RESEARCH ARTICLE

Editorial Process: Submission:12/01/2022 Acceptance:06/15/2023

Providing Suggested Rules for Multiple Primary Cancer Recording, Coding and Registering in Population-based Cancer Registry

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Abstract

Background: Multiple primary cancers (MPC) present many coding difficulties, while a distinction should be made between new cases and those with metastasis and/or extension and recurrence of the primary ones. We aimed to reflect on the experiences and results of data quality control of the East Azerbaijan/Iran Population-Based Cancer Registry and present our suggested rules for reporting, recording and registering multiple primary cancer. **Methods:** Comparability, validity, timeliness, and completeness of data assessment were performed. As a result, we created a consulting team including expert oncologists, pathologists, and gastroenterologists to discuss for multiple primary tumors recording, identifying, coding and registering. **Results:** In case of confirmed Blood malignancies with definite BMB results, Brain and/or Bone involvements are always metastatic. In most cases of multiple cancers with the same morphological types, the earlier should be registered as primary tumor. In most of the synchronous multiple cancers, familial cancer syndromes should be considered and rules out. In case of two tumors diagnosed at the same time in colon and rectum, primary site should be detected by T stage or tumor sizes. In case of multiple tumors in Recto-sigmoid, Colon , and Rectum the earlier history of tumor should be considered as primary site. This rule was applied for Female Genital tumors, as earlier site is always the Primary cancer and other tumors should be registered as metastatic sites. **Conclusion:** Given the complexity of coding MPCs, we suggested some additional rules for identifying, recording, coding, and registering multiple primary cancers in the context of the EA-PBCR program.

Keywords: Comparability- validity- timeliness- completeness- cancer registry

Asian Pac J Cancer Prev, **24 (6)**, 1905-1916

Introduction

In 2020, there were 19.3 million incident cases of cancer and 10.0 million cancer deaths worldwide (Sung et al., 2021). Recent statistics produced by the Iranian Ministry of Health and Medical Education indicate that cancer is the third overall leading cause of death in Iran. Given that this mortality has also been rising over the past few decades (Hajizadeh and Monaghesh, 2021).

The value and importance of well-established and high-quality population-based cancer registries (PBCR) are un-doubtful in improving and providing epidemiologic cancer researches and health policy making programs (Bray and Parkin, 2009; Parkin and Bray, 2009). Key issues in the evaluation of data quality in PBCRs have four quality indicators including comparability, completeness, validity and timeliness of registry data. "Comparability" indicator is the context in which the coding and classification of international guidelines have been performed, compatible with established and confirmed guidelines (Bray and Parkin, 2009; Parkin and Bray, 2009)."Completeness" indicator is the context of all included diagnosed incident cancers over a desired period of time in a desired population. "Validity" is the exact proportion of cancer cases registered based on the desired source and characteristics in coding, recording and registering. "Timeliness" refers to timely and rapid cancer data collecting, obtaining and registering over a desired period of time (Bray and Parkin, 2009; Parkin and Bray, 2009; Bray and Ferlay, 2017).

The rules for registering and recording the multiple primary cancers occurring in the same individual, are among the most challenging dimensions of comparability. Multiple primary neoplasms present many coding

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difficulties, while a distinction should be made between new cases and those with metastasis and/or extension and the recurrence of the primary ones. Warren and Gates explained multiple primary cancer (MPC) for the first time as "definitive malignant tumors", "distinct tumors", and "excluded metastasis tumors"(Warren and Ehrenreich, 1944).Based on International Classification of Diseases for Oncology (ICD-03) guidelines, the best and reliable definitions are:

1. Two or more separate neoplasms in different topographic sites

2. Certain conditions characterized by multiple tumors

3. Lymphomas which often involve multiple lymph nodes or organs at diagnosis

4. Two or more neoplasms of a different morphology arising in the same site

5. A single neoplasm involving multiple sites whose precise origin cannot be determined

6. Not being the result of metastasis or recurrence of primary cancer

7. The recognition of the existence of two or more primary cancers does not depend on time

For synchronous and/or metachronous multiple cancer a clear distinction should be applied between new tumors and extension, recurrence, and metastases. The jointly developed IARC/IACR rules (IARC,2004) provided coding guideline as "International Rules for Multiple Primary Cancers (ICD-O Third Edition)" including rules for reporting incidence and survival, Groups of topography codes considered a single site in the definition of multiple cancers, and Groups of malignant neoplasms considered to be histologically 'different' for the purpose of defining multiple tumors (Curado et al., 2004). However, some additional recommendations for Recording of two and/or more tumors at the same time in an individual provided as:

"1. Two tumors of different laterality, but of the same morphology, diagnosed in paired organs (e.g., breast) should be registered separately unless stated to have originated from a single primary.

2. Cancers which occur in any 4th character subcategory of colon (C18) and skin

(C44) should be registered as multiple primary cancers (International Association of Cancer, 2005; Working Group, 2005)."

