Review Article

An Overview of Clinical and Pathological Characteristics and Survival Rate of Colorectal Cancer in Iran

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Context: Colorectal cancer is one of the most common cancers and the leading cause of cancer death in Iran. This study aimed to identify the clinical and pathological characteristics, as well as survival rate of colorectal cancer in Iran.
Evidence Acquisition: The articles published in PubMed without language and time restrictions were included in this review. Only original clinical articles were included in the review and non-clinical studies, including cellular, molecular, genetics, and animal reports, were excluded. The case reports, letters, reviews, and clinical reports with less than 100 patients were excluded, as well. All the clinical data regarding the patients' demographics, tumor characteristics, and survival rate were collected.
Results: A total of 178 studies were identified at the initial step of literature search. After applying the inclusion and exclusion criteria, 27 studies, including 37901 patients were eligible. The mean age of the patients was 57.2 years, and the male-female ratio was 1.38. Colon, rectum, and rectosigmoid junction accounted for 58%, 28%, and 14% of all colorectal primary sites, respectively. Moreover, the average proportion of the patients with stages 0-I, II, III, and IV was 9%, 39%, 36%, and 16%, respectively. Besides, tumor grades 1, 2, and 3 were reported in 52%, 37%, and 11% of the patients, respectively. Adenocarcinoma (96.8%) was the most frequent histological type. The mean and median survival rate was 80.1 and 55.2 months, respectively. Additionally, the average 5-year overall survival rate was 52.5%.
Conclusions: In Iran, colorectal cancer tends to manifest at locally advanced stage with poor prognosis. Therefore, public health strategies, such as screening programs, should be planned for early detection of this aggressive neoplasm.

Keywords: Colorectal Neoplasms; Clinical Characteristics; Pathology; Survival

1. Context

Malignant neoplasms arising from colon, rectum, and anal canal are categorized as colorectal cancer; however, colorectal cancer is usually used for histological type of adenocarcinoma (1, 2). Colorectal cancer is the third most common cancer in men and the second one in women worldwide. This malignancy is the fifth most frequently diagnosed cancer and the leading cause of cancer death in developing countries (3). Based on the Iranian annual national cancer registration report, this neoplasm is the fifth common cancer in Iranian men and the third one in women (4).

There is a wide range of different regional incidence rates among continents and countries. The highest incidence rates have been found in Eastern European countries, Japan, New Zealand, Australia, Germany, and North America (America Africans). On the other hand, the lowest rates have been reported from Central and South America, Africa, as well as South and Central Asia (5). Although the incidence rate of colorectal cancer has been stabilized and declined in traditionally high-risk areas, such as North America and New Zealand, a rapid increase has been observed in low-risk Asian countries, such as Japan, Korea, and China. Changing toward western dietary and lifestyle, smoking, and obesity are believed to contribute to this increase in the incidence rates in these countries (5, 6).

Colorectal cancer tends to have a high mortality rate, and its outcome is closely related to the extent of lymph node involvement and disease stage at presentation (7). Abdominal pain, change in bowel habits, rectal bleeding, weakness, anemia, and weight loss are the most frequent symptoms in the patients with colorectal cancer. Moreover, alarm symptoms, such as dark red rectal bleeding and abdominal mass, are more specific than

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Implication for health policy/practice/research/medical education:
Colorectal cancer is one of the most common and leading causes of cancer death in Iran. In Iran, colorectal cancer tends to present at locally advanced stage with poor prognosis. Therefore, public health strategies, like screening programs, should be planned for early detection of this aggressive neoplasm.

individual symptoms for diagnosing colorectal cancer. Symptomatic presentation is usually a manifestation of locally advanced disease (8).

Surgical resection is the mainstay of therapy in locoregional and eligible metastatic colorectal cancer (9). Colectomy, low anterior excision, or abdominoperineal resection may be performed through laparoscopic or open surgery for the patients with colorectal cancer (10, 11).

Some reports have suggested a higher colorectal mortality in men than women (12). In addition, age, tumor grade and differentiation, mucinous subtype, geographic region, total lymph node harvested, and lymph node ratio were found as prognostic factors for overall survival in the patients with colorectal cancer (7, 10, 13). There are some concerns regarding the adequacy of lymph node staging as well as different patterns of clinical and pathological features and outcomes of Iranian patients with colorectal cancer compared to other parts of the world (13-17).

