Colonoscopy as Part of Pre-Transplant Work-Up in Successful Kidney Transplant Candidates: Single-Center Experience and Review of Literature

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Background: Screening colonoscopy is not obligatory in kidney pre-transplant work-up guidelines. According to recommendations, only transplant recipients over age 50 years should be screened. The aim of this study was to characterize endoscopic findings revealed as part of pre-transplant work-up.

Material/Methods: We retrospectively reviewed pre-transplant work-up charts of 434 adult patients who received a cadaveric donor kidney transplantation (KT) from 2012 to 2015. Endoscopic findings analysis with age subgroup (<50 and ≥50) analysis were performed.

Results: Out of 434 of patients that underwent KT, 29% have had a colonoscopy. In 75.6% of those, pathologies were found. Hemorrhoids were found in 33% and polyps in 30.7% of patients. Adenoma detection rate (ADR) was 18.1% (67.5% distal predominance). Advanced ADR was 10.2% (distal predominance). Diverticulosis was found in 28.3% of patients and ulcerative colitis was found in 2.4%. In age subgroup analysis, ADR was higher in patients ≥50 years compared to those <50 years (21.6% *vs.* 4%; p=0.041).

Conclusions: Colonoscopy as part of pre-transplant work-up enables removal of precancerous lesions and management of benign findings. All candidates meeting criteria for the general population should be screened. Patients under age 50 years could also benefit from colonoscopy as part of the pre-transplant work-up. Therefore, we suggest that baseline colonoscopy should be included in pre-transplant work-up guidelines for all patients, regardless of age. However, further studies are needed to confirm this recommendation.

MeSH Keywords: Colonoscopy • Colorectal Neoplasms • Early Detection of Cancer • Kidney Transplantation • Primary Prevention

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Background

The prevalence of end-stage renal disease (ESRD) is increasing worldwide [1,2]. Kidney transplantation has become a preferred treatment option in patients with ESRD [3–5]. A successful kidney transplant is associated with lower mortality, as well as with improved quality of life compared to either type of dialysis [3,4,6,7]. Moreover, the benefits of transplantation increase over time after the surgery [8], which might be related to better management of associated diseases. However, kidney transplantation is associated with several possible adverse effects, including increased risk of cancers [9–13]. ESRD itself may be associated with increased risk of cancer development [14–17]. Immunosuppression impairs cancer surveillance mechanisms of the body, leading to a higher risk of *de novo* malignancy as well as blastic transformation of precancerous or benign lesions. A 2–3-fold increase in colorectal cancer (CRC) incidence compared to the general population has been reported [18]. Moreover, CRC in immunosuppressed patients develops at a younger age and has a worse 5-year prognosis in comparison to the general population [19,20]. CRC is the third most prevalent type of cancer and the third most frequent cause of death among patients diagnosed with malignancy in the United States [21]. In 2013, CRC was the second most common cancer in women and the third in men, constituting 10% and 12.2% of cancer diagnoses, respectively. In Poland, it is the third most common cancer-related deaths in women and the second in men [22]. Screening colonoscopy is not obligatory in the pre-transplant work-up guidelines [23–25]. Potential transplant recipients should be screened for cancer during pre-transplant evaluation according to clinical practice guidelines developed for the general population [25]. The recommend CRC screening starts at the age of 50 years [26,27]. However, this standard regimen of screening has been questioned, as over 25% of transplant patients at risk would not be included and might develop CRC [28]. Screening colonoscopy in this particular population of patients can potentially offer benefits exceeding those in the general population. Detection of benign conditions that can be exacerbated after transplantation might also be of value.

The aim of the study was to characterize endoscopic findings of colonoscopies performed as part of the pre-transplant work-up before kidney transplantation.

Material and methods

Subjects

In this study, we retrospectively reviewed pre-transplant work-up charts of 434 adult patients who received a cadaveric donor kidney transplantation in the Department of General, Endocrine, and Transplant Surgery of the Medical University of Gdansk, Poland, from January 1, 2012 to December 31, 2015. Patients with complete colonoscopy as part of their pre-transplant work-up were identified for further analysis in the study.