However, as PBCRs have wide implications in the monitoring and updating the International Agency for Research on Cancer/International Association of Cancer Registries (IARC/IACR) standards and international rules, so different registry program is comparable in collecting, coding and presenting cancer data worldwide. The last version of ICD-O-3.1 and ICD-O-3.2 has been provided additional international rules for multiple primary cancers including updated table as : "Groups of malignant neoplasms considered to be histologically different for the purpose of defining multiple tumors" and was recommended for use from 2020 by IARC/IACR (Curado et al., 2004). At this time, apart from several provided rules for MPCs coding and registering, additional evidence and results should be present for the practical and clinical management and treatment strategies(Vogt et al., 2017). This evidence will be helpful and applicable for other communities and PBCRs.

The National Cancer Control Program in Iran has remits for the prevention, (early) diagnosis, and treatment of various cancers including the provision of palliative care. PBCR is the key to the success of the National Cancer Control Program in Iran (Somi et al., 2018).The most current and reliable data for PBCR in East Azerbaijan has been established to allow accurate estimates of annual statistics in the province and has been presented in 2018, while records from additional sources were also used to improve the completeness and validity of the EA-PBCR (Somi et al., 2018). However, PBCRs increase the coverage and quality indicators of cancer registries. These studies have less potential bias compared with pathology and hospital based registries (Wanner et al., 2018).

We undertake this study due to some gaps in the handling of multiple primaries based on current guidelines and to be relevant for many cancer registries in improving their quality of reporting MPCs, especially for newly established population-based cancer registries. We aimed to reflect experiences and results of data quality control in EA-PBCR and present our suggested rules and provided rules for reporting, recording, and registering the multiple primary cancer cases in cancer registry database.

Materials and Methods

We used the results of East Azerbaijan Population based Cancer Registry (EA-PBCR) data, which included all cancer cases with confirmed primary and newly diagnosed cancers (Figure 1). Quality control, consistency checks and basic analysis, were performed based on the IARC criteria (2015). This involved assessing factors which influence comparability, validity, timeliness, and completeness (Arndt et al., 2020; Subedi et al., 2020; Wei et al., 2020; Redondo-Sanchez et al., 2021). All newly diagnosed/confirmed cancer cases (total 21,462) from the year 2015 to 2017 were included for recording and coding of MPCs.

Multiple Primary Cancers

The quality control of our database was performed by computerized and manual validity methods to assess comparability, validity, timeliness, and completeness of EA-PBCR data. Duplicated cases were checked in three steps using patients' first name, family name, father name and finally with patients' National Identification (NID) numbers. We followed the "Rules for Reporting Incidence and Survival" published by The International Agency for Research on Cancer (IARC) (Supplementary Tables 1,2,3)(International Association of Cancer, 2005; Working Group, 2005),and Surveillance Epidemiology and End Results (SEER) program (Ditsch et al., 2019), for multiple primary tumors recording, identifying, coding and registering; However, in some cases, we could not find any related data in published and established rules. As a result, we created an expert panel as a consultation team including expert oncologists, pathologist, and gastroenterologist to discuss each case. They discussed and provided their agreed approach to distinguish each primary tumor from invasion, metastasis, or recurrence

cancer cases according to the morphology and behavior of cancers and determined those that are eligible to be coded as multiple primary cases. Meanwhile, MPC in the same organ or in different organs is a clinical issue; therefore, we referred to the hospitals and medical records of each case to find any additional information about the basic information of tumor progression and TNM staging and/or imaging reports (CT, MRI).

Results

Meanwhile for the first three years the number and frequency of registered multiple primary cases are as follow:

2015: 10 MPCs out of 6,655 cases (4 male and 6 female) were registered; one had three cancers at the same time, and 9 had two,

2016: 12 MPCs out of 7,042 cases (3 male and 9female) were registered; all cases had had two primary cancers

2017: 13 MPCs out of 7,765 cases (5 male and 8 female) were registered; one case had three cancers at the same time, and 12 had two.

