Cancer Epidemiology 62 (2019) 101587

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Metformin increases cancer specific survival in colorectal cancer patients—National cohort study

Audrius Dulskas[a,b,c,*], Ausvydas Patasius[d,e], Donata Linkeviciute-Ulinskiene[f], Lina Zabuliene[c], Vincas Urbonas[g], Giedre Smailyte[d,e]

[a] Department of Abdominal and General Surgery and Oncology, National Cancer Institute, 1 Santariskiu Str., Vilnius LT-08406, Lithuania
[b] University of Applied Sciences, Faculty of Health Care, 45 Didlaukio Str., LT-08303 Vilnius, Lithuania
[c] Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, 1 Santariskiu Str., Vilnius LT-08406, Lithuania
[d] Laboratory of Cancer Epidemiology, National Cancer Institute, LT-08406 Vilnius, Lithuania
[e] Institute of Health Sciences, Faculty of Medicine, Vilnius University, LT-03101 Vilnius, Lithuania
[f] Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[g] Laboratory of Clinical Oncology, Department of Medical Oncology, National Cancer Institute, Lithuania

ARTICLE INFO

Keywords:
Colorectal cancer
Overall survival
Cancer specific survival
Metformin
Diabetes
Population-based study

ABSTRACT

Purpose: We aimed to assess oncological outcomes in colorectal cancer patients with type 2 diabetes mellitus (T2DM) using metformin.

Methods: Patients with colorectal cancer and T2DM during 2000–2012 period were identified form Lithuanian Cancer Registry and the National Health Insurance Fund database. Colorectal cancer-specific survival (CS) was the primary outcome. It was measured from date of colorectal cancer diagnosis to date of death due to colorectal cancer, or last known date alive.

Results: 15,052 people who met eligibility criteria for this analysis, including 1094 (7.27%) with pre-existing type 2 diabetes (271 metformin never users and 823 metformin users) and 13 958 people without diabetes assessed. During follow-up (mean follow-up time was 4.4 years, with range from 1 day to 17 years) there were 10,927 deaths including 8559 from colorectal cancer. Significantly lower risk in CS between diabetic and non-diabetic people with lower risk of cancer-specific mortality (HR 0.87, 95% CI 0.80–0.94) in diabetic patient population was seen. After adjustment for age, stage at diagnosis and metformin usage, significant difference in colorectal CS between metformin users in diabetic patient population compared to non-diabetics and metformin non-users in diabetic patient population was found (0.80 (0.72–0.89) vs 1.00 and vs 1.05 (0.91–1.23)). Overall survival (OS) was better for diabetic patients with significant difference in diabetic metformin users (HR 0.91, 95% CI 0.79–0.94).

Conclusions: Colorectal cancer patients with T2DM treated with metformin as part of their diabetic therapy appear to have a superior OS and CS. However, prospective controlled studies are still needed to evaluate the efficacy of metformin as an anti-tumor agent.

1. Introduction

Colorectal cancer is the third most common cancer and second leading cause of death worldwide [1]. Known risk factors are as follows: age, male gender, smoking, obesity, low fibre diet, insulin resistance, and the metabolic syndrome. Increase in incidence of metabolic syndrome is seen worldwide. The syndrome is defined as the presence of at least three of components: increased circumference of the waist, hypertriglyceraemia, low high-density lipoprotein (HDL), hypertension, and hyperglycaemia [2]. The International Diabetes Federation (IDF) estimated that around 425 million of adults had diabetes mellitus globally in 2017 and one in two remains undiagnosed [3].

Overall survival is influenced by several factors: sex, age, tumour stage, and American Society of Anaesthesiologists (ASA) score [4]. The association between diabetes mellitus and decreased overall survival in patients with cancer is expected due to hyperinsulinemia, hyperglycaemia, and chronic inflammation.

Metformin is the first line treatment for T2DM. It suppresses cancer growth – so has a protective effect [5]. Few mechanisms have been suggested, but still it is under careful investigation [6,7].