We aim to conduct a survey of colorectal cancer reports of Iran for detailing the clinical as well as pathological features and outcomes of these patients.

2. Evidence Acquisition

The articles published in PubMed, including Iranian population studies, without language and time restrictions were included in this survey. Only original clinical articles were included and non-clinical studies, including cellular, molecular, genetics, and animal studies, were excluded. Case reports, letters, reviews, clinical reports with less than 100 patients, and statistical and epidemiologic studies lacking clinical data were excluded.

All the clinical data regarding the patients' demographics, tumor characteristics, and survival rates were collected. In this review, all included studies were retrospective series, with relative similar follow-up and quality. Therefore, we performed summation of study results with simple weighting based on the sample sizes. The data were extracted from the eligible studies which included authors' names, year of publication, study period, geographical region, authors' institution, the number of patients, baseline characteristics, primary tumor site, preoperative stage of disease, histological type, tumor grade, and disease free and overall survival rates.

The following keywords were used in the article title or author's affiliation: "colorectal cancer" or "colorectal carcinoma," "colon cancer" or "colon carcinoma," "rectal cancer" or "rectal carcinoma," and "anal canal cancer" or "anal canal carcinoma,", and "Iran".

Then, two authors independently reviewed all the eligible studies and extracted the studies' characteristics. Duplicated articles were checked regarding the authors, study population, publication year, and the study period and those with similar study populations but different authors, institutions, or study periods were included.

3. Results

3.1. Literature Search and Study Selection

Our initial PubMed search found 178 studies reporting on Iranian colorectal cancer. Among these, the majority of the references (n=92) identified with non-clinical abstracts that were excluded. Genetic, molecular, and cell studies were found to be the most frequent researches investigating colorectal cancer in Iran. Additional excluded references were ineligible clinical studies (n=59). The reports with inadequate sample sizes (< 100 cases), reviews, colorectal polyps, screening, and diagnostic methods were the most frequent excluded articles in this category.

Ultimately, 27 articles were found eligible (11, 13, 15, 16, 18-40) (Figure 1). All those articles were published from 2004 to 2013. Overall, the study periods were between 1986 and 2012; however, about two-third of all the articles had been accomplished after 2000. All the studies, but two, included both colon and rectal as the primary sites. Tehran (70%) and Research Center for Gastroenterology and Liver Disease (30%) were the most common geographic region and research center where the articles were reported from.
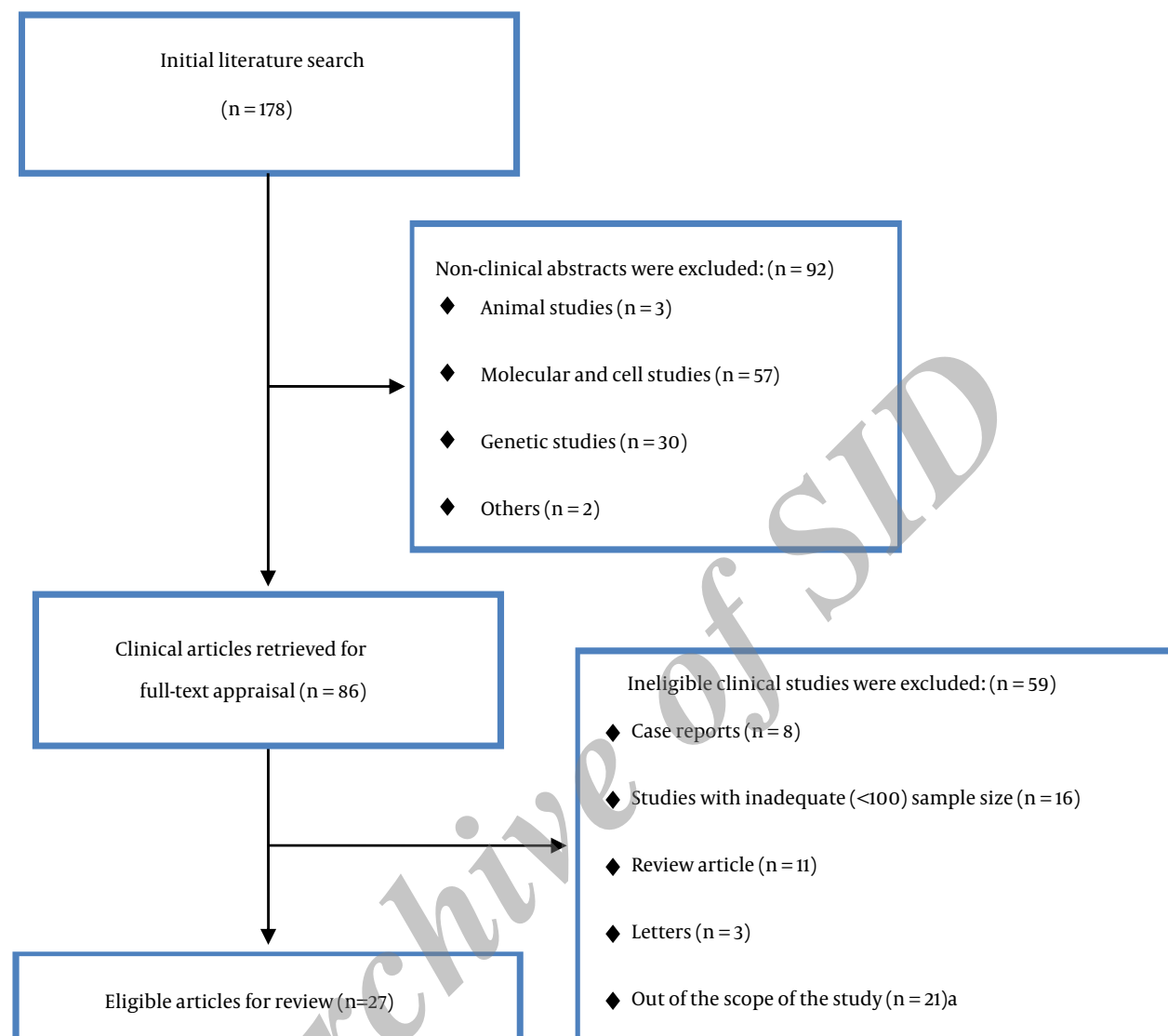
There was a significant population study overlap particularly among the reports from Tehran province. However, due to different authors, institutions, or study periods, these reports were included in the review (11, 13, 15, 16, 18-40) (Table 1).

