Comparative Effectiveness of 5-Fluorouracil with and without Oxaliplatin in the Treatment of Colorectal Cancer in Clinical Practice

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Abstract. *Background: First-line chemotherapeutic treatment of colorectal cancer (CRC) typically comprises oral (capecitabine) or intravenous 5-fluorouracil (5-FU) plus leucovorin (LV), in combination with oxaliplatin (XELOX or FOLFOX, respectively), although debate exists regarding the best course of treatment by modality in clinical practice. Evidence from practice comparisons is important in considering the net benefit of alternative chemotherapy regimens, given expected differences in survival associated with compliance and age of patients treated in real life versus controlled trial settings. Patients and Methods: Practice variation in 5-FU treatment (i.e. 5-FU/leucovorin, FOLFOX, capecitabine and XELOX) of patients with CRC from an Australian area health service (n=636) was analyzed between modalities by patient age, tumour stage and site using non-parametric tests. Survival analyses (n=434) were conducted over a three-year follow-up period using Cox regression, adjusting for observed confounders. Results: FOLFOX was the most commonly administered regimen. 5-FU modality was significantly associated with patient age (p<0.001), tumour stage (p<0.001) and site (p<0.001). Cox regression analyses found no significant difference in survival with the addition of oxaliplatin to 5-FU regimens. Conclusion: Our findings suggested no survival benefit with the addition of oxaliplatin to 5-FU modalities in treating CRC in practice. This raises questions as to the net benefit of oxaliplatin, given its known toxicity profile and expense.*

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Key Words: Colorectal cancer, 5-fluorouracil, capecitabine, oxaliplatin, comparative effectiveness research, treatment effectiveness, cost effectiveness.

Since the late 1950s, chemotherapeutic treatment of colorectal cancer (CRC) has centred on the use of fluoropyrimidine 5-fluorouracil (5-FU), with varying administration and scheduling regimens, ranging from bolus injection to continuous infusion, as well as oral pro-drug forms (1, 2). In randomised control trials (RCTs) intravenous (*i.v.*) 5-FU-alone was shown to be efficacious in the treatment of only 10-15% of TNM stage III resected CRCs, but when used in combination with its synergistic biomodulator leucovorin (LV; calcium folinate) with or without the addition of oxaliplatin (commonly referred to as FOLFOX or FLOX), survival outcomes are significantly, albeit modestly, improved in the adjuvant treatment of stage II or III resected CRCs or colon cancer (2-5). In Australia, the use of FOLFOX for the adjuvant treatment of stage III CRC has been listed on the Pharmaceutical Benefits Scheme (PBS) since December 2005, giving subsidised access to this group of patients only.

Oral pyrimidines such as capecitabine provide an alternate treatment to *i.v.* regimens (6). The different modes of administration and range of *i.v.* schedules has arisen not only because of schedule-dependent side-effects typically associated with cytotoxic drugs (*e.g.* diarrhoea, stomatitis, neutropenia, nausea and alopecia), but also because of a number of *i.v.* administration complications associated with the insertion of a catheter, including phlebitis, sepsis and blockages, as well as convenience (7, 8). In large RCTs, capecitabine and *i.v.* 5-FU/LV were shown to have comparable efficacy in the adjuvant treatment of resected stage III colon cancer (9), and for the treatment of metastatic

CRC (10), although hand-foot syndrome and stomatitis are common side-effects associated with capecitabine (1, 10, 11). Several RCTs have compared capecitabine plus oxaliplatin (XELOX) to FOLFOX regimens and reported slightly improved outcomes with FOLFOX for patients with metastatic CRC, although these differences were not significant (12-14). Capecitabine has been subsidised on the PBS for the adjuvant treatment of stage III colon cancer since April, 2006. The listing was extended to include XELOX in February, 2011.

