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

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ABSTRACT

Objective: 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 cancers.

Methods: Comparability, validity, timeliness, and completeness of data assessment were performed. We followed the established "rules for reporting incidence and survival". 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 consulting team including expert oncologists, pathologists, and gastroenterologists to discuss each case.

Results: Overall, among 21,462 total cancer cases registered in EA-PBCR from 2015 to 2017, 35 cases were registered as MPCs, as follows: 10 out of 6655 in 2015, 12 out of 7042 in 2016, and 13 out of 7765 in 2017. In most cases, we coded the MPCs as the previous guidelines and provided tables that were somehow according to guidelines, with some more information and case presentations. Importantly, these suggested rules included cancers in the blood, breast, lung, stomach, small intestine, colorectal, bone, prostate, bladder, skin, and some additional hints.

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.

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Keywords: Multiple primary cancers; Comparability; Validity; T imeliness; Completeness; Cancer registry; Population

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

INTRODUCTION

In 2020, there were 19.3 million incident cases of cancer and 10.0 million cancer deaths worldwide. 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 [1,2].

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 [3,4]. 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. "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 [5]. 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 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 Cancers (MPC) for the first time as "definitive malignant tumors", "distinct tumors", and "excluded metastasis tumors" [6]. Based on International Classification of Diseases for Oncology (ICD-0-3) guidelines, the best and reliable definitions are:

- Two or more separate neoplasms in different topographic sites.
- Certain conditions characterized by multiple tumors.
- Lymphomas which often involve multiple lymph nodes or organs at diagnosis.
- Two or more neoplasms of a different morphology arising in the same site.
- A single neoplasm involving multiple sites whose precise origin cannot be determined.
- Not being the result of metastasis or recurrence of primary cancer.
- The recognition of the existence of two or more primary cancers does not depend on time.

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 programs are 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 [7]. At this time, apart from several provided rules for MPCs coding and registering, additional evidences and results should be present for the practical and clinical management and treatment strategies [8]. These evidences 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. 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 [9]. However, PBCRs increase the coverage and quality indicators of cancer registries. These studies have less potential bias compared with pathology and hospital based registries [10].

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

Research Design

The methodology used for the cancer registry in the East Azerbaijan/Iran Population Based Cancer Registry (EA-PBCR) was based on the operational program of the national cancer registry of the ministry of health and medical education (**Figure 1**).

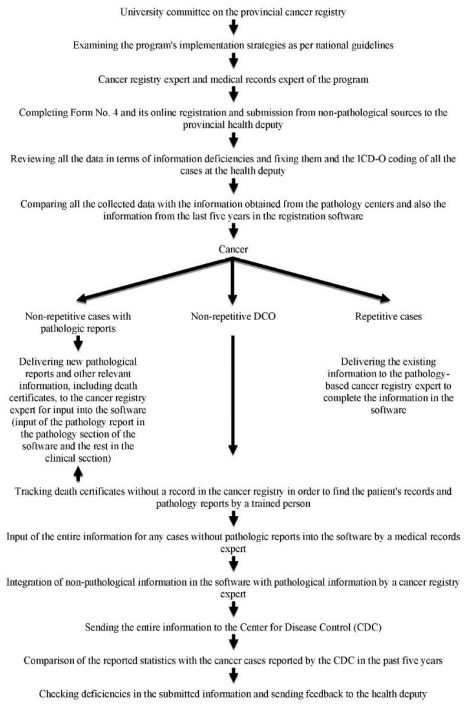

Figure 1: The Population based cancer registry algorithm.

The registered data were all population based and obtained from the following sources:

- Pathobiology centers.
- Hospital medical records (*i.e.*, The Hospital Information System: HIS).
- Provincial mortality data.
- Outpatient departments.
- Hematology oncology centers.
- Radiotherapy centers.
- Public and private imaging centers.
- Public and private clinics and health centers.

Data collection was performed using active and passive methods on a standardized form by well trained staff. Also some data sources sent the filled information as manually, as a copy of pathology reports and/or filled standard forms (paper based).

Study Subjects

East Azerbaijan is the largest and most populous province located at the Northwest of Iran, while more than 95% of the local population is of Azeri ethnicity. It covers an area of 45,620 km^2 and had a total population of 3,911,278 according to the 2015 national census in Iran. East Azerbaijan province includes 20 counties, 62 cities, and 44 districts, with 71.68% urban composition. The population pyramid for the East Azerbaijan province by age and sex group, emphasizing that the population was young, with a predominance of people aged 20 years-24 years. East Azerbaijan province is in regions 3 of Iran, while the EA-PBCR is held in the capital city, Tabriz.