* Corresponding author at: Department of Abdominal and General Surgery and Oncology, National Cancer Institute, 1 Santariskiu Str., Vilnius LT-08406, Lithuania.
E-mail address: Audrius.Dulskas@NVI.lt (A. Dulskas).

https://doi.org/10.1016/j.canep.2019.101587
Received 22 May 2019; Received in revised form 2 August 2019; Accepted 18 August 2019
Available online 03 September 2019
1877-7821/

Previous studies showed positive effect of metformin on overall survival [8–16] with only few studies showing effect on cancer-specific survival [11–16].

Our goal was to perform a large nation-wide cohort study that examined metformin effect on survival of patients with colorectal cancer.

2. Materials and methods

2.1. Study population

The study protocol was approved by the Institutional Review Board of National Cancer Institute (no. 2018-0063). The need for informed consent was waived by the institutional review board due to the minimal risk retrospective study. The study design followed all relevant principles of the Declaration of Helsinki.

The study is based on the Lithuanian Cancer Registry database covering a population of around three million residents according to 2011 census. The analysis included patients with primary invasive colorectal cancer (ICD-10 C18-C21) diagnosed between January 1, 2001 and December 31, 2012. The database contains personal and demographic information, as well as information on diagnosis of all people diagnosed with cancer in Lithuania. Data of the Lithuanian Cancer Registry has been published in the publications of the International Association of Cancer Registries 'Cancer Incidence in Five Continents', which are submitted to systematic quality control. From this database, we obtained information regarding age at diagnosis, date of diagnosis, tumour classification (TNM), cause and date of death. Identified patients were followed till 2017 12 31, or date of death, whichever came first. Information regarding the diagnosis of T2DM and antidiabetic medication were obtained from the National Health Insurance Fund (NHIF) database. Diabetic status was assigned to patients who were reported as T2DM patients and received prescriptions of antidiabetic medications in the NHIF database. Data from the Lithuanian NHIF database encompasses about 98% of inpatient cases and 90% of outpatient visits (up to 100% of primary health care visits) in Lithuania, covering the entire territory of the country. (*Navickas et al. Eur J Intern Med. 2015* https://www.ncbi.nlm.nih.gov/pubmed/25726495).

We excluded patients identified as death certificated only cases, patients with prior malignancy, cases with diabetes diagnosed after colorectal cancer diagnosis (Fig. 1).

2.2. Outcome measures

We analysed survival outcomes in colorectal cancer patients. Colorectal cancer-specific survival was the primary outcome, measured from the date of colorectal cancer diagnosis to date of death due to colorectal cancer, or last known date alive (for 41 lost to follow-up patients). Patients who were not deceased or who died of causes other than colorectal cancer were censored at the last known date alive or date of death, respectively. Overall survival was analysed as a secondary outcome, and defined as the period from the date of diagnosis of colorectal cancer to the date of death or last known date alive. For this secondary outcome, only those patients who were not deceased were censored at the last known date alive.

2.3. Statistical analyses

Univariate Cox proportional hazard models were used to estimate hazard ratios and their 95% confidence intervals to compare colorectal cancer-specific and overall survival differences by known prognostic factors. These included sex, age at diagnosis, stage at diagnosis, and metformin use (yes/no). Unadjusted and multivariate adjusted Cox proportional hazards models including sex, age and stage at diagnosis were also conducted to estimate the effect of diabetes status on colorectal cancer-specific and overall survival. All statistical analyses were carried out using STATA 11 statistical software (StataCorp. 2009. Stata Statistical Software: Release 11.0. College Station, TX, USA).

3. Results

After excluding those for whom colorectal cancer was not a first cancer diagnosis, diabetes diagnosed after colorectal cancer and DCO cases, there were 15,052 people who met eligibility criteria for this analysis, including 1094 (7.27%) with pre-existing T2DM and 13,958 without diabetes (Fig. 1). During follow-up there were 10,927 deaths including 8559 from colorectal cancer. Mean follow-up time was 4.4 years, with range from 1 day to 17 years.

Demographic and staging information for the three exposure cohorts is presented in Table 1. The mean age at diagnosis was slightly higher in men with diabetes who used metformin. There were no significant differences in stage of disease at diagnosis between groups.