We present some additional rules in the context

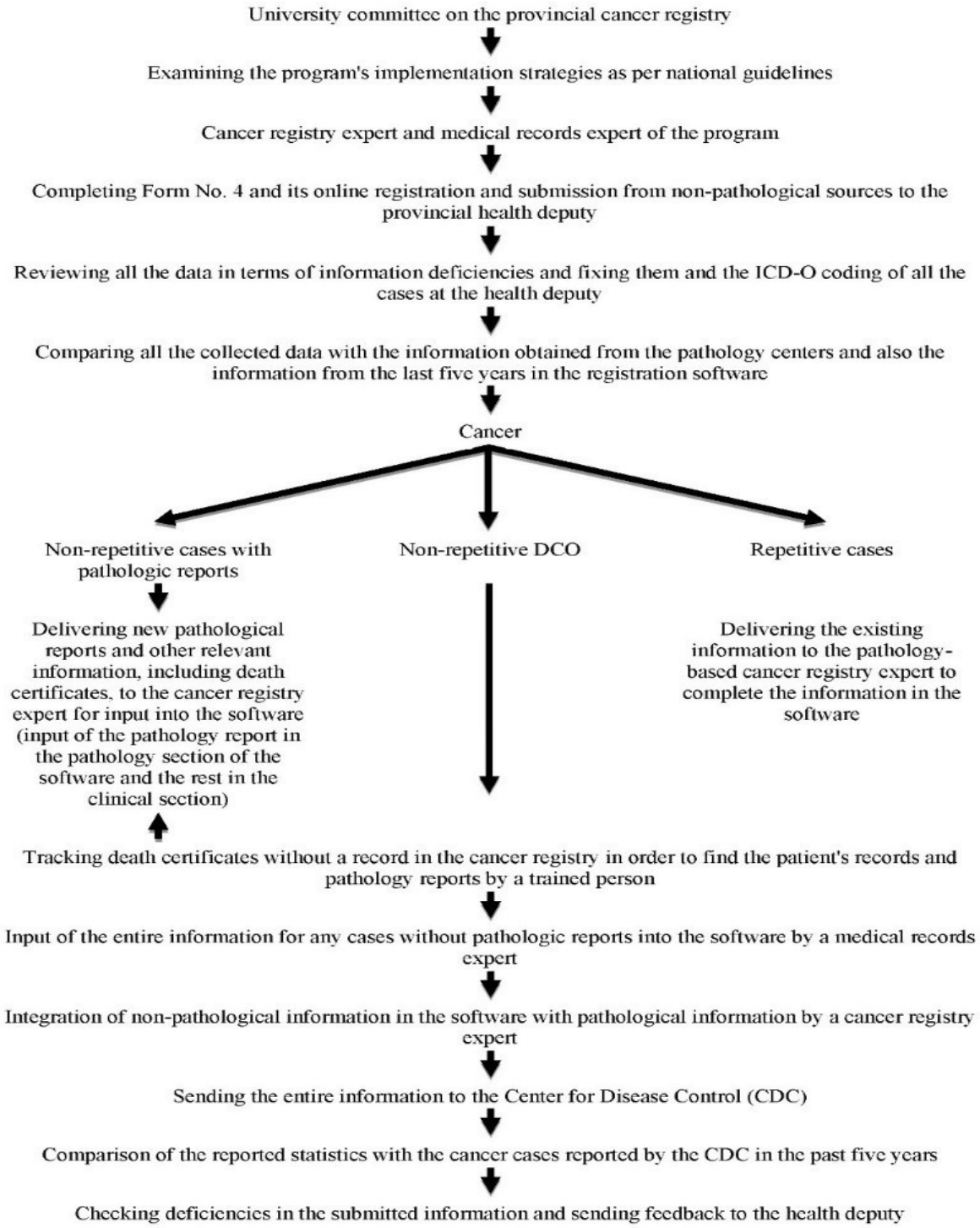

Figure 1. The Population-based Cancer Registry Algorithm

Table 1. Suggested Rules for Multiple Primary Cancer Recording, Coding and Registering in East Azerbaijan Population-based Cancer Registry (EA-PBCR), Part I

	Label	Verification (as single primary and/or multiple primary)
Blood	1.Blood & Brain	In case of definite BMB* results, blood is primary
	2.Blood & Bone	In case of definite BMB* results, blood is primary
	3.Blood & Prostate	Both
	4.Blood & Stomach	Both
	5.Blood & Bladder	Both
	6.Blood & Head and Neck	Both
	7.Blood & Colon	Both
	8.Blood & Breast	Both
Breast	1.Breast &Thyroid	Both
	2.Breast & Esophagus	Both
	3.Breast & Stomach	Both
	4.Breast & Colon	Both Familial cancer syndromes should be rule out (Peutz-Jeghers and Lynch syndrome, and "breast-colon" cancer)
	5.Breast & Rectum	Both
	6.Breast & Bladder	Both
	7.Breast & Bone	Breast as Primary, Bone as Metastatic Cancer
	8.Breast & Mediastinum	a) Breast as Primary, Mediastinum as Metastatic Cancer b) If thymus was involved, we verified both as primary
	9.Breast & Liver	Breast as Primary, Liver as Adenocarcinoma Metastatic Cancer Breast as Primary, Liver as other morphologies, Both
	10.Breast & Lung	Breast as Primary, Lung as Adenocarcinoma, Both Breast as Primary, Lung as other morphologies, Metastatic Cancer
	11. Breast & Ovary	Both
Lung	1.Lung & Head and Neck	Both
	2.Lung & Sigmoid	Sigmoid as Primary, Lung as Metastatic Cancer
	3.Lung & Esophagus	Esophagus as Primary, Lung as Metastatic Cancer
	4.Lung & Stomach	Stomach as Primary, Lung as Metastatic Cancer
	5.Lung & Skin	Lung as Primary, Skin as Metastatic Cancer
	6.Lung & Pleura	Lung as Primary, Pleura as Metastatic Cancer
Stomach	1.Stomach & Prostate	Both
	2.Stomach & Esophagus	Both
	3. Stomach & Thyroid	Both
	4.Stomach & Ovary	Both (Krukenberg tumor should be rule out)
	5.Stomach & Colon	Both
	6.Stomach & Pleura	Stomach as Primary, Pleura as Metastatic Cancer
	7.Stomach & Liver	a) Stomach as Primary, Liver as Adenocarcinoma Metastatic Cancer b) Stomach as Primary, Liver as other morphologies, Both
	8.Stomach & Small intestine & Colon (Rectum, Recto Sigmoid)	Stomach and Colon
	9. Stomach & Uterus	Both
	10.Stomach & Endometrium	-If both have Adenocarcinoma morphology, Endometrium is metastatic -If have different morphology, should be registered as multiple primary cancers
Small intestine	1.Small intestine & Pancreas	Both
	2.Small intestine & Peritoneum	Small intestine as Primary, Peritoneum as Metastatic Cancer
Colon & Rectum & Recto Sigmoid	1.Colon & Cardia	Both