While many 5-FU-based RCTs and randomised crossover trials have quantified information on side-effects, efficacy and preference, few studies have been conducted which follow-up on patients treated in practice. Comparative analyses of therapy effectiveness in practice take into account factors that differ substantially from the RCT setting. Compliance rates during clinical trials are likely to be higher than in a patient-practice setting and therefore the estimated efficacy of oral chemotherapy in RCTs may be inflated relative to use in practice. Additionally, strict exclusion criteria often lead to older populations being omitted from RCTs, despite the fact that they often represent a large proportion of patients with cancer in practice (15-17). Recently-conducted USA-based cohort studies examining patients with stage III colon cancer in practice reported a benefit of oxaliplatin addition to *i.v.* 5-FU chemotherapy for patients under 75 (18) but not over 75 years (19). Herein, we conducted the first Australian retrospective cohort study to examine whether patterns of overall survival associated with oxaliplatin *versus* non-oxaliplatin containing *i.v.* and oral 5-FU treatment of CRC in practice are consistent with those observed in RCTs.

Patients and Methods

Data collection. CRC is currently the second most common non-melanomatous skin cancer in New South Wales (NSW) Australia (20). De-identified CRC patient data from all six public hospitals in the South Eastern Sydney and Illawarra Area Health Service (SESIAHS), which services 17% of the NSW population (21), were obtained from the SESIAHS Clinical Cancer Registry (ClinCR) for patients diagnosed with CRC between 1 January, 2006 and 31 December, 2009 (n=2,321). Data supplied included patient age, sex, date of diagnosis, date of death, cancer morphology, tumour site, surgery, radiotherapy and chemotherapy treatment dates and information. While cancer staging (based on the TNM and Dukes' stage system) was not recorded for some patients, degree of spread was universally reported in this registry. The four indicators for degree of spread were "localised to tissue of origin" (comparable to TNM stage I), "invasion of adjacent tissues/organs" (comparable to TNM stage II), "regional lymph node involvement" (comparable to TNM stage III), and "distant metastasis" (comparable to TNM stage IV). In cases where data was missing for staging, the degree of spread indicator was used to provide staging information.

Statistical analysis. All 2,321 patients were included in analysis of CRC epidemiology. Further analyses were restricted to the four most commonly used chemotherapy modalities: *i.v.* 5-FU/LV (de Gramont, Mayo and Roswell Park regimens), FOLFOX (or FLOX), capecitabine or XELOX (n=636). Differences between treatments were statistically tested using Pearson's Chi-square test, Mann-Whitney *U*-test, and Kruskal-Wallis one-way ANOVA. *p*-values less than 0.05 were considered statistically significant. Bonferroni adjustment was used where relevant.

Overall survival analyses were conducted with three years' follow-up from chemotherapy commencement, with administrative censoring at 19 June, 2011 for those observed for less than three years. Patients who underwent chemotherapy more than once, or changed chemotherapy were not included in comparative survival analyses. Patients from outside the SESIAHS were excluded, as deceased status was not always reported to the SESIAHS ClinCR for these individuals. This conservative approach to undertaking survival analysis in practice reduced the total number of patients to 434 for the estimation of hazard ratios (HR) using Cox regression analysis. This analysis was adjusted for potential confounders, including age, sex, cancer site (rectal or colon), stage of cancer (stages I-IV), and other treatments (radiotherapy, surgery or both). The time difference between date of diagnosis and start of chemotherapy treatment (<6 months for 98% of individuals) was not included as a confounder as its interaction with survival time was not significant (p=0.234). All HR estimates from the Cox regression models were tested for proportionality using methods proposed by Schoenfeld (22, 23). Proportionality of HRs over the follow-up period is an underlying assumption of the Cox regression model. As RCTs generally examine adjuvant treatments for stage III CRCs, we also performed unadjusted survival analyses using Kaplan Meier estimates and the log-rank test for stage III patients to compare *i.v.* 5-FU/LV *versus* FOLFOX (n=175).

Ethics approval. This study was reviewed and approved by the University of Wollongong Human Research Ethics Committee (HE11/244) and by the SESIAHS ClinCR steering committee.

Results

Colorectal cancer profile within SESIAHS. Out of the 2,321 patients with CRC recorded in the study period, 81.1% resided locally (as defined by local government area geographical boundaries) in the SESIAHS. There were significantly more males (56.3%) diagnosed with CRC (χ^2=36.49, df=1, p<0.001), consistent with broader NSW data where 55% of new CRC cases in 2008 were male. The median age of a patient at diagnosis was 69 years for males and 71 years for females, consistent with the NSW median ages of 69 and 72 for males and females, respectively (20). More individuals had cancer of the colon (64.7%) than of the rectum (36.3%).

