut-off point. The moving average for robotic console time decreased steadily and showed a biphasic pattern, with the first plateau at 34 cases and the second plateau at 72 cases. Therefore, learning process was divided into 3 periods based on these findings. Robotic console time decreased significantly with each learning phase (phase 1 vs. 2 vs. 3, 112.3 min vs. 90.0 min vs. 68.4 min, respectively, *P < 0.001). Lower rectal cancer and preoperative chemoradiation were more frequent in the later phases. However, the incidence of postoperative complications remained constant throughout the series (*P = 0.818).

Conclusion: Our study shows that the learning process for robotic TME affects the first 32 cases most heavily in terms of operative time and perioperative outcomes. It also suggests that with accumulation of experience it is possible to perform more difficult robotic procedures without increasing postoperative morbidity. These results may impact the settings used in ongoing and future trials and help form a basis for performance monitoring of robotic TME.