Table 1. Continued

	Label	Verification (as single primary and/or multiple primary)
Colon & Rectum & Recto Sigmoid	2.Colon & Endometrium	-If both have Adenocarcinoma morphology, Endometrium is metastatic -If have different morphology, should be registered as multiple primary cancers
	3.Colon & Brain	Colon as Primary, Brain as Metastatic Cancer
	4.Colon & Liver	a) Colon as Primary, Liver as Adenocarcinoma Metastatic Cancer b) Colon as Primary, Liver as other morphologies, Both
	5.Colon & Prostate	Both
	6.Colon & Small intestine	Both
	7.Colon & Esophagus	Both
	8.Colon & Female Genitals	Both
	9.Rectum & Female Genitals	Both
	10.Sigmoid & Ureter	Both
	11.Sigmoid & Skin	Both
	12.Recto Sigmoid & Lung	Recto Sigmoid as Primary, Lung as Metastatic Cancer
	13.Recto Sigmoid &Anus	Both (FAP and other polyposis should be rule out)
	14.Rectum & Liver	a) Rectum as Primary, Liver as Adenocarcinoma Metastatic Cancer b) Rectum as Primary, Liver as other morphologies, Both
	15. Colon& Rectum& Ovary	Both (Familial cancer syndromes should be rule out (Peutz-Jeghers and Lynch syndrome)
Bone	1.Femur & Connective tissue of the upper limb	Both
	2.Femur & other Bones	Both
	3.Bone & Skin	Bone as Primary, Skin as Metastatic Cancer
Prostate	1.Prostate & Gallbladder	Both
	2.Prostate & Adrenal glands	Both
Bladder	Bladder & Gallbladder	Both
Skin	1.Ear Skin & Scalp skin	a) If both have same morphology, earlier is primary, other one metastatic b) If have different morphology, should be registered as multiple primary cancers
	2.Eye Skin & Skin of Nose and Face	a) If both have same morphology, earlier is primary, other one metastatic b) If have different morphology, should be registered as multiple primary cancers
	3.Skin & Parotid Gland	Parotid Gland as Primary, Skin as Metastatic Cancer
Other	1.Esophagus & Trachea	Both
	2.Nasopharynx & Larynx	Both
	3.Lower Limb & Soft connective tissue of Lower Limb	Both
	4.Thyroid & Adrenal Gland	Both
	5.Liver & Brain	Liver as Primary, Brain as Metastatic Cancer
	6.Ovary &Omentum	Ovary as Primary, Omentum as Metastatic Cancer
	7.Head of Pancreas & Cerebellum of brain	Pancreas as Primary, Cerebellum as Metastatic Cancer

*Bone Marrow Biopsy

of East Azerbaijan population-based cancer registry program. In most cases we coded the MPCs according to the previous guidelines and provided tables with some more information and case presentations. Importantly, these suggested rules for hematological malignancies are provided for the first time. All the cases mentioned in the tables were microscopically verified.

In case of confirmed Blood malignancies with definite

Table 2. Suggested Rules for Multiple Primary Cancer Recording, Coding and Registering in East Azerbaijan Population-based Cancer Registry (EA-PBCR), Part II

Label	Verification
Two tumors diagnosed at the same time in colon and rectum	Primary site should be registered by T stage or tumor sizes If the above was not available, tumor in third end of Distal Colon, should be registered as Rectum If tumor was in the other sites of Distal Colon, should be registered as colon
Two tumors diagnosed at the same time in Duodenum and Pancreas	Pancreas is usually Invasion of Duodenum
Two tumors diagnosed at the same time in Colorectal and Bladder	If both have Adenocarcinoma morphology, Bladder is metastatic If have different morphology, should be registered as multiple primary cancers
Two tumors diagnosed at the same time in Colorectal and Liver	If both have Adenocarcinoma morphology, liver is metastatic If have different morphology, should be registered as multiple primary cancers
Two tumors diagnosed at the same time in Colon and Bladder	Tumor in Sigmoid Colon, Bladder should be Registered as Metastasis cancer Tumor in upper subsites of Colon, Bladder should be registered as multiple primary cancers
Two tumors diagnosed at the same time in Prostate and Bladder	Prostate Cancer with Adenocarcinoma Morphology, Bladder should be registered as Metastasis cancer Prostate Cancer with Transitional Morphology, Bladder should be registered as Primary cancer
Two tumors diagnosed at the same time in Thyroid and Lung	Thyroid Cancer with Papillary or Follicular Morphology, should be registered as Primary cancer and multiple primary cancers Thyroid Cancer Adenocarcinoma or SCC Morphology, should be registered as Metastasis of Lung
Recto-sigmoid , colon , Rectum	Earlier History
Two tumors diagnosed at the same time in Pancreas and Stomach	Both Invasion should be rule out
Two tumors diagnosed at the same time in Liver and Pancreas	Earlier History
Female Genital	Earlier History and the rest should be registered as Metastasis Cancers