Treatment modality. Most patients with CRC (88.8%, n=2,060) underwent some form of treatment. The most common treatment was surgery, with 77.5% of all patients having surgery with or without adjuvant treatment. Of patients treated with chemotherapy, 26.6% received either the

Table I. *Chemotherapy treatments administered to patients with colorectal cancer from the South Eastern Sydney Illawarra Area Health Service diagnosed between 1 January, 2006 and 31 December, 2009.*

Chemotherapy treatment	Frequency	Percentage
Oral 5-FU		
Capecitabine	187	21.6%
XELOX	43	5.0%
Sub-total	230	26.6%
Intravenous 5-FU		
FOLFOX	339	39.2%
5-FU/LV (*e.g.* de Gramont, Roswell Park, Mayo regimen)	67	7.8%
Sub-total	406	47.0%
Other		
FOLFIRI	26	
Intraperitoneal 5-FU chemotherapy[1]	52	
Unknown 5-FU (registry reports labelled '5-FU' without any further specification)	89	
Biological agents (*e.g.* cetuximab, imatinib, mitomycin-C, or a trial protocol)	61	26.4%
Sub-total	228	
Total	864	100%

[1]Experimental treatment limited to one hospital within SESIAHS. XELOX: capecitabine/oxaliplatin; FOLFOX: 5-fluorouracil/leucovorin/oxaliplatin; 5-FU/LV: 5-fluorouracil/leucovorin; FOLFIRI: 5-fluorouracil/leucovorin/irinotecan.

oral form of 5-FU (capecitabine) with or without oxaliplatin (XELOX) (n=230), while 47.0% received *i.v.* 5-FU/LV with or without oxaliplatin (FOLFOX) (n=406) (Table I). The remaining patients (*n*=228; 26.4%) were treated with a range of other regimens (Table I) and were excluded from further analyses.

Capecitabine use in the SESIAHS increased from approximately 22% in 2006 to a peak of 30% in 2008, suggesting early and relatively high implementation of this medication. In contrast *i.v.* 5-FU use remained relatively stable over the period 2006-2009 (inclusive), accounting for between 49-52% of all chemotherapy treatments prescribed in each year.

Associations between chemotherapy treatment and patient diagnoses. The 5-FU modality was significantly associated with mean age of patients at diagnosis (F=8,166.6, n=636, df=3, p<0.001) (Table II). Oral 5-FU was more frequently used than *i.v.* 5-FU in older patients (75+ years: 66% oral *vs.* 34% *i.v.* patients). 5-FU treatment allocation also differed based on stage of cancer (H=90.17, n=634, df=9, p<0.001) (Table II). Patients with more advanced cancer (stage III and IV) were more likely to receive an oxaliplatin-based chemotherapy treatment. A significant association was found between 5-FU modality and tumour site (χ^2=44.65, n=636, df=3, p<0.001), with colon cancer patients more likely to receive FOLFOX (Table II).

Variations in survival relative to chemotherapy treatment. A number of patients either changed chemotherapy treatment or had a second round of treatment (Table III; n=107). This occurred more frequently with individuals whose first treatment was either XELOX (30.2%) or FOLFOX (19.8%). The reasons for changing therapy are not reported but are expected to be due to relapse and toxicity. These patients were excluded from the following survival analyses (n=434 remaining).

Cox regression adjusting for confounders (Table IV) found no significant difference in survival with the addition of oxaliplatin to *i.v.* (5-FU/LV *vs.* FOLFOX) or oral (capecitabine *vs.* XELOX)-based regimens (Table V). There was evidence of HR non-proportionality between capecitabine and XELOX, but not between 5-FU/LV and FOLFOX. While not statistically significant, the HR of 1.89 for 5-FU/LV *vs.* FOLFOX favours 5-FU/LV.

Cox regression modelling suggested evidence of higher survival in CRC patients treated with *i.v.* compared to oral 5-FU (HR=1.58, p=0.014) (Table V). However, there was strong evidence (p=0.003) of non-proportional HRs due to converging survival curves, with the HR attenuating to 1.0 as time progresses. Notwithstanding, the overall HR estimate was significantly larger than 1.0 which suggested evidence of at least an initial survival benefit to patients treated with *i.v.* therapy.