3.2. Patients' Demographic Characteristics

The mean age of the patients was 57.2 years (ranging from 47.3 to 63 years) in 26 studies with age information. Besides, the mean age of the male patients was slightly higher than that of the female patients (59.1 years vs. 57.6 years). A wide age range of 4 to 103 years was observed; nonetheless, the peak frequency was observed between the sixth and seventh decades of life in both sexes. The mean proportion of males was 56% across 26 eligible studies, and the average male-female ratio was 1.38 (range 098-1.66) (Table 2).

3.3. Distribution of Primary Site

Out of the 27 eligible articles, distribution of the primary tumor site was partially or completely available in 17 studies, including 37716 patients. Colon, rectum, and rectosigmoid junction accounted for 58%, 28%, and 14% of all colorectal primary sites, respectively. By adding the rectosigmoid junction to rectal primary site, the mean proportion of the rectum as the primary site increased to 42%. Only 4 studies, including 7561 patients provided a detailed information regarding the sublocation of colon primary site as follows: Sigmoid colon 43%, ascending clon 21%, cecum 21%, descending colon 12%, and transverse colon 3% (11, 13, 15, 16, 18-29, 31-40).

Figure 1. Flow Chart of the Literature Search Strategy

Initial literature search

(n = 178)

Non-clinical abstracts were excluded: (n = 92)

♦ Animal studies (n = 3)

♦ Molecular and cell studies (n = 57)

♦ Genetic studies (n = 30)

♦ Others (n = 2)

Clinical articles retrieved for

full-text appraisal (n = 86)

Ineligible clinical studies were excluded: (n = 59)

♦ Case reports (n = 8)

♦ Studies with inadequate (<100) sample size (n = 16)

♦ Review article (n = 11)

♦ Letters (n = 3)

♦ Out of the scope of the study (n = 21)a

Eligible articles for review (n=27)

a, Screening and diagnostic methods and colorectal polyps were the most frequent in this category.

3.4. Distribution of Disease Stage

In this review, 10 out of the 27 eligible studies had information on the disease stage. However, detailed information was available only for 3728 patients (87%), and the 605 remaining patients (13%) had no staging data. Accordingly, by excluding the patients with unknown staging status, the mean proportion of the patients with stage 0-I was 9%. The mean values for stages II, III, and IV were 39%, 36%, and 16%, respectively (11, 13, 15, 19, 20, 24, 29, 31, 32, 37).