BMB results, Brain and/or Bone involvements are always metastatic, however synchronous Prostate, Stomach, Bladder, Colon, or Breast cancers with hematologic malignancies should be registered as second primary cancers. Synchronous Bone and/or Mediastinum tumors with Breast cancer are always metastatic, but for Thyroid, Esophagus, Stomach, and colorectal cancer were registered both as MPCs. In cases of common metastatic sites, tumor morphology is helpful for define of primary and/or metastatic sites. In most cases of multiple cancers with the same morphological types, the earlier should be registered as primary tumor.

In most of the synchronous multiple cancers familial cancer syndromes should be considered and rules out, for example in case of synchronous tumors of Stomach and Ovary tumors, Krukenberg syndrome should be considered. In case of two tumors diagnosed at the same time in colon and rectum, primary site should be detected by T stage or tumor sizes, however if the above was not available, tumor in third end of Distal Colon, should be registered as Rectum, and if tumor was in the other sites of Distal Colon, should be registered as colon. In synchronous tumors of Colon and Bladder, the subsite of Colon cancer determines the final decision. While in case of two tumors diagnosed at the same time in Colon and Bladder, in case of sigmoid tumors, Bladder should be considered as metastatic site, but if tumor was in upper subsite of Colon, Bladder cancer should be considered as second primary cancer.

In case of multiple tumors in Recto-sigmoid, Colon, and Rectum the earlier history of tumor should be considered as primary site. This rule was applied for Female Genital tumors, as earlier site is always the Primary cancer and other tumors should be registered as metastatic sites.

In case of synchronous prostate and bladder tumors, prostate cancer morphology plays a major role in final decision. Also, in the case of synchronous thyroid and lung cancer, the morphology of thyroid cancer is decisive.

Some Hints

-The rectum can metastasize to the lungs but not to the genital organs

-Lymph nodes, Omentum, Peritoneum, and Pleura are mostly metastatic sites

- When we have two Primary diagnoses with most metastatic possibility, invasion and/or metastasis always should be rule out

Table 3. Multiple Primary Cancers Reports during 2015, based on Our Provided Rules

	Age	Sex	Topography Code	Morphology	Final Diagnosis
Case 1	53	Female	C 06.9	8070	Mouth,Squamous Cell Carcinoma
			C 21.1	8070	Anal Canal,Squamous Cell Carcinoma
			C 73.9	8260	Thyroid Gland,Papillary Carcinoma
International Rules For Multiple Primary Cancers, Rulr 4.2 , Supplement Table 3					
Case 2	69	Male	C 16.9	8140	Stomach, Adenocarcinoma
			C 18.8	8140	Overlapping Lesion Of Colon,Adenocarcinoma
Table 1, Stomach : Rule No 5					
Case 3	63	Male	C 16.9	8140	Stomach, Adenocarcinoma
			C 19.9	8140	Rectosigmoid Junction, Adenocarcinoma
Table 1, Stomach : Rule No 5					
Case 4	52	Female	C 19.9	8140	Rectosigmoid Junction, Adenocarcinoma
			C 50.9	8500	Breast, Infiltrating Duct Carcinoma
Table 1, Breast: Rule No 4,5					
Case 5	37	Female	C 26.8	8000	Overlapping Lesion Of Digestive System Adenocarcinoma
			C 56.9	8140	Ovary, Adenocarcinoma
Table 1, Colon & Rectum: Rule No 15					
Case 6	66	Female	C 16.9	8010	Stomach, Adenocarcinoma
			C 50.9	8500	Breast, Infiltrating Duct Carcinoma
Table 1, Colon & Rectum: Rule No 8,9					
Case 7	63	Female	C 50.9	8500	Breast, Infiltrating Duct Carcinoma
			C 67.9	8130	Bladder, Papillary Transitional Cell Carcinoma,Non-Invasive
Table 1, Breast: Rule No 6					
Case 8	84	Female	C 50.9	8520	Breast, Lobular Carcinoma
			C 73.9	8260	Thyroid Gland, Papillary Adenocarcinoma
Table 1, Breast: Rule No 1					
Case 9	77	Male	C 18.9	8140	Colon, Adenocarcinoma
			C 22.0	8170	Liver, Hepatocellular Carcinoma
Table 1, Colon & Rectum: Rule No 4,B.					
Case 10	56	Male	C 16.9	8140	Stomach, Adenocarcinoma
			C 73.9	8140	Thyroid Gland, Adenocarcinoma
Table 1, Stomach: rule no 3					

-When we have two Primary diagnoses and metastasis at the same time (patient had a tumor as primary and a metastasis of another tumor with unknown primary site) we keep both

Note

• Recording of MPCs with neuro-endocrine components in tumors, collision tumors and other rare tumors (Hybrid tumors and others) will need to be classified according to IARC guidelines and coded as in ICD-O to make it comparable and complete.