Mean survival times up to three years were not significantly different for patients with stage III CRC treated with 5-FU/LV, compared to those treated with FOLFOX (χ^2=0.280, df=1, p=0.596, Figure 1).

Discussion

Despite the rise of novel chemotherapeutic regimens (such as cetuximab), this study confirmed 5-FU to be the most commonly-administered drug for the treatment of CRC in this Australian area health service, with FOLFOX administered more frequently than any other CRC chemotherapy regimen. Evidence of improved efficacy in RCT settings (4) provides a rationale for the high administration rate seen in our study. However, no survival benefit was evident with the addition of oxaliplatin to *i.v.* 5-FU/LV in treating patients with CRC in this practice. While larger Australian cohort studies are warranted to investigate this further, a recent pooled analysis of individual patient data from four RCTs of stage III colon cancer patients concluded that the 5-year disease-free survival (62.8%) was equivalent for capecitabine with/without oxaliplatin and 5-FU/LV with/without oxaliplatin (24). Furthermore, RCTs comparing

Table II. *Percentage of 5-fluorouracil-treated colorectal cancer cases by first-line treatment modality.*

	Capecitabine (n=187)	XELOX (n=43)	FOLFOX (n=339)	5-FU/LV (n=67)	Total (n=636)
Mean age at diagnosis (years)	68.3	61.0	60.2	64.6	63.2
Degree of spread/TNM[1] stage					
Localised to tissue of origin/I (n=17)	1.1%	0%	0.8%	0.8%	4.9%
Invasion of adjacent tissues/organs /II (n=60)	4.9%	0.2%	1.6%	2.8%	7.4%
Regional lymph nodes/III (n=329)	13.7%	2.7%	28.9%	6.4%	51.6%
Distant metastasis/IV (n=228)	9.4%	3.9%	22.0%	0.5%	35.8%
Unknown[2] (n=2)	0.3%	0%	0%	0%	0.3%
Tumour site					
Colon (n=441)	17.9%	5.5%	41.5%	4.4%	69.3%
Rectum (n=195)	11.5%	1.3%	11.8%	6.1%	30.7%
Total (n=636)	29.4%	6.8%	53.3%	10.5%	100%

[1]TNM classification of malignant tumours based on tumour size, lymph node involvement and metastasis. [2]Excluded from statistical analysis. XELOX: capecitabine/oxaliplatin; FOLFOX: 5-fluorouracil/leucovorin/oxaliplatin; 5-FU/LV: 5-fluorouracil/leucovorin.

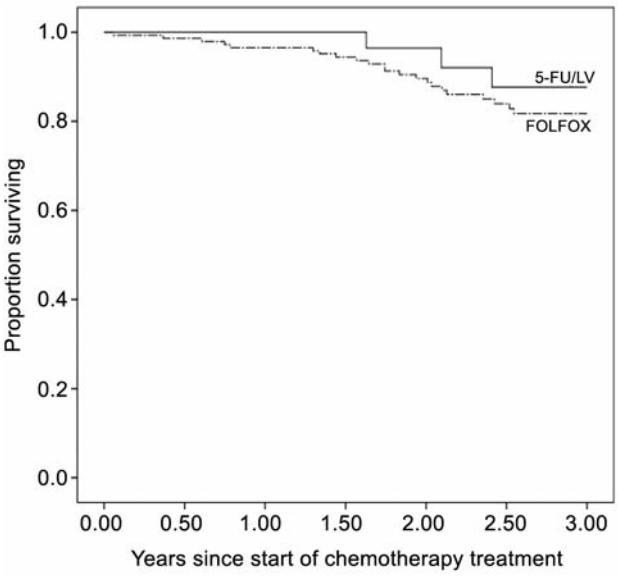
Table III. *Number of CRC patients who changed chemotherapy treatment or had a second round of treatment.*

	Second chemotherapy treatment (#)					
First chemotherapy treatment (#)	Capecitabine	XELOX	FOLFOX	5-FU/LV	Other[1]	Total who changed treatment (%)
Capecitabine (187)	2	3	7	2	10	24 (12.8%)
XELOX (43)	1	0	6	1	5	13 (30.2%)
FOLFOX (339)	12	3	10	7	35	67 (19.8%)
5-FU/LV (67)	0	0	2	0	1	3 (4.5%)