Methods

We reviewed pre-transplant work-up charts of patients, in search of colonoscopy examination reports. We collected patients' basic clinical characteristics, including the type of kidney disease leading to ESRD. We analyzed the prevalence and type of pathologies found in pre-transplant colonoscopy. Advanced adenomas were defined as lesions ≥10 mm or with a villous component in pathology or with high-grade dysplasia (HGD). Proximal adenomas were considered for locations proximal to the splenic flexure of the colon. The cut-off point for age-based subgroup analysis was set at 50 years, according to current general population CRC screening guidelines [26,27]. The adenoma detection rate (ADR) was defined as the percentage of patients in whom 1 or more conventional adenomas were detected.

Statistical analysis

For age subgroup analyses, the chi-squared test was used, with statistical significance set as $p < 0.05$.

Results

From the total of 434 patients who underwent kidney transplantation in the studied period in our institution, 127 patients (29%) had a colonoscopy performed within the pre-transplant work-up. The pre-transplant colonoscopy examination was performed within an average of 416 (range 18–1702) days before transplant surgery. Clinical characteristics of the study group are presented in Table 1.

Pre-transplant colonoscopy results

Of the 127 patients in whom colonoscopy was performed in the pre-transplant work-up, pathologies were found in 96 patients (75.6%). In 17 patients, colonoscopy was repeated in the pre-transplant period. The frequencies of individual pathologies are summarized in Table 2.

The most common pathologies found in baseline colonoscopy were hemorrhoids and polyps (33% and 30.7% of patients, respectively). Adenomas were diagnosed in 23 patients, which constitutes an ADR of 18.1%. The advanced adenoma detection rate was 10.2%. In 36 (28.3%) patients, diverticular disease was found. Ulcerative colitis was found in 3 patients (2.4%). Other pathologies found included non-ulcerative colitis in 2 cases

Table 1. Clinical characteristic of study group of 127 patients.

	N	
Male	97	(76.4%)
Age average in years (range)	57	(29.72)
BMI average in kg/m^2 (range)	26	(18.34)
Kidney disease		
Glomerulonephritis	28	(22%)
Chronic Interstitial nephritis	4	(3.1%)
ADPKD	22	(17.3%)
Diabetic nephropathy	19	(15%)
Hypertensive nephropathy	15	(11.8%)
Reason unknown or not well investigated	20	(15.7%)
Other	13	(10.2%)
No data	6	(4.7%)
Comorbidities		
Arterial hypertension	99	(77.9%)
Diabetes Mellitus	32	(25.1%)
Cardiovascular	45	(35.4%)
Thyroid diseases	19	(15%)
Respiratory tract	17	(13.4%)
Skeletal	17	(13.4%)
Gastrointestinal*	56	(44,1%)

* Most common gastrointestinal diseases identified in medical history of the patients: duodenal and peptic ulcer disease, Crohn disease, chronic gastritis, diverticular disease, esophagitis, gastroesophageal reflux disease.

and 1 case of each of the following: colonic melanosis, colonic erosions, lipoma, and telangiectasia.

Age-based subgroup analysis

A clear majority (102, 80.3%) of the baseline colonoscopies was performed in patients 50 years of age or older and 25 colonoscopies were performed in patients younger than 50 years of age. This is 43.97% and 12.38% of patients in respective age groups. No pathologies were found in 23.5% and 32% of the patients, respectively (chi-squared p=0.382). Hemorrhoids were found in 30.4% and 44% of patients, respectively (chi-squared p=0.195). Colonic diverticula were found in 30.4% of the ≥50 years of age subgroup and 20% in the <50 years of age subgroup (chi-squared p=0.301). Polyps were found in 34.3% and 16% of patients in respective subgroups (chi-squared

Table 2. Endoscopic findings in colonoscopies within the pre-transplant work-up.