• MPCs where origin of primary tumor cannot be ruled out, tumors with different morphologies in the same organ, lymphomas and or when determining true second primary is confusing, further consultation with the experts is advisable. Available laboratory reports including IHC can also be helpful. The results are summarized and showed in both Table 1 and Table 2.

The identified and recorded multiple primary cancers in our study during 2015, 2016 and 2017 are provided in detail in Tables 3-5 respectively.

Discussion

The rules suggested in this study for multiple primary cancers were provided from our previous 3-year experiences in the EA-PBCR for reporting data on cancer incidence. All newly diagnosed/confirmed cancer cases (total 21,462) from the year 2015 to 2017 were included for recording and coding of MPCs. In most cases, we coded the MPCs as the previous guidelines, however, additional suggested rules provided for malignancies of the Blood, Breast, Lung, Stomach, Small Intestine, Colorectal, Bone, Prostate, Bladder, Skin, and some additional hints. All the cases mentioned were microscopically verified. The provided hints emphasized that in multiple primary

Table 4. Multiple Primary Cancers Reports during 2016, based on Our Provided Rules

	Age	Sex	Topography Code	Morphology	Final Diagnosis
Case 1	48	Female	C 44.3	9080	Skin Of Face, Basal Cell Carcinoma
			C 18.7	8140	Sigmoid Colon, Adenocarcinoma
Table 1. Colon & Rectum: Rule No 11					
Case 2	51	Male	C 44.9	8090	Skin, Basal Cell Carcinoma
			C 20.9	8140	Rectum, Adenocarcinoma
Table 1. Colon & Rectum: Rule No 11					
Case 3	57	Female	C 56.9	8140	Ovary, Adenocarcinoma
			C 50.9	8500	Breast, Ductal Carcinoma
Table 1. Breast: Rule No 11					
Case 4	53	Female	C 73.9	8260	Thyroid Gland, Papillary Carcinoma
			C 64.9	8312	Kidney, Renal Cellcarcinoma
International Rules For Multiple Primary Cancers, Rulr 4.2 , Supplement Table 3					
Case 5	86	Male	C 50.9	8500	Breast, Infiltrating Duct Carcinoma
			C 16.9	8144	Stomach, Adenocarcinoma, Intestinal Type
Table 1. Breast: Rule No 3					
Case 6	56	Female	C 54.1	8800	Endometrium,Sarcoma
			C 18.9	8140	Colon, Adenocarcinoma
Table 1. Colon & Rectum: Rule No 2					
Case 7	78	Female	C 56.9	8140	Ovary, Adenocarcinoma
			C 20.9	8140	Rectum, Adenocarcinoma
Table 1. Colon & Rectum: Rule No 15					
Case 8	63	Female	C 50.9	8500	Breast, Ductal Carcinoma
			C 18.9	8140	Colon, Adenocarcinoma
Table 1. Breast: Rule No 4					
Case 9	88	Male	C 61.9	8140	Prostate Gland, Adenocarcinoma
			C 44.1	8090	Eyelid, Basal Cell Carcinoma
International Rules For Multiple Primary Cancers, Rulr 4.2 , Supplement Table 3					
Case 10	67	Female	C 53.9	8140	Cervix Uteri,Adenocarcinoma
			C 20.9	8140	Rectum, Adenocarcinoma
Table 1. Colon & Rectum: Rule No 9					
Case 11	78	Female	C 50.9	8500	Breast, Infiltrating Duct Carcinoma
			C 18.9	8490	Colon, Signet Ring Cellcarcinoma
Table 1. Breast: Rule No 4					
Case 12	60	Female	C 56.9	8441	Ovary, Serouscystadenocarcinoma
			C 18.9	8140	Colon,Adenocarcinoma
Table 1. Colon & Rectum: Rule No 15					

diagnosis, invasion and/or metastasis always should be rule out, and some organs including Lymph nodes, Omentum, Peritoneum, and Pleura are mostly metastatic sites. However, the morphological aspects of multiple cancers always may help us to differential diagnosis of the MPCs.

Recording, coding, and studying of multiple primary cancers provide an insight into Gene-Environmental carcinogenesis in individuals with different cancers at different times. Evaluating and following of these cases can lead to risk estimation and familial aggregation, studies of potential familial cancers and risk of developing second or third cancers. Meanwhile, detecting and recording of these cases may provide some information about chemical and radiation side effects of different cancer treatment protocols which lead to an increased risk of another cancer and also the quality of cancer care they received (Wanner et al., 2018; Demoor-Goldschmidt and de Vathaire, 2019). Furthermore, diagnosis of multiple primary cancers in early stages and even asymptomatic cases have the same value along with all other cancer surveillance efforts (Amikura et al., 2020; Feller et al., 2020).