The *Kaplan-Meier* survival analysis revealed significant differences

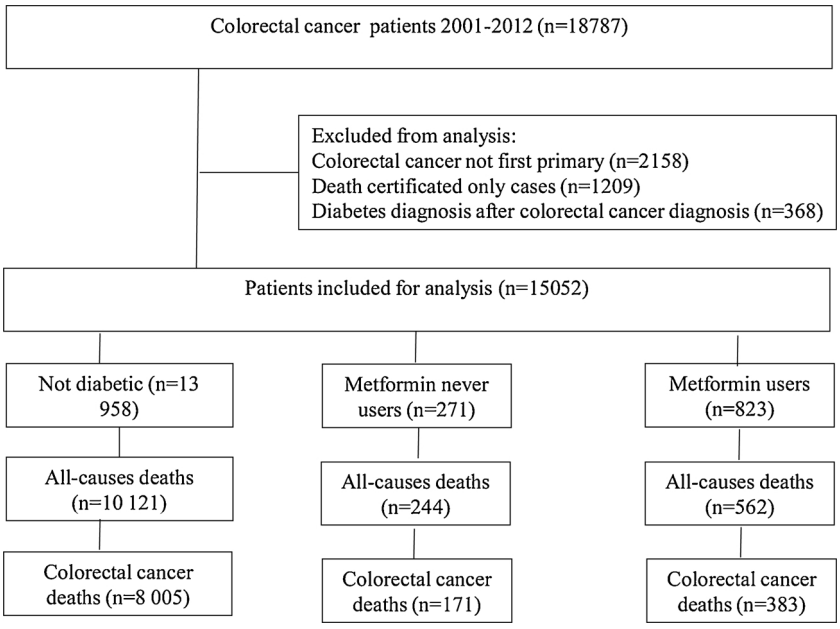

Fig. 1. Flow diagram summarizing the process of enrolment of colorectal cancer patients.

Table 1
Demographic and clinical characteristics of people with colorectal cancer, by diabetes and metformin status.

	Non-diabetic		Diabetic			
			Metformin users		Metformin non-users	
	N	%	N	%	N	%
Total	13 958	92.73	823	5.47	271	1.80
Gender						
Male	6.882	92.77	135	1.82	401	5.41
Female	7.076	92.69	136	1.78	422	5.53
Age at diagnosis						
Mean(SD)	68.31 (11.46)		73.20 (8.49)		69.20 (8.74)	
Age groups						
< 65	4.734	94.12	4.794	91.75	4.429	92.35
65–75	43	0.85	105	2.01	123	2.56
> 75	253	5.03	326	6.24	244	5.09
Stage						
1	1365	9.77	122	14.82	24	8.86
2	4128	29.57	272	33.05	76	28.04
3	3857	27.63	207	25.15	79	29.15
4	3345	23.97	149	18.10	65	23.99
unknown	1263	9.05	73	8.87	27	9.96

SD, standard deviation.

in colorectal cancer-specific survival between diabetic and non-diabetic patients (Fig. 2). In multivariate analysis after adjustment for age and stage at diagnosis significantly lower risk in colorectal cancer-specific mortality was observed between diabetic and non-diabetic patients with lower risk in diabetic patient population (HR 0.87, 95% CI 0.80–0.94) (Table 2). In diabetic patients' group there was significant difference in colorectal cancer-specific survival between metformin users and non-users (Fig. 2). After adjustment for age and stage at diagnosis significantly lower risk in colorectal cancer-specific mortality was observed in metformin users (HR 0.75, 95% CI 0.64–0.87). In overall survival significant differences were observed between metformin users and non-users (Fig. 3, Table 3). However, there were no differences in overall survival between diabetic and non-diabetic patients.

4. Discussion

Our Lithuanian cohort study, one of the largest cohort studies so far of more than 110,000 patients with T2DM, showed that overall survival and cancer-specific survival was significantly increased in metformin-treated group compared with non-metformin group and even non-diabetes group. Even after adjusting for clinical relevant factors, we still found decreased all-cause mortality. There might be two reasons for the

Table 2
Diabetes and colorectal cancer-specific and overall survival.