We included all cases with confirmed primary and newly diagnosed cancers during 2015 to 2017 years from different data sources. Data collection was performed using active and passive methods. During active data collection, the required cancer registry information was collected from information sources by the cancer registration personnel from three main data sources including pathology reports, medical records and death certificate registry (e.g., we visited hospitals and collected or copied required data). Additional data collection was done regularly when the registry office received forms, copies of discharge summaries and reports from participating institutions.

After completing data entry, quality control, consistency checks and basic analysis, manual quality controls and computerized validity checks of the cancer registry system were performed based on the IARC criteria in the cancer registry office of East Azerbaijan province. This involved assessing factors which influence comparability, validity, timeliness, and completeness [10-15]. Case duplication across the registry databases was checked in three steps, first with patient first name, family name; then by including patient fathers' name; and finally with patient NID number. Linking the database with current and previous cancer registries, we tried to find tumor information from various sources and improve the validity of our results, and decrease the percentage of cases obtained from the causes of death registry without pathology or clinical data were reported as Death Certificate Only (DCO) cases, and increase the frequency of cases with microscopic MV or clinical data. The mortality data were collected from our cancer registry, observed deaths (reports from follow-up records), or the national death certificate registry (reported deaths). We then used data from death certificates and contacted the hospitals and relatives of patients, which uncovered the clinical or pathology reports that allowed us to change the basis of the diagnoses accordingly.

Sample Size Determination

In this study, all newly diagnosed/confirmed cancer cases (total 21,462) from the year 2015 to 2017 were included for recording and coding of MPCs.

Measurements

The coding system used for the EA-PBCR is based on the latest version of the International Classification of Diseases for Oncology (ICD-O-3). Each tumor is handled as a single entity, meaning that each patient can have more than one tumor simultaneously or at different times and that each tumor can have several reports. We estimated crude incidence rates and Age Standardized Incidence Rates (ASIR) per 100,000 populations using the 2000 standard world population. Age-specific incidence rates were also reported for each cancer in 18 strata of 5-years age groups.

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) and Surveillance Epidemiology and End Results (SEER) program 19, 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 6655 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 7042 cases (3 male and 9 female) were registered; all cases had had two primary cancers.
- **2017:** 13 MPCs out of 7765 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 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. The results are summarized and showed in both **Tables 1 and 2**. All the cases mentioned in the tables were microscopically verified.

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	Blood and brain	In case of definite BMB* results, blood is primary
	Blood and bone	In case of definite BMB* results, blood is primary
	Blood and prostate	Both
	Blood and stomach	Both
	Blood and bladder	Both
	Blood and head and neck	Both
	Blood and colon	Both
	Blood and breast	Both
Breast	Breast and thyroid	Both
	Breast and esophagus	Both
	Breast and stomach	Both
	Breast and colon	Both
	Breast and rectum	Both
	Breast and bone	Breast as primary, bone as metastatic cancer

	Breast and mediastinum	Breast as primary, mediastinum as metastatic cancer
		If thymus was involved we verified both as primary
	Breast and liver	Breast as primary, liver as adenocarcinoma metastatic cancer
		Breast as primary, liver as other morphologies, both
	Breast and lung	Breast as Primary, Lung as Adenocarcinoma, both
		Breast as primary, lung as other morphologies, metastatic cancer
Lung	Lung and head and neck	Both
	Lung and sigmoid	Sigmoid as primary, lung as metastatic cancer
	Lung and esophagus	Esophagus as primary, lung as metastatic cancer
	Lung and stomach	Stomach as primary, lung as metastatic cancer
	Lung and skin	Lung as primary, skin as metastatic cancer
	Lung and pleura	Lung as primary, pleura as metastatic cancer
Stomach	Stomach and prostate	Both
	Stomach and esophagus	Both
	Stomach and ovary	Both (krukenberg tumor should be rule out)
	Stomach and colon	Both
	Stomach and pleura	Stomach as primary, pleura as metastatic cancer
	Stomach and liver	Stomach as primary, liver as adenocarcinoma, metastatic cancer
		Stomach as primary, liver as other morphologies, both
	Stomach and small intestine and colon (rectum, recto sigmoid)	Stomach and colon
Small intestine	Small intestine and pancreas	Both
	Small intestine and peritoneum	Small intestine as primary, peritoneum as metastatic cancer
Colon and rectum and recto sigmoid	Colon and cardia	Both
	Colon and endometrium	If both have adenocarcinoma morphology, endometrium is metastatic
		If have different morphology, should be registered as multiple primary cancers
	Colon and brain	Colon as primary, brain as metastatic cancer
	Colon and liver	Colon as primary, liver as adenocarcinoma metastatic cancer
		Colon as primary, liver as other morphologies, both
	Colon and prostate	Both
	Colon and small intestine	Both