	Baseline colonoscopy n=127		Repeated colonoscopy n= 17	
No pathology	31	(24.4%)	4	(23.5%)
Hemorrhoids	42	(33%)	4	(23.5%)
Diverticular disease	36	(28.3%)	4	(23.5%)
Polyps	39	(30.7%)	8	(47.1%)
Adenomas	23	(18.1%)	3	(17.6%)
Ulcerative colitis	3	(2.4%)	0	
Other	6	(4.7%)	0	

p=0.075). One adenoma (advanced; size criteria) was found in the proximal colon in the <50 years subgroup, constituting an ADR of 4.0%, and in the older group the ADR was 21.6% (chi-squared p=0.041). Advanced adenomas were found in 1 case in the <50 group (4.0%) and in 12 cases in the ≥50 group (11.8%) (chi-squared p=0.251).

Repeated colonoscopy results

In 17 out of 127 patients (13.4%), colonoscopy was repeated in the pre-transplant period. The average interval between baseline and follow-up colonoscopy was 376 days (range 34–820 days). Indication for repeated examination was post-polypectomy surveillance in 3 cases and ulcerative colitis surveillance in 1 case. The remaining 13 (76.5%) studies were performed as a scheduled update in the transplant registry. In 4 transplant candidates, no pathologies were found on colonoscopy. Eight patients had polyps found, whereas hemorrhoids and diverticular disease were found in 4 cases. The ADR for the repeated colonoscopy was 17.6% (3 patients out of 17). Four out of the total of 8 polyps removed were advanced adenomas.

Histopathology of the polyps

Polyps were found in 39 patients during baseline colonoscopy, of which histopathology specimens were obtained in 38 cases. Adenomas were diagnosed in 23 patients (ADR=18.1%). A total of 40 adenomas were removed in 23 patients: 32.5% were proximally located lesions whereas 67.5% were localized distally to the splenic flexure. The detection rate for advanced adenomas was 10.2%, with the majority of lesions found in the distal colon. Size ≥10 mm was the predominant definition characteristic of advanced adenomas. Detailed characteristics of adenomas detected on baseline colonoscopy are summarized in Table 3.

Table 3. Adenomas detected during baseline colonoscopy.

	Total	Proximal	Distal
Adenoma	40	13 (32.5%)	27 (67.5%)
Advanced adenoma	16	2 (12.5%)	14 (87.5%)
HGD (high grade dysplasia)	5	0	5
Tubulovillous pathology*	6	0	6
Size ≥10 mm	13	2	11

* No pure villous pathology was found.

Colorectal cancer in kidney transplant patients

We searched the institutional cancer registry for CRC diagnoses in the studied group of transplanted patients and found that colorectal cancer was detected in none of them. CRC incidence in renal transplant recipients from our center and another representative transplant center in Katowice, Poland, was previously reported. In a cohort of 3069 patients engrafted between 1995 and 2015, there were 16 cases of CRC, which constituted 14.3% of solid organ malignancies. CRC was diagnosed at an average age of 57.8±10.4 years, being an average of 74.3±56.4 (range 7–195) months after transplantation [unpublished data].

Discussion

In this study, we reviewed endoscopic findings of colonoscopies performed within the pre-transplant work-up of successful kidney transplant candidates. Colonoscopy was performed in 29% of the patients, although 80.3% were eligible for a screening colonoscopy recommendation meeting the age ≥50 years criterion. Therefore, a significant percentage of patients at risk were not examined. Several studies have found that after kidney transplantation, patients are at increased risk of malignancy development [12,29–32]. Cancer is responsible for 9–12% of deaths in post-transplant patients [33]. It becomes the most common cause of death after the first year following transplantation [34]. The mean time from transplantation and any cancer occurrence was 9.4 years [30]. It was found that cancers diagnosed in transplanted patients are more aggressive and responsiveness to therapy is poor [35]. This leads to a worse survival rate in this group of patients. Some studies suggest that effective screening and management of precancerous lesions could reduce the risk of post-transplant malignancy [36–38]. Several studies reported that ESRD was an independent risk factor of cancer, especially in elderly patients [39–41]. The ESRD population often has other known risk factors for colorectal cancer, such as diabetes. Arterial hypertension and both types of diabetes and were the most frequent comorbidities in our ESRD group, which is to be expected, given that they are the 2 most common causes of

ESRD [42–45]. Diabetes has been previously shown to be an independent risk factor for colorectal cancer [46,47].