	Unadjusted HR (95% CI)	p-value	Multivariate-Adjusted[a] HR (95% CI)	p-value
Colorectal cancer specific survival				
Non-diabetic	1.00	ref.	1.00	ref.
Diabetic	0.85 (0.78–0.92)	< 0.001	0.87 (0.80–0.94)	0.001
Overall survival				
Non-diabetic	1.00	ref.	1.00	ref.
Diabetic	0.99 (0.92–1.06)	0.26	0.99 (0.92–1.06)	0.40

CI – Confidence Interval, HR – Hazard Ratio.
[a] Adjusted for age (as continuous variable) and stage at diagnosis; ref.

increased oncologic parameters: first of all, metformin might have some anticancer effect. Secondly, patients with diabetes might see the doctor more often and they can get screened easily with less stigmas.

Few cohort studies demonstrated the positive metformin use effect in increase of overall survival [9–11]. A study of almost 5000 patients showed that patients with T2DM and colorectal cancer treated with metformin as one of their diabetic medications had a survival of 76.9 months compared with 56.9 months in those not treated with metformin [9]. A Danish nation-wide cohort study of more than 30,000 patients with colorectal cancer of which 3391 were diagnosed with diabetes demonstrated that treatment with metformin was associated with a 15% decreased all-cause mortality compared with insulin-treated patients [10]. There was no significant difference in all-cause mortality regarding exposure and dose of metformin. In a study from US colorectal cancer patients with diabetes, metformin users had a 13% improved overall survival despite adjustments for diabetes severity and other risk factors versus patients taking other anti-diabetic medications, while patients not on any anti-diabetic medications did not differ with respect to overall survival [11]. However, these studies are hindered by assessing only all-cause mortality and not cancer specific survival.

Few other small retrospective analyses showed longer cancer specific survival in diabetes patients using metformin [12–16]. One study showed that only high-intensity metformin use was associated with a significant reduction in colorectal cancer-specific mortality (HR 0.44; 95% CI 0.20–0.95) [12]. Lee et al. showed metformin use was associated with decreased overall mortality (p = 0.018) and colorectal cancer-specific mortality (p = 0.042) by univariate analysis [13]. However, individuals in this study were improperly classified as exposed to metformin in the period from cohort entry to first metformin prescription and therefore these findings have been attributed to immortal time bias. A Singaporean study among 344 colorectal cancer patients with diabetes detected marked improvements in recurrence-free survival (HR 0.63; 95% CI, 0.41–0.96) and overall survival (HR 0.23, 95% CI 0.15–0.35) in those exposed to metformin at diagnosis

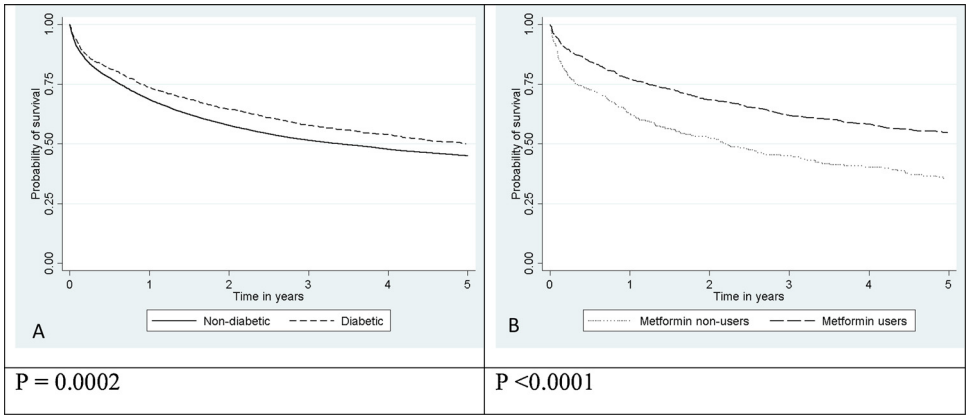

Fig. 2. Kaplan-Meier survival curve comparing colorectal cancer-specific survival between diabetic and non-diabetic patients (A), metformin users on metformin non-users (B).