3.5. Tumor grade

Out of the 27 eligible articles, 12 studies, including 5733 patients had information on tumor grade. In these studies, 1229 patients had unknown tumor grade. Therefore, the distribution of tumor grade among the 4504 patients was as follows: grade 1, 52%; grade 2, 37%; and grade 3.11% (11, 13, 15, 19, 20, 22, 24, 26, 31, 32, 37, 39).

3.6. Distribution of Histological Types

Histological type was available in 6 eligible studies, including 3811 cases. Accordingly, adenocarcinoma was

the most frequent" has been cut and it should be continuedby its rest "histological type and accounted for 96.8% of all colorectal cancers followed by lymphoma (1.5%) and squamous cell carcinoma (0.4%). Carcinoid tumor, malignant melanoma, and sarcoma were the uncommon histological types in this region (13, 15, 20, 27, 34, 35).

3.7. Mean, median, and Overall Survival

A total of 11 out of the 27 studies included information on the mean, median, or overall survival rates. The mean overall survival period in 7 studies with 4780 patients was 80.1 months (range: 42.8-119.7). In addition, the median overall survival in 5 studies with 4746 patients was 55.2 months (range: 42-94.5). Besides, the average 1-, 2-, 3-, 4-, 5-, 10-, and 15-year overall survival rates were 85.9%, 74%, 64.9%, 55.3%, 52.5%, 47.9%, and 25.9%, respectively (11, 26, 29, 31-34, 36-39) (Table 3).

Table 1. Twenty-Seven Large Clinical Studies on Colorectal Cancer in Iran Published in PubMed (11, 13, 15, 16, 18-40) [a]

Authors	Year of publication	Study period	Number of patients	Primary tumor site	Geographical region (Province)	Authors' institution
Samareh Pahlavan (18)	2005	1996-2000	1628	colorectal	Multiple provinces[b]	Multicenter
Omranipour (19)	2012	1994-2009	442	colorectal	Tehran	Cancer Institute of Tehran
Mahmodlou (20)	2012	2001-2008	546	colorectal	West Azerbaijan	West Azerbaijan
Foroutan (21)	2008	1989–2004	977	colorectal	Tehran	SBMUH
Safaee (22)	2008	2000-2007	1138	colorectal	Tehran	RCGELD
Nikbakht (23)	2013	2001-2010	792	colorectal	Kerman	Research Center for Modeling
Ansari (16)	2006	1996-2000	2055	colorectal	Multiple provinces[c]	Multicenter
Forootan (24)	2012	2008-2012	200	colorectal	Tehran	Imam Hossein Hospital
Ghabeljoo (25)	2011	2002-2007	748	colorectal	Tehran	RCGELD
Aghili (15)	2010	1999-2005	130	colorectal	Tehran	IHSTHs
Safaee (26)	2010	2002-2008	110	colorectal	Tehran	RCGELD
Hosseini (27)	2004	1980–2000	328	colorectal	Shiraz	Colorectal Research Center
Safaee (28)	2012	2005-2009	19617	colorectal	INCR[c]	INCR
Aryaie (29)	2013	2004-2008	227	colorectal	Golestan	GRCGEH
Fatemi (30)	2010	Not mentioned	355	colorectal	Tehran	RCGELD
Asghari-Jafarabadi (31)	2009	2002-2007	1219	colorectal	Tehran	RCGELD
Moghimi-Dehkordi (32)	2008	2002-2007	1127	colorectal	Tehran	RCGELD
Mehrkhani (33)	2008	1999-2002	1090	colorectal	Tehran	Shariati Hospital
Moradi (34)	2009	2000-2005	2192	colorectal	INCR[d]	INCR
Samareh Pahlavan (35)	2006	2000-2003	200	colorectal	Tehran	Shohada General Hospital
Gohari (36)	2011	2002-2007	1007	colorectal	Tehran	RCGELD
Omidvari (11)	2013	2004-2010	153	Rectum	Shiraz	Colorectal Research Center
Jafari Nadoshan (37)	2013	Not mentioned	128	Rectum	Tehran	Cancer Institute of Tehran
Heidarnia (38)	2013	2005-2006	559	colorectal	Tehran	CRC of SBUMS
Fazeli (13)	2007	1995-2001	419	colorectal	Tehran	IKHCI
Haghighi (39)	2008	2003-2008	121	colorectal	Tehran	Taleghani hospital
Safaee (40)	2010	Not mentioned	393	colorectal	Tehran	RCGELD
Overall	2004-2013	1989-2012	37901	colorectal	Iran	-