[1]See Table I for 'other' treatments. XELOX: capecitabine/oxaliplatin; FOLFOX: 5-fluorouracil/leucovorin/oxaliplatin; 5-FU/LV: 5-fluorouracil/leucovorin.

chemoradiotherapy with *i.v.* or oral 5-FU regimens with/without oxaliplatin for patients with rectal cancer, found a significant increase in grade 3 toxicity with oxaliplatin, and no improvement in survival or pathological complete response (25, 26). As there are a number of side-effects associated with oxaliplatin, including paresthesia and neutropenia (5), it is not surprising that in our study the rate of change from first-line therapy was considerably higher for XELOX and FOLFOX (30.2% and 19.8%, respectively), compared to 5-FU/LV (4%). As a result both compliance and survival with use of oxaliplatin in practice are likely to be compromised relative to that in trial settings. Response to oxaliplatin may also be somewhat age- dependent. A recent large American retrospective study found that the addition of oxaliplatin did have an effect on improving survival outcomes in patients less than 75 years, which was consistent across five practice settings (18), but this does not appear to extend to patients over age 75 (19). Limited clinical evidence to support the administration of oxaliplatin in elderly patients is amplified by the concern of possible long-term neuropathy, a side-effect which is seldom reported in clinical trials (15). The National Surgical Adjuvant Breast and Bowel Project C-07 trial found 31% of patients still suffered neuropathy at 18 months, and for 10% patients this was unresolved at 27 months (27). The patient numbers in our study did not allow for similar age-stratified analyses. Nevertheless, the cohort aged over 75 years accounted for a large proportion of new CRC diagnoses in our study, with 33% of individuals diagnosed being 75 years or older.

Any incremental survival benefit of using oxaliplatin therapy in practice needs to be considered alongside side-effects in estimating net clinical benefit (incremental quality adjusted life years). In addition to concerns regarding the net clinical benefit of oxaliplatin in practice, oxaliplatin is also particularly expensive. In Australia, the FOLFOX6



	Number at risk				Mean survival time, years
Year	0	1	2	3	
5-FU/LV	31	31	22	16	2.88
FOLFOX	144	139	102	57	2.76
Total	175	170	124	73	$p = 0.395$

Figure 1. *Kaplan Meier plot showing 3-year survival of patients with stage III colorectal cancer based on i.v. chemotherapy treatment (unadjusted). 5-FU/LV: 5-fluorouracil/leucovorin; FOLFOX: 5-fluorouracil/leucovorin/oxaliplatin.*

regimen costs AUD17,040 for a complete treatment (12 cycles at AUD1,420 per cycle), while the *i.v.* 5-FU/ LV deGramont regimen in comparison costs AUD$960 for a complete treatment (12 cycles at AUD$80 per cycle). Direct and follow-up costs of treatment would additionally need to be allowed for in extending this to the assessment of net economic benefit (28, 29). As reported by Field *et al*. (30), even an oxaliplatin dose reduction of 10% would be expected to lead to a national cost saving of AUD2.5 million annually. Furthermore, given the relatively low cost and high survival benefits of *i.v.* 5-FU/LV, research that enhances the use of this regimen is of high clinical and economic value to health system decision-making and practice (31, 32).

The improvement we observed in adjusted three-year survival outcomes of CRC patients treated with *i.v. versus* oral 5-FU-based regimens in practice, is consistent with RCT evidence of equivalence (12-14) and a compliance advantage of *i.v. versus* oral drug use in practice (33). An adherence study specific to capecitabine found an overall compliance rate of 91% in 161 patients (34), however, this rate was self-reported. Reasons cited for non-compliance include forgetting to take medication, misunderstanding instructions and potential for side-effects (34) such as hand-foot syndrome (11). In an American study of over 3,000 patients with stage III colon cancer, age was found to be a statistically significant predictor of chemotherapy treatment completion, with older patients less likely to complete treatment (35). Not surprisingly, discontinuation of treatment was associated with higher risk of death (35). Hence, while adherence could not be assessed in our study, lower compliance rates would be expected in older patients who were prescribed capecitabine. The more frequent administration of capecitabine in older patients is likely attributable to perceptions of oral chemotherapy being better tolerated than *i.v.* chemotherapy (36), especially in patients less resilient-to-aggressive therapies and with more comorbidities (37). In other studies, age and comorbidities have been shown to significantly affect a physician's recommendation for chemotherapy of stage III CRC (38, 39). However, a pooled analysis of seven clinical trials of 5-FU-based chemotherapy found no interaction between age and the effect of treatment on disease-free and overall survival, suggesting that older patients can experience similar benefits from chemotherapy to younger patients with CRC (40).