Nowadays, two guidelines are more widely used worldwide for multiple primary cancers, Surveillance Epidemiology and End Results (SEER) program, and International Association of Cancer Registries (IACR) and the IARC rules (International Association of Cancer, 2005; Working Group, 2005; Ditsch et al., 2019). Based

Table 5. Multiple Primary Cancers reports during 2017, based on Our Provided Rules

	Age	Sex	Topography Code	Morphology	Final Diagnosis
Case 1	45	Female	C 18.1	8240	Appendix, Carcinoid Tumor
			C 55.9	8140	Uterus, Adenocarcinoma
			C 16.9	8140	Stomach, Adenocarcinoma
Table 1. Stomach: Rule No 9					
Case 2	77	Male	C 61.9	8140	Prostate Gland, Adenocarcinoma
			C 18.7	8140	Sigmoid Colon, Adenocarcinoma
Table 1. Colon & Rectum: Rule No 5					
Case 3	64	Male	C 16.0	8145	Cardia, Carcinoma,Diffuse Type
			C 67.9	8130	Bladder,Papillary Transitional Cell Carcinoma
International Rules For Multiple Primary Cancers, Rule 4.2 , Supplement Table 3					
Case 4	74	Female	C 23.9	8140	Gallbladder, Adenocarcinoma
			C 67.9	8130	Bladder, Papillary Transitional Cell Carcinoma, Non-Invasive
International Rules For Multiple Primary Cancers, Rule 4.2 , Supplement Table 3					
Case 5	68	Male	C 18.0	8140	Cecum, Adenocarcinoma
			C 64.9	8260	Kidney, Papillary Adenocarcinoma
International Rules For Multiple Primary Cancers, Rule 4.2 , Supplement Table 3					
Case 6	52	Female	C 16.9	8145	Stomach, Carcinoma, Diffuse Type
			C 17.1	8140	Jejunum, Adenocarcinoma
International Rules For Multiple Primary Cancers, Rule 4.2 , Supplement Table 3					
Case 7	59	Female	C 50.9	8500	Breast, Infiltrating Ductal Carcinoma
			C 42.1	9835	Bone Marrow, Precursor Cell Lymphoblastic Leukemia
Table 1. Blood: Rule No 8					
Case 8	70	Female	C 16.9	8144	Stomach, Adenocarcinoma, Intestinal Type
			C 54.1	8380	Endometrium, Endometrioid Carcinoma
Table 1. Stomach: Rule No 10					
Case 9	51	Male	C 44.3	8090	Skin Of Face, Basal Cell Carcinoma
			C 71.9	9400	Brain, Astrocytoma
International Rules For Multiple Primary Cancers, Rule 4.2 , Supplement Table 3					
Case 10	77	Male	C 44.3	8090	Skin Of Face, Basal Cell Carcinoma
			C 18.7	8140	Sigmoid Colon, Adenocarcinoma
Table 1. Colon & Rectum: Rule No 11					
Case 11	50	Female	C 56.9	8010	Ovary, Carcinoma
			C 20.9	8010	Rectum, Carcinoma
Table 1. Colon & Rectum: Rule No 15					
Case 12	60	Female	C 17.9	8140	Small Intestine, Adenocarcinoma
			C 56.9	8380	Ovary, Endometrioid Carcinoma
International Rules For Multiple Primary Cancers, Rule 4.2 , Supplement Table 3					
Case 13	36	Female	C 34.9	8041	Lung, Small Cell Carcinoma
			C 73.9	8340	Thyroid Gland, Papillary Carcinoma,Follicular Variant
International rules for multiple primary cancers, rule 4.2 , supplement Table 3					

on IARC/IACR recommendations, all established rules for MPCs are comparable among different populations. Each PBCR may provide and suggest some specific and more detailed rules, and also share with other registries. These data together may be used to conform to the international rules for PBCR data quality indicators (International Association of Cancer, 2005).

Warren and Gates emphasized for the first time that the incidence of multiple primary cancers is more than to be counted as accidental. Also they provide some more information about synchronous and/or metachronous nature of second primary cancer based on the time of tumor onset (Warren and Ehrenreich, 1944). By improving treatment outcomes of cancer patients, because of early diagnosis and screening modalities, and specific and targeted chemo- radio-therapy protocols, the number of MPCs increased in the last decades (Ye et al., 2016; Amikura et al., 2020). However, it has recently been

approved that there was inheriting susceptibility of familial multiple primary cancers in different populations (Warren and Ehrenreich, 1944).

It has been revealed that a second or more primary cancer risk is higher in cancer survivors than normal population, and the time interval between first and other primary cancers differed, but is high after approximately 10 years for all cancers and all sites (Zhang et al., 2019; Tanjak et al., 2021; Odani et al., 2022). This is because of genetic susceptibility in familial cases and side effects of different cancer treatment modalities. All cancer survivors should benefit and are mandated to continue the screening and early diagnosis of cancer at any ages and conditions for any MPCs.