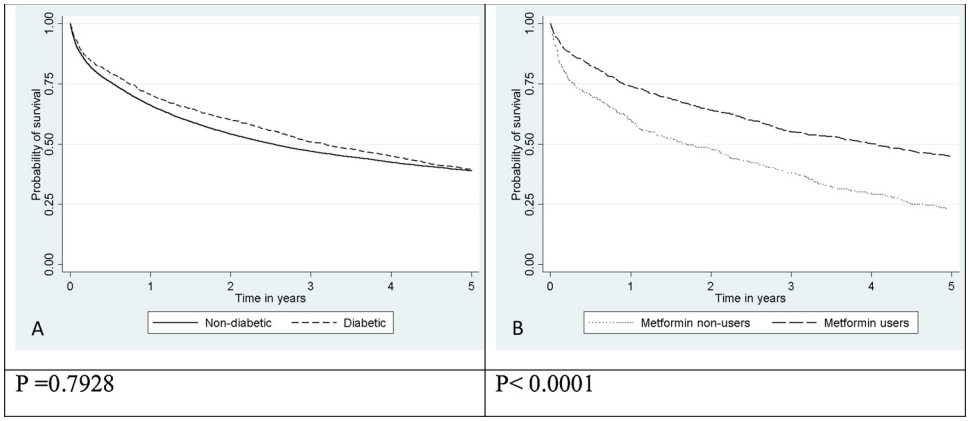

Fig. 3. Kaplan-Meier survival curve comparing overall survival between diabetic and non-diabetic patients (A), metformin users on metformin non-users (B).

Table 3
Metformin treatment and colorectal cancer-specific and overall survival.

	Unadjusted HR (95% CI)	p-value	Multivariate-Adjusted[a] HR (95% CI)	p-value
Colorectal cancer specific survival				
Metformin non-users	1.00	ref.	1.00	ref.
Metformin users	0.57 (0.48–0.69)	< 0.001	0.77 (0.64–0.93)	0.007
Overall survival				
Metformin non-users	1.00	ref.	1.00	ref.
Metformin users	0.55 (0.48–0.64)	< 0.001	0.75 (0.64–0.87)	< 0.001

CI – Confidence Interval, HR – Hazard Ratio.
[a] Adjusted for age (as continuous variable) and stage at diagnosis; ref.

[14]. Interesting results where shown with 413 patients diagnosed with colorectal cancer and T2DM [15]. In multivariate analysis, survival benefit was associated with metformin administration. Furthermore, subgroup analysis revealed significant differences in colorectal cancer -specific mortality between the metformin and non-metformin groups in female patients (HR 0.501; 95% CI. 0.286–0.879, p = 0.013) but not male patients (HR 0.848; 95% CI, 0.594–1.211, p = 0.365). Recent study from MD Andersen found that diabetic patients using metformin had significantly longer overall survival (89 months; 95% CI, 66–112 months) and progression-free survival (47 months; 95% CI, 15–79 months) than patients using other antidiabetic drugs (overall survival: 36 months; 95% CI, 24–48 months; p ≤ 0.001; progression-free survival: 21 months; 95% CI, 13–29 months; p = 0.016) [16].

Alternatively, in recent study 2066 postmenopausal women with colorectal cancer were followed for a median of 4.1 years and found no metformin effect on OS or CS [17]. Similarly, in a study from Ireland with almost 1200 colorectal cancer patients with T2DM assessed, authors showed no protective association between metformin and survival in colorectal cancer patients [18]. Others assessed patients using metformin, statins and aspirin. Authors found no independent association between cumulative exposure to metformin, aspirin and overall mortality [19]. In a large prospective randomised controlled study authors did not find any relationship between metformin use or its duration and disease-free survival, time to recurrence, and overall survival in a large cohort of patients with resected stage III colon cancer receiving adjuvant FOLFOX (folic acid, fluorouracil, oxaliplatin)-based chemotherapy [20]. Just recently systematic review and meta-analysis on metformin as an adjuvant treatment modality for few cancer locations was published, including colorectal cancer [21]. Authors found that in those with early-stage colorectal cancer, metformin use was associated with a significant benefit in all outcomes.

