



<b>Title</b>	<b>Inhibition of ornithine decarboxylase facilitates pegylated arginase treatment in lung adenocarcinoma xenograft models</b>
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## Inhibition of ornithine decarboxylase facilitates pegylated arginase treatment in lung adenocarcinoma xenograft models

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**Introduction:** Arginine depletion has shown anticancer effects among arginine auxotrophic cancers. Pegylated arginase (BCT-100) depletes arginine by converting arginine to ornithine. In this study, BCT-100 inhibited cell growth in a panel of lung adenocarcinoma cell lines while stimulated tumour growth in most lung adenocarcinoma xenograft models. Furthermore, ornithine decarboxylase (ODC) was induced by BCT-100 in two solid xenograft models with tumour growth stimulating effect. We postulated that accumulated ornithine was used to produce polyamines by ODC which promoted tumour growth, and ODC inhibition might rescue the therapeutic effect of BCT-100 treatment in lung adenocarcinoma.

**Methods:** A panel of seven lung adenocarcinoma cell lines (H23, H358, HCC827, H1650, H1975, HCC2935, and HCC4006) was used to study the in-vitro and in-vivo effects of BCT-100. Protein expression, arginine level, and apoptosis were investigated by Western blot, ELISA, and TUNEL assay, respectively.

**Results:** BCT-100 reduced in-vitro cell viability across different cell lines and HCC4006 xenograft model while paradoxical growth stimulation was observed in H358, HCC827, H1650, and H1975 xenograft models. Upon BCT-100 treatment, ODC was induced in two solid tumour xenograft models (H1650 and H1975), while unaltered in cystic tumour xenograft models (H358 and HCC827) and the remaining solid tumour (HCC4006) xenograft model. In both H1650 and H1975 xenografts, combined -difluoromethylornithine (DFMO, an ODC inhibitor) and BCT-100 significantly suppressed tumour growth compared with control or single-arm treatments. In HCC4006 xenograft model, the tumour suppression effect of BCT-100 arm and DFMO/BCT-100 arm was similar. The tumour suppression effect was partially mediated by arginine and polyamines depletion resulted in apoptosis.

**Conclusion:** Inhibition of ODC by DFMO is essential in BCT-100 (pegylated arginase) treatment in lung adenocarcinoma.

## Adenoma recurrence rates after curative resection for right-side or left-side colonic cancer

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**Introduction:** Patients with a history of colorectal cancer (CRC) are at increased risk of developing metachronous lesions including adenoma and cancer. We aimed to determine the rates of colorectal polyp and adenoma recurrence on surveillance colonoscopy in patients after colonic resection for right-side (R-CRC) and left-side CRC (L-CRC).

**Methods:** Consecutive patients with CRC who had undergone surgical resection in our hospital between January 2001 and December 2004 were identified from our colorectal cancer database. Patients were included only if they had undergone curative surgical resection and had a clearing colonoscopy performed either before or within 6 months after the operation. Patients with familial colorectal cancer syndrome (familial adenomatous polyposis, hereditary non-polyposis colorectal cancer syndrome), subtotal or total colectomy, and inflammatory bowel syndrome were excluded. Findings of surveillance colonoscopy performed up to 5 years after colonic resection were included in the analysis. Patient's baseline characteristics, tumour locations, type of surgical intervention, and surveillance colonoscopy findings were retrieved. In this study, R-CRC was defined as cancer at and proximal to splenic flexure and L-CRC included all other distal cancers.

**Results:** A total of 863 patients underwent curative surgical resection for CRC during the study period and 473 patients (172 patients with R-CRC and 301 with L-CRC) fulfilled our inclusion criteria. Among them, 107 (62.2%) patients with R-CRC and 220 (73.1%) patients with L-CRC had at least one surveillance colonoscopy, with a total of 474 colonoscopies performed. The proportion of patients who had polyp and adenoma detected on surveillance colonoscopy was higher for those who had surgery for L-CRC compared to those who had surgery for R-CRC (polyp 30.9% vs 19.6%,  $P=0.03$ ; adenoma 25.5% vs 13.1%,  $P=0.01$ ). The mean number of adenoma on surveillance colonoscopy was also higher for patients with L-CRC compared to R-CRC (0.52, 95% confidence interval [CI] 0.37-0.68 vs 0.22, 95% CI 0.08-0.35;  $P<0.01$ ). On multivariate analysis, increasing age, male gender, longer follow-up time, and L-CRC were independent predictors of adenoma detection on surveillance colonoscopy after curative surgical resection for CRC.

**Conclusion:** Patients who had surgery for L-CRC have a higher chance of developing metachronous polyps and adenoma than those with R-CRC. Our findings may imply a need to have a different surveillance strategy for patients with L-CRC or R-CRC.