	Colon and esophagus	Both
	Colon and female genitals	Both
	Rectum and female genitals	Both
	Sigmoid and ureter	Both
	Sigmoid and skin	Both
	Recto sigmoid and lung	Recto sigmoid as primary, lung as metastatic cancer
	Recto sigmoid and anus	Both (FAP and other polyposis should be rule out)
	Rectum and liver	Rectum as primary, liver as adenocarcinoma metastatic cancer
		Rectum as primary, liver as other morphologies, both
Bone	Femur and connective tissue of the upper limb	Both
	Femur and other bones	Both
	Bone and Skin	Bone as primary, skin as metastatic cancer
Prostate	Prostate and gallbladder	Both
	Prostate and adrenal glands	Both
Bladder	Bladder and gallbladder	Both
Skin	Ear skin and scalp skin	If both have same morphology, earlier is primary, other one metastatic
	Eye skin and skin of nose and face	If have different morphology, should be registered as multiple primary cancers
		If both have same morphology, earlier is primary, other one metastatic
	Skin and parotid gland	If have different morphology, should be registered as multiple primary cancers
		Parotid gland as primary, skin as metastatic cancer
Other	Esophagus and trachea	Both
	Nasopharynx and larynx	Both
	Lower limb and soft connective tissue of lower limb	Both
	Thyroid and adrenal gland	Both
	Liver and brain	Liver as primary, brain as metastatic cancer
	Ovary and omentum	Ovary as primary, omentum as metastatic cancer
	Head of pancreas and cerebellum of brain	Pancreas as primary, cerebellum as metastatic cancer
	*Bone marrow biopsy	

Table 2: Suggested rules for multiple primary cancer recording, coding and registering in East Azerbaijan coding 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 subsides of colon, 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
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
	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 neuroendocrine components in tumors, collision tumors and other rare tumours (hybrid tumours 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 tumour 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 identified and recorded multiple primary cancers in our study during 2015, 2016 and 2017 are provided in details in (**Tables 3-5**) respectively.

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
Case 2	69	Male	C 16.9	8140	Stomach, adenocarcinoma
			C 18.8	8140	Overlapping lesion of colon, adenocarcinoma
Case 3	63	Male	C 16.9	8140	Stomach, adenocarcinoma
			C 19.9	8140	Recto-sigmoid junction, adenocarcinoma
Case 4	52	Female	C 19.9	8140	Recto-sigmoid junction, adenocarcinoma
			C 50.9	8500	Breast, infiltrating duct carcinoma
Case 5	37	Female	C 26.8	8000	Overlapping lesion of digestive system adenocarcinoma
			C 56.9	8140	Ovary, adenocarcinoma
Case 6	66	Female	C 16.9	8010	Stomach, adenocarcinoma
			C 50.9	8500	Breast, infiltrating duct carcinoma
Case 7	63	Female	C 50.9	8500	Breast, infiltrating duct carcinoma
			C 67.9	8130	Bladder, papillary transitional cell carcinoma, non-invasive
Case 8	84	Female	C 50.9	8520	Breast, lobular carcinoma
			C 73.9	8260	Thyroid gland, papillary adenocarcinoma
Case 9	77	Male	C 18.9	8140	Colon, adenocarcinoma
			C 22.0	8170	Liver, hepatocellular carcinoma
Case 10	56	Male	C 16.9	8140	Stomach, adenocarcinoma
			C 73.9	8140	Thyroid gland, adenocarcinoma