One study suggested that metformin together with conventional chemotherapy could be an effective treatment regimen for colorectal cancer patients with T2DM [22].

Our population-based cohort study has several strengths. First, we used real-world data on prescriptions and diagnoses in primary care practices where most patients with T2DM are treated. Second, we could study a large number of colorectal cancer cases in a longitudinal, well-established, and validated database. Due to the recording of individual prescriptions by the General Practitioners for reimbursement in the NHIF database, we were able to stratify use of antidiabetic drugs by duration of use. Third, extended follow-up for more than 10 years – it takes at least 10 years for colorectal cancer to develop.

Limitations of our study should not be ignored. First, we have not assessed the potential confounders such as body mass index, smoking and drinking status, comorbidities, other drugs used by the patients. Patients with diabetes tend to have more comorbidities, such as hypertension, ischaemic heart disease, or metabolic syndrome. These diabetes related complications may also contribute to a higher non-cancer-specific mortality rate. These confounders could not be extracted from our database. Although this limitation might be decreased as in our database the deaths from cancer progression and other factors are separated. Secondly, users of metformin were compared with never users of metformin. This makes it difficult to interpret results because both groups are heterogeneous. In ever users, metformin is often but not always used as first-line therapy, and it might be combined with various other diabetes drugs, whereas never users comprise patients who have never used any diabetes drugs or who use a combination of any other antidiabetic medications except metformin.

5. Conclusion

In conclusion, this large observational study showed that patients with T2DM using metformin have higher cancer specific survival compared with the non-diabetic cancer patients in Lithuanian population. However, prospective controlled studies are still needed to evaluate the efficacy of metformin as an anti-tumour agent.

Authorship contribution statement

A.D. and G.S. conceived the idea of the study. A.D., A.P., D.L.U., L.Z., V.U. and G.S. designed the article methodology. A.D., A.P., D.L.U. and L.Z., conducted screening of articles and data extraction. A.D. and A.P. wrote the first draft of the article and all authors critically reviewed subsequent drafts.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. (2018) 68394–68424.

[2] R. Kaneko, N. Nakazaki, T. Tagawa, C. Ohishi, S. Kusayanagi, M. Kim, T. Baba, M. Ogawa, Y. Sato, A new index of abdominal obesity which effectively predicts risk of colon tumor development in female Japanese, Asian Pac. J. Cancer Prev. 5 (2014) 1005–1010.

[3] International Diabetes Federation, IDF Diabetes Atlas, 8th edition, Diabetes Atlas, 2017, http://www.diabetesatlas.org/.

[4] B.B. Barone, H.-C. Yeh, C.F. Snyder, K.S. Peairs, K.B. Stein, R.L. Derr, A.C. Wolff, F.L. Brancati, Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis, JAMA 300 (2008) 2754–2764.

[5] M.P. Wrobel, B. Marek, D. Kajdaniuk, D. Rokicka, A. Szymborska-Kajanek, K. Strojek, Metformin—a new old drug, Endokrynol. Pol. 68 (4) (2017) 482–496.

[6] X. Sui, Y. Xu, X. Wang, W. Han, H. Pan, M. Xiao, Metformin: a novel but controversial drug in cancer prevention and treatment, Mol. Pharm. 12 (2015) 3783–3791.

[7] P. Nangia-Makker, Y. Yu, A. Vasudevan, L. Farhana, S.G. Rajendra, E. Levi, A.P. Majumdar, Metformin: a potential therapeutic agent for recurrent colon cancer, PLoS One 9 (2014) e84369.

[8] G.W. Landman, N. Kleefstra, K.J. van Hateren, K.H. Groenier, R.O. Gans, H.J. Bilo, Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16, Diabetes Care 33 (2010) 322–326.

[9] C.R. Garrett, H.M. Hassabo, N.A. Bhadkamkar, S. Wen, V. Baladandayuthapani, B.K. Kee, C. Eng, M.M. Hassan, Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer, Br. J. Cancer 106 (8) (2012) 1374–1378.