[a] Abbreviations: CRC of SBUMS, cancer research center of Shahid Beheshti University of Medical Science; GRCGEH, Golestan Research Center of Gastroenterology and Hepatology; IHSTH, Imam Hussein and Shohadaye-Tajrish hospitals; IKHCI, Imam Khomeini Hospital and Cancer Institute; INCR, Iranian National Cancer registry; pts, patients; RCGELD, Research Center for Gastroenterology and Liver Disease; SBMUH, Shahid Beheshti Medical University hospitals.
[b] Including Mazandaran, Golestan, Ardabil, and Kerman.
[c] including Gilan, Mazandaran, Golestan.
[d] INCR, Ardabil, and Kerman.

Table 2. The Parents' Demographic Characteristics in 26 Large Clinical Studies on Colorectal Cancer in Iran Published in PubMed (11, 13, 15, 16, 18-29, 31-40) [a]

Authors	Number of patients	Number of Men	Male/Female ratio	Mean age	Male mean age	Female mean age	Minimum age	Maximum age
Samareh Pahlavan (18)	1628	935	1.35	57	-	-	-	-
Omranipour (19)	442	220	0.99	53	-	-	18	88
Mahmodlou (20)	546	306	1.28	55.2	-	-	-	-
Foroutan (21)	977	534	1.21	-	-	-	-	-
Safaee (22)	1138	696	1.57	54.1	54.3	53.9	-	-
Nikbakht (23)	792	413	1.09	59.4	-	-	18	93
Ansari (16)	2055	1129	1.22	57	-	-	-	-
Forootan (24)	200	115	1.35	57.1	-	-	-	-
Ghabeljoo (25)	748	-	-	53.9	-	-	-	-
Aghili (15)	130	73	1.28	49.7	-	-	-	-
Safaee (26)	110	69	1.68	50.1	-	-	-	-
Hosseini (27)	328	186	1.31	54.9	56.7	52.3	14	90
Safaee (28)	19617	10985	1.27	58.9	59.6	58.1	-	-
Aryaie (29)	227	138	1.55	54	-	-	14	85
Asghari-Jafarabadi (31)	1219	720	1.44	54	-	-	-	-
Moghimi-Dehkordi (32)	1127	690	1.58	53.6	-	-	14	94
Mehrkhani (33)	1090	741	2.12	50.5	-	-	-	-
Moradi (34)	2192	1235	1.29	57.8	-	-	4	103
Samareh Pahlavan (35)	200	114	1.33	55.1	55.7	54.3	13	90
Gohari (36)	1007	628	1.66	53.2	-	-	-	-
Omidvari (11)	153	89	1.39	57	-	-	23	84
Jafari Nadoshan (37)	128	67	1.09	49	-	-	16	85
Heidarnia (38)	559	299	1.15	63	-	-	23	88
Fazeli (13)	419	223	1.13	52.3	53.7	51.2	14	83
Haghighi (39)	121	60	0.98	47.3	-	-	22	78
Safaee (40)	393	231	1.42	53.5	-	-	-	-
Total	36798	20896	1.38 [b]	57.2	59.1	57.6	4	103

[a] Abbreviations: pts, patients.
[b] For this mean value, Ghabeljoo's study was excluded.

Table 3. The Mean, Median, and Overall Survival Rates of the Iranian Patients With Colorectal Cancer in 11 Large Clinical Studies Published in PubMed (11, 26, 29, 31-34, 36-39) [a]

