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**Adjuvant Chemotherapy Following Potentially Curative Resection of  
Colorectal Cancer Metastases: A Meta-Analysis of Two Phase III  
Randomized Controlled Trials**

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**Background:** Adjuvant systemic chemotherapy (CT) after resection of colorectal cancer (CRC) metastases (M) may reduce the risk of recurrence and improve survival, but such benefit has never been proven in a prospective clinical trial. Two phase III trials of similar design (FFCD 9002 and EORTC/NCIC CTG/GIVIO [ENG] trials) showed a trend for improvement in survival after adjuvant CT but had to close prematurely due to slow accrual, and are therefore underpowered to demonstrate a significant survival advantage. We report here a pooled analysis based on individual data from these trials.

**Methods:** In both trials, patients were required to have a World Health Organization (WHO) performance status  $\leq 2$  and histologically proven CRC with a complete (R0) surgical resection of the primary tumor and  $\leq 4$  liver or lung metastases. Patients were randomized to either post-operative chemotherapy (CT arm – 5-FU 400 mg/m<sup>2</sup> and dl-leucovorin 200 mg/m<sup>2</sup> [FFCD] or 370 mg/m<sup>2</sup> intravenous [IV] and l-leucovorin 100 mg/m<sup>2</sup> [ENG] IV every day  $\times$  5 days, at 28-day intervals for 6 cycles), or surgery alone (S arm).

**Results:** A total of 129 patients were enrolled in the ENG trial between 1994 and 1998, and 173 in the FFCD trial between 1991 and 2001. Twenty-eight patients (ENG: 26, FFCD: 2) were excluded from analysis for missing post-baseline data. There are 274 patients included in the present analysis (CT: 137, S: 137) with a median follow-up of 9.8 years (FFCD: 9.1, ENG 10.2). Baseline characteristics by treatment arm in the pooled analysis (% CT/S) include male gender:

58.0/63.6; age < 70 years: 79.7/79.3; disease-free interval > 1 year: 56.5/57.1; liver M: 94.2/93.6; and  $\geq 2$  M resected: 33.3/31.4. Outcomes are listed in the Table below. Treatment with CT (versus observation) and number of metastases (1 versus 2+) were significantly associated with improved overall survival (OS) and progression-free survival (PFS) after multivariate analysis.

**Conclusion:** Adjuvant CT with a bolus 5-FU-based regimen tends to improve survival after complete resection of CRC metastases. The observed improvement in median PFS approached statistical significance whereas the absolute improvement in median OS of more than 1 year did not. There likely remains a lack of statistical power despite this pooled analysis. Our analysis supports the use of adjuvant CT after potentially curative resection of CRC metastases, perhaps with more effective agents.

	n	Median PFS (months) [95%CI]	5-year PFS (%)	Median OS (months) [95%CI]	5-year OS (%)
<b>CT</b>	137	27.9 [21.0–41.9]	32.8	62.2 [45.2–NR]	52.9%
<b>S</b>	137	18.8 [14.7–23.8]	28.1	47.3 [40.6–57.2]	39.6%
<b>Hazard ratio (S vs CT)</b>		1.32 [1.00–1.76]		1.32 [0.95–1.82]	
<b>P value (log-rank test)</b>		.058		.095	

CI = Confidence interval, NR = no response.