As the aging of the populations and increasing the number of cancer survivors the occurrence and incidence of MPCs is likely to increase (Soerjomataram and Coebergh, 2009). The incidence of MPCs varies from 2.15% to 17.2% in USA, and 2.4 to 8.17% in different European countries, however geographical region, coverage of cancer registries, mean follow-up times (for metachronous MPCs) and definition used for recording MPCs had significant impact on this percentages (Vogt et al., 2017). As the low coverage of population based cancer registry in most Asian countries, this percentages are lower than most developed countries (Jena et al., 2016). The percentage of MPCs in our study was 0.16% (35 out of 21,462 registered cases), which is comparable with previous years and neighboring countries.

The collaborative studies are important to share any new rules and experiences between PBCRs, which provide information and evidence about the potential causes and absolute risks of different types of multiple primary cancers and their estimated risks(Bray and Parkin, 2009). Local and international agreement for recording, coding and classification of multiple primary cancers are important in any new established PBCR program. Recently, by availability of new chemo- and radio-therapy protocols and with increasing survivorship from different primary cancers, we face with an increasing risk of secondary cancers (Temming et al., 2017; Krug et al., 2018).Therefore, establishing and using comprehensive and principal rules for secondary cancers as "true second primary cancer" are necessary in every local PBCRs. However, the IARC and IACR provide some useful international as well as conservative and general guidelines (International Association of Cancer, 2005; Working Group, 2005).

Iran has faced an increase in the incidence of all cancers by about 10% over the last 10 years, but this has occurred in tandem with a declining trend in the mortality rates by about 10% over the same period. The EA-PBCR has helped us to provide important information about the high incidence of gastrointestinal cancers in this Province, (notably gastric and colorectal cancers), and non- gastrointestinal cancers (such as breast, Lung, and thyroid cancers). Prevention and early diagnosis strategies, particularly those of the gastrointestinal tract, breast and lung cancers must now be considered as public health priorities both at national and local levels.

Strengths and Limitations

This study design was not in a systematic approach but to provide some ideas and "Providing Suggested Rules for Multiple Primary Cancer Recording, Coding and Registering". As of our knowledge, these suggested rules for hematological malignancies were provided for the first time. Data collection and quality and coverage of data sources remain as our major limitations. We could not analyze the inherited and cancer-predisposing mutations in MPC cases. This information will be helpful to evaluate even early diagnosis of cancer risk in second or more other sites, and risk estimation in first and/or second-degree relatives of cases. Due to time limitation of the study (3 years) we presented here only newly diagnosed cancers during the 2015 to 2017 years, as synchronous MPCs, and we are working on our next studies on most comprehensive and mono-chronous cases, as including wider follow-up times.

Improving data collection quality and adding additional information including molecular and genetic diagnosis of the cancers will be our uppermost aim in our upcoming reports.

In conclusion, we wanted to present some additional rules for identifying, recording, coding and registering multiple primary cancers in the context of East Azerbaijan population-based cancer registry program. The quality of the EA-PBCR is promising however the study design was not in a systematic approach but to provide some ideas and "Providing Suggested Rules for Multiple Primary Cancer Recording, Coding and Registering" in our cancer registry and provide of some of the available data on multiple primaries.

Abbreviations

MPC: Multiple primary cancer
PBCR: Population Based Cancer Registry
EA-PBCR: East Azerbaijan Population Based Cancer Registry
IARC: International Agency for Research on Cancer
SEER: Surveillance Epidemiology and End Results
IACR: International Association of Cancer Registries
ICD-O: International Classification of Diseases for Oncology
ASIR: Age-Standardized Incidence Rate
NID: National Identification numbers
TNM: Tumor, Node, Metastasis
CT: Computerized Tomography
MRI: Magnetic Resonance Imaging
BMB: Bone Marrow Biopsy

Author Contribution Statement

RD, SS, NY, and MN: analysed and interpreted the patient data regarding the guidelines. MHS, IAK, and BAA: performed the quality control of the data set and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The datasets analyzed and presented in this study are available from the corresponding authors on reasonable

request.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of Tabriz University of Medical Sciences as a confirmed research project (Code: IR.TBZMED.REC.1396.524). As the ethics rules of EA-PBCR, all patients' information and records are confidential.

Consent for publication

As the ethics rules of EA-PBCR, all patients' information and records are confidential. Written informed consent to publish this information was obtained from study participants.

Availability of data and materials

Data are openly available in a public repository that issues datasets with the responsibility of the corresponding author.

Funding

This study was supported and funded based on Population Based cancer Registry program of East Azerbaijan from Ministry of Health and Medical Education, Deputy of Research Technology and covered the design of the study and collection, analysis, and interpretation of data (Grant Number: 700/1480, 1395.10.4).

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Competing interests

The author reports no conflicts of interest in this work.

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