Authors	Number of patients	Mean OS, mo	Median OS, mo	Overall Survival Rates, %						
				1-y	2-y	3-y	4-y	5-y	10-y	15-y
Safaee (26)	110	91.5	48.6	92.6	-	-	-	-	-	-
Aryaie (29)	227	43.4	42.8	71.8	-	80.1	-	41.3	-	-
Asghari-Jafarabadi (31)	1219	119.7	-	93.1	-	-	-	42.6	-	-
Moghimi-Dehkordi (32)	1127	105.1	94.5	91.1	86.2	78.5	72	67.4	-	-
Mehrkhani (33)	1090	42.8	44.3	72	-	73.1	-	61	47.9	25.9
Moradi (34)	2192	-	42	84.9	-	54	-	47	-	-
Gohari Mahmood (36)	1007	51.7	-	90.7	67.2	55.2	46.1	42.3	-	-
Omidvari (11)	153	-	-	-	-	71	-	46.7	-	-
Jafari Nadoshan (37)	128	-	-	89.8	-	-	-	69.4	-	-
Heidarnia (38)	559	-	-	-	-	-	-	26.5	-	-
Haghighi (39)	121	-	-	-	-	-	-	68.3	-	-
Total	7933	80.1	55.2	85.9	74	64.9	55.3	52.5	47.9	25.9

[a] Abbreviations: OS, Overall Survival.

4. Conclusions

In this research, we reviewed 27 eligible studies comprising 37901 patients to yield a summation of clinical and pathological characteristics and survival rates of colorectal cancer in Iran. In this study, the mean age of the patients was 57.2 years that showed at least a decade younger in comparison to the same patients in western countries. In Iran, the peak frequency was observed between the sixth and seventh decades of life in both sexes. In western countries, however, the peak frequency was observed between the seventh and eighth decades of life (41).

This difference may be due to the younger Iranian population or genetic factors (22, 42). In addition, in Iran, no significant difference was found between the rectal and colon primary sites regarding the patients' mean age (42). This is, on the contrary, to the western countries in which the age of the patients with rectal cancer was lower than that of colon cases (41). In a study using the Surveillance, Epidemiology, and End Results (SEER) database, the patients in all Asian-American subgroups who lived in the USA were younger at diagnosis compared to non-Hispanic white patients (median age: 68 vs. 72 years). In addition, the Asian-American subgroups had more advanced diseases and better disease free survival rates compared to non-Hispanic white patients (43).

In Iran, the male-female ratio in the patients with colorectal cancer showed slight male predominance, which is in contrast to the West in which there is no significant sex predilection. In West, colon cancer is slightly more common in female patients, while rectal cancer in slightly more common among males (41, 44). Previous reports indicated a higher portion of the rectal primary site in Iranian population compared to the West (20, 22, 34).

In this study, rectum and rectosigmoid junction accounted for 42% of all colorectal primary sites. This proportion was compatible with the data from European countries, but higher than the USA (37, 41, 45, 46). Figure 2 A-C illustrates the distribution of the primary tumor sites of colorectal cancer in Iran, Europe, and the USA (46).

Stage distribution of colorectal cancer in Iran is somewhat different from the West. In the USA, 25%, 32%, 24%, and 19% of the patients with colorectal cancer showed stages I, II, III, and IV, respectively. Table 4 compares the distribution of disease stage in Iran, Europe, and the USA (10, 46). In the current study, we found a lower proportion for stages, I and IV, but a higher proportion of stage III. The use of screening program in developed countries might have played an important role in detecting a higher percentage of stage I, and a lower percentage of stage III compared to our country (12, 47). In addition, the lack of optimal metastatic work-up, such as chest Computed Tomography (CT) scan and Integrated Positron Emission Tomography (PET-CT) scan, in our patients may be an important contribution to the lower proportion of stage IV in our reports.
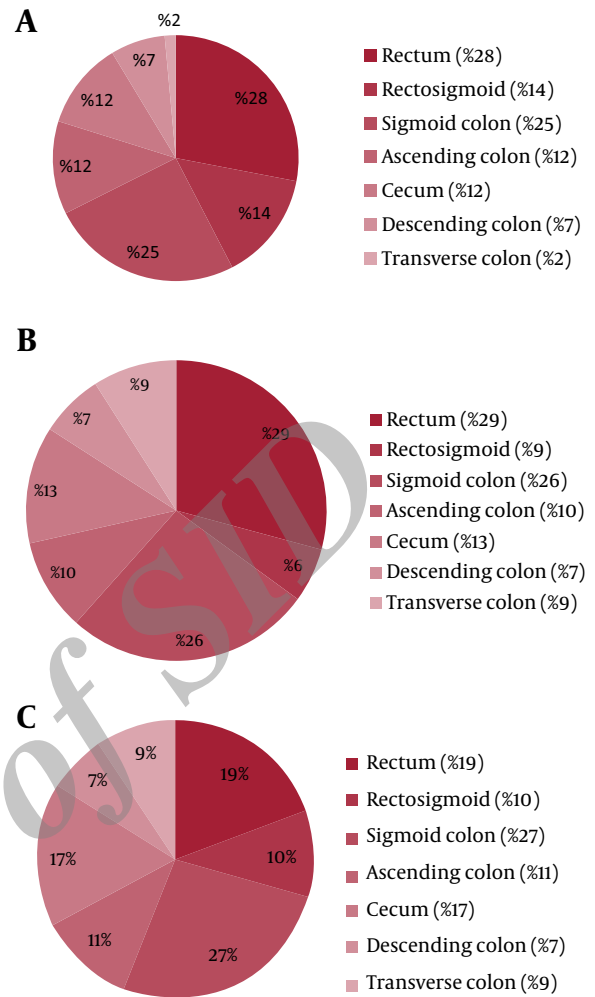