Limitations. A data limitation of this study is the lack of detailed comorbidity information to allow for expected impacts of comorbidity factors on physician's recommendation for chemotherapy in stage III colorectal cancer (38, 39). This information was not available from the ClinCR registry at the time of data collection, and further research allowing for this would be valuable.

Conclusion

The inclusion of oxaliplatin did not confer a survival advantage to CRC patients in this Australian practice, raising questions as to whether the significantly greater cost of FOLFOX therapy is justified. While a survival advantage of *i.v.* 5-FU over oral regimens was observed in this practice, a larger scale analysis of Australia-wide practice-based survival outcomes of patients with CRC treated with these 5-FU modalities is warranted. Our study suggests the value of further research on factors such as compliance in practice and associated net clinical benefit between alternate chemotherapy regimens in target populations of patients with CRC.

Conflicts of Interest Statement

None.

Table IV. *Cox regression analysis for interaction of individual patients' characteristics on survival.*

Patients' characteristics	Deceased (of total) n=141 (434)	Hazard ratio (95% CI)[3]	*p*-Value
Age, years		1.029 (1.013-1.045)[1]	<0.001
15-44 (reference)	7 (28)	1	
45-54	16 (67)	0.93 (0.38-2.26)	0.872
55-64	30 (118)	1.04 (0.46-2.38)	0.917
65-74	51 (137)	1.62 (0.74-3.57)	0.231
75-84	33 (80)	1.83 (0.81-4.14)	0.146
85-99	4 (4)	9.73 (2.82-35.60)	<0.001
Gender			
Male (reference)	87 (242)	1	
Female	54 (192)	0.73 (0.52-1.02)	0.067
Cancer type			
Rectal (reference)	32 (119)	1	
Colon	109 (315)	1.32 (0.89-1.96)	0.165
Stage[2]			
I	0 (10)	Excluded due to 0 deaths	
II (reference)	6 (44)	1	
III	36 (248)	1.03 (0.43-2.44)	0.953
IV	98 (131)	9.53 (4.17-21.78)	<0.001
Treatment Type			
Chemotherapy-only (reference)	43 (77)	1	
Chemotherapy + surgery	87 (307)	0.34 (0.23-0.49)	<0.001
Chemotherapy + radiotherapy	9 (10)	2.32 (1.13-4.76)	0.022
All three modalities	2 (40)	0.55 (0.13-0.29)	<0.001

[1]As a continuous variable. [2]One patient had unknown stage of cancer. [3]Values >1 favour the reference group.

Acknowledgements

We are grateful to June Rose and Bronwyn Hodges at the SESIAHS Clinical Cancer Registry (ClinCR) for their assistance with obtaining cancer registry data and to Associate Professor Michael Coory at the Murdoch Children's Research Institute for his statistical advice.

Table V. *Cox regression analysis for survival outcomes: 5-fluorouracil treatment effect (excludes patients treated with more than one round of chemotherapy)[1].*

	Hazard ratio[2] (95% CI)	p-value	Evidence of non-proportionality
5-FU/LV (ref)			
versus FOLFOX	1.89 (0.62-5.71)	0.260	No (p=0.896)
Capecitabine (ref)			
versus XELOX	0.99 (0.47-2.10)	0.980	Yes (*p*=0.014)
i.v. 5-FU (ref)			
versus oral 5-FU	1.58 (1.10-2.28)	0.014	Yes (p=0.003)

[1]Adjusted for colon/rectal, sex, age, stage of cancer, and whether the patient also had surgery or radiotherapy. [2]Values >1 favour the reference (ref) treatment. 5-FU/LV: 5-fluorouracil/leucovorin; FOLFOX: 5-fluorouracil/leucovorin/oxaliplatin; XELOX: capecitabine/oxaliplatin.

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Received January 13, 2013
Revised February 18, 2013
Accepted February 18, 2013