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
Case 2	51	Male	C 44.9	8090	Skin, basal cell carcinoma
			C 20.9	8140	Rectum, adenocarcinoma
Case 3	57	Female	C 56.9	8140	Ovary, adenocarcinoma
			C 50.9	8500	Breast, ductal carcinoma
Case 4	53	Female	C 73.9	8260	Thyroid gland, papillary carcinoma
			C 64.9	8312	Kidney, renal cell carcinoma
Case 5	86	Male	C 50.9	8500	Breast, infiltrating duct carcinoma
			C 16.9	8144	Stomach, adenocarcinoma, intestinal type
Case 6	56	Female	C 54.1	8800	Endometrium, sarcoma
			C 18.9	8140	Colon, adenocarcinoma
Case 7	78	Female	C 56.9	8140	Ovary, adenocarcinoma
			C 20.9	8140	Rectum, adenocarcinoma
Case 8	63	Female	C 50.9	8500	Breast, ductal carcinoma
			C 18.9	8140	Colon, adenocarcinoma
Case 9	88	Male	C 61.9	8140	Prostate gland, adenocarcinoma
			C 44.1	8090	Eyelid, basal cell carcinoma
Case 10	67	Female	C 53.9	8140	Cervix uteri, adenocarcinoma
			C 20.9	8140	Rectum, adenocarcinoma
Case 11	78	Female	C 50.9	8500	Breast, infiltrating duct carcinoma
			C 18.9	8490	Colon, signet ring cell carcinoma

Case 12	60	Female	C 56.9	8441	Ovary, serous cystadenocarcinoma
			C 18.9	8140	Colon, adenocarcinoma

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
Case 2	77	Male	C 61.9	8140	Prostate gland, adenocarcinoma
			C 18.7	8140	Sigmoid colon, adenocarcinoma
Case 3	64	Male	C 16.0	8145	Cardia, carcinoma, diffuse type
			C 67.9	8130	Bladder, papillary transitional cell carcinoma
Case 4	74	Female	C 23.9	8140	Gallbladder, adenocarcinoma
			C 67.9	8130	Bladder, papillary transitional cell carcinoma, non-invasive
Case 5	68	Male	C 18.0	8140	Cecum, adenocarcinoma
			C 64.9	8260	kidney, papillary adenocarcinoma
Case 6	52	Female	C 16.9	8145	Stomach, carcinoma, diffuse type
			C 17.1	8140	Jejunum, adenocarcinoma
Case 7	59	Female	C 50.9	8500	Breast, infiltrating ductal carcinoma
			C 42.1	9835	Bone marrow, precursor cell lymphoblastic leukemia
Case 8	70	Female	C 16.9	8144	Stomach, adenocarcinoma, intestinal type

			C 54.1	8380	Endometrium, endometrioid carcinoma
Case 9	51	Male	C 44.3	8090	Skin of face, basal cell carcinoma
			C 71.9	9400	Brain, astrocytoma
Case 10	77	Male	C 44.3	8090	Skin of face, basal cell carcinoma
			C 18.7	8140	Sigmoid colon, adenocarcinoma
Case 11	50	Female	C 56.9	8010	Ovary, carcinoma
			C 20.9	8010	Rectum, carcinoma
Case 12	60	Female	C 17.9	8140	Small intestine, adenocarcinoma
			C 56.9	8380	Ovary, endometrioid carcinoma
Case 13	36	Female	C 34.9	8041	Lung, small cell carcinoma
			C 73.9	8340	Thyroid gland, papillary carcinoma, follicular variant

DISCUSSION

The rules suggested in this study for multiple primary cancers were provided from our previous 3 years 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 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. Furthermore, diagnoses of multiple primary cancers in early stages and even asymptomatic cases have the same value along with all other cancer surveillance efforts. 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 [15-19]. Based 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. 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. By improving treatment outcomes of cancer patients, because of early diagnosis and screening modalities, and also specific and targeted chemo-radio-therapy protocols, the number of MPCs increased in the last decades. However, it has recently been approved that there was inheriting susceptibility of familial multiple primary cancers in different populations. 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. 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. 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. As the low coverage of population based cancer registry in most Asian countries, this percentages are lower than most developed countries. The percentage of MPCs in our study is 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. 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. Therefore, establishing and using comprehensive and principal rules for secondary cancers as "true second primary cancer" are necessary in every local PBCR. However, the IARC and IACR provide some useful international as well as conservative and general guidelines. 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 [20].

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.

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 still 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-chromos 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.

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.

COMPETING INTERESTS

The author reports no conflicts of interest in this work.

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AUTHOR'S CONTRIBUTIONS

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.

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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.

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