A
Rectum (%28)
Rectosigmoid (%14)
Sigmoid colon (%25)
Ascending colon (%12)
Cecum (%12)
Descending colon (%7)
Transverse colon (%2)

B
Rectum (%29)
Rectosigmoid (%9)
Sigmoid colon (%26)
Ascending colon (%10)
Cecum (%13)
Descending colon (%7)
Transverse colon (%9)

C
Rectum (%19)
Rectosigmoid (%10)
Sigmoid colon (%27)
Ascending colon (%11)
Cecum (%17)
Descending colon (%7)
Transverse colon (%9)

Figure 2. Distribution of the Primary Sites of Colorectal Cancer in Iran (A), Europe (B), and the U.S.A. (C)

Most colorectal cancers are well or moderately differentiated tumors. In one study, among the 146574 patients with colorectal cancer, 81% of cancers were well or moderately differentiated, and 19% were poorly differentiated (41). In the present study, 89% of all the tumors were well or moderately differentiated, and 11% were poorly differentiated that is compatible with the West. Adenocarcinoma consists of the vast majority of colorectal cancer worldwide (46). However, other histological types, such as squamous cell carcinoma and lymphomas, are uncommon (2, 34, 48). The histological types in this study were compatible to the literature. Accordingly, adenocarcinoma was the most frequent histological type followed by lymphoma and squamous cell carcinoma.

Colorectal cancer is an aggressive tumor with poor prognosis and decimal outcome particularly in advanced disease stage. In developing countries, 5-year overall survival rates for this neoplasm ranged from 28% to 42%, compared to more than 60% in developed countries, such as the USA, Japan, and Switzerland (5, 6, 49, 50). In this survey, the average 5-year survival of the Iranian patients-

Table 4. Distribution of the Stage of Colorectal Cancer in Iran, Europe, and the USA (10)

Authors	Number of patients	Stage				
		0-I, %	II, %	III, %	IV, %	Unstaged, %
Iran	3728	7	33	34	13	13
Europe	2492	14	34	21	21	10
USA	11191	24	30	23	18	5

-with colorectal cancer was 52.5% which was between the values obtained in European countries (43%) and the USA (62%) (5, 46). However, there are some concerns regarding the under reporting of colorectal cancer mortality in Iran. In a study, Pourhoseingholi et al. used a Bayesian approach to estimate the mortality rates in the patients with colorectal cancer and found a 30-40% underreported mortality records in colorectal cancer death (17). Therefore, healthcare policy revision for early detection of colorectal cancer, accurate staging, mortality recording, and registry is warranted.

In Iran, colorectal cancer tends to manifest at locally advanced stage with poor outcome. Therefore, public health strategies, such as screening programs, should be planned for early detection of this aggressive neoplasm. In addition, a well-designed population-based cancer registry with acceptable coverage is needed to improve cancer reporting in our country.

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Authors' Contribution

Sareh Hoseini: Involved in study design, literature review, data collection, writing and revising the manuscript, and approval of the final version. Leila Moadshoar: Involved in study conception and design, literature review, writing the manuscript and approval of the final version. Simin Hemati: Involved in study conception and design, literature review, writing the manuscript and approval of the final version. Mohammad Mohammadianpanah: Involved in study conception and design, data collection, literature review, writing and revising the manuscript, and approval of the final version.

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