[10] T. Fransgaard, L.C. Thygesen, I. G€ogenur, Metformin increases overall survival in patients with diabetes undergoing surgery for colorectal cancer, Ann. Surg. Oncol. 23 (2016) 1569–1575.

[11] J.K. Paulus, C.D. Williams, F.I. Cossor, M.J. Kelley, R.E. Martell, Metformin, diabetes, and survival among U.S. veterans with colorectal cancer, Cancer Epidemiol. Biomark. Prev. 25 (2016) 1418–1425.

[12] S. Spillane, K. Bennett, L. Sharp, T.I. Barron, A cohort study of metformin exposure and survival in patients with stage I-III colorectal cancer, Cancer Epidemiol. Biomark. Prev. 22 (2013) 1364–1373.

[13] J.H. Lee, T.I. Kim, S.M. Jeon, S.P. Hong, J.H. Cheon, W.H. Kim, The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus, Int. J. Cancer 131 (2012) 752–759.

[14] G.E. Lee, T. Aung, K.H. Lim, W.S. Tan, W. Meng, D. Tai, N.-A. Binte, S.M.H. Tan, I.B. Tan, Examining the effects of metformin on survival outcome in stage II/III colorectal cancer patients with diabetes mellitus, J. Clin. Oncol. 30 (2012) (Suppl; abstr 3589).

[15] J.W. Park, J.H. Lee, Y.H. Park, S.J. Park, J.H. Cheon, W.H. Kim, T.I. Kim, Sex-dependent difference in the effect of metformin on colorectal cancer-specific mortality of diabetic colorectal cancer patients, World J. Gastroenterol. 23 (2017) 5196–5205.

[16] A. Al Omari, H. Abdelkhaleq, M. Al-Hussaini, R. Turfa, N. Awad, M.M. Hassan, M.A. Alfaqih, C.R. Garrett, Validation of the survival benefits of metformin in middle eastern patients with type II diabetes mellitus and colorectal cancer, J. Glob. Oncol. 4 (2018) 1–10.

[17] F.I. Cossor, L.L. Adams-Campbell, R.T. Chlebowski, M.J. Gunter, K. Johnson, R.E. Martell, A. McTiernan, M.S. Simon, T. Rohan, R.B. Wallace, J.K. Paulus, Diabetes, metformin use, and colorectal cancer survival in postmenopausal women, Cancer Epidemiol. 37 (2013) 742e749.

[18] U.C. Mc Menamin, L.J. Murray, C.M. Hughes, C.R. Cardwell, Metformin use and survival after colorectal cancer: a population-based cohort study, Int. J. Cancer 138 (2) (2016) 369–379.

[19] M.M. Zanders, M.P. van Herk-Sukel, P.A. Vissers, R.M. Herings, H.R. Haak, L.V. vande Poll-Franse, Are metformin, statin and aspirin use still associated with overall mortality among colorectal cancer patients with diabetes if adjusted for one another? Br. J. Cancer 113 (3) (2015) 403–410.

[20] P.P. Singh, Q. Shi, N.R. Foster, A. Grothey, S.G. Nair, E. Chan, A.F. Shields, R.M. Goldberg, S. Gill, M.S. Kahlenberg, F.A. Sinicrope, D.J. Sargent, S.R. Alberts, Relationship between metformin use and recurrence and survival in patients with resected stage III colon cancer receiving adjuvant chemotherapy: results from north central cancer treatment group N0147 (Alliance), Oncologist 21 (12) (2016) 1509–1521.

[21] C. Coyle, F.H. Cafferty, C. Vale, R.E. Langley, Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis, Ann. Oncol. 27 (12) (2016) 2184–2195.

[22] V.C. Miranda, M.I. Braghiroli, L.D. Faria, G. Bariani, A. Alex, J.E. Bezerra Neto, F.C. Capareli, J. Sabbaga, J.F. Lobo Dos Santos, P.M. Hoff, R.P. Riechelmann, Phase 2 trial of metformin combined with 5-fluorouracil in patients with refractory metastatic colorectal cancer, Clin. Colorectal Cancer 15 (2016) 321–328.