No pathologies were found in only 24.4% of the examinations. We found an overall adenoma detection rate of 18.1% of the patients who underwent endoscopy within the pre-transplant work-up. These results correspond to results in the literature for the general population, as well as the ESRD population [36,48–50]. The studied population of patients with ESRD is a subgroup that actually received a kidney graft. The reported endoscopic examinations are therefore a baseline for these patients as transplanted patients.

For this specific group of patients, there are still no recommendations for colonoscopy screening or endoscopic surveillance, and there is no general consensus on screening colonoscopy recommendations in the ESRD patients group. That these patients require post-transplant endoscopic surveillance was previously reported by our team and other authors [36,38,51,52]. The intervals of endoscopic surveillance should depend on the result of the baseline pre-transplant colonoscopy, as it is recommended in the general population.

In the general population, CRC screening begins at age 50, with colonoscopy every 10 years [53]. Other recommendations include annual fecal occult blood test and sigmoidoscopy every 5 years [53]. Although screening colonoscopy was proven to reduce incidence and mortality from CRC in the general population, this effect was never demonstrated in the group of ESRD patients.

Baseline colonoscopy in kidney transplant candidates offers several benefits exceeding screening in the general population. In the general population, it enables removal of precancerous lesions or early cancers and sets the surveillance scheme. In kidney transplant candidates, it might also influence the decision about qualification for kidney transplantation. CRC is an absolute contraindication for transplantation, unless the criteria of radical treatment and appropriate waiting time without cancer recurrence are met. Pre-transplant colonoscopy may prevent disastrous decisions in the qualification of

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transplant candidates with asymptomatic CRC. Further, it defines pre-existing benign conditions that could potentially become symptomatic after transplantation. Early detection of adenomas may reduce morbidity in the post-transplant period. Our baseline colonoscopy detection rate for advanced adenomas was 10.2%, which is almost twice the rate observed in screening of the general population ≥50 years (5.9%) and 3 times the rate for <50 years (3.4%) [54]. Proximally located lesions were found in 32.5% of patients, whereas distally located lesions were found in 67.5% of patients. Several other studies have shown similar results [37,55,56]. The prevalence of proximal lesions supports the need for total colonoscopy in the pre-transplant work-up. This is additionally supported by the reports on significant increase of proximal colorectal cancers, but not distal colon and rectum cancers, after kidney transplantation [37]. This favors the role of full colonoscopy screening as opposed to sigmoidoscopy.

In our cohort in patients 50 years or older, ADR was 21.6% as compared to 4% in the younger group. The advanced adenoma detection rate was 11.8% in the ≥50 years group and 4% in the <50 years group. This might suggest that screening recommendations for ESRD patients should follow those for the general population with the exception of age limits. Recommending screening colonoscopy could also be beneficial in a subgroup of patients under 50 years of age. Patient age, as well as size and histology of the polyp, are important factors in adenoma carcinogenesis [33]. The length of time needed for transformation of an adenoma into a carcinoma varies from 3.6 to 9.5 years in the general population [57], but this is not known for the ESRD population.

Hemorrhoids were detected in 33% of patients and diverticula were found in 28.3%. Considering these are the of most common benign sources of lower GI bleeding, pre-transplant diagnosis and possible management are of interest. Diverticulosis is a common intestinal pathology found in dialyzed patients [58,59]. In immunosuppressed patients, diverticulitis is a potentially life-threatening condition. Interestingly, diverticulitis is the most common cause of colon perforation in renal transplant recipients [60] and the mortality rate is reported to be 17–43% [59–61]. Spontaneous colon perforation after kidney transplantation was described in the course of non-occlusive bowel ischemia, and in most cases it was localized in the sigmoid colon [62]. In our study group, 28.2% of all patients and 50% of patients with autosomal dominant polycystic kidney disease (ADPKD) had colon diverticulosis detected during baseline colonoscopy. In the literature, there is a reported correlation between diverticulosis and colonic perforation in patients with ADPKD [63–65].

Hemorrhoids are found in 4.4–36% of patients in the general population [66,67]. The incidence rate in post-transplant

patients is unknown. In our cohort, hemorrhoids were found in colonoscopy reports of one-third of the patients. Immunosuppressive therapy may play an important role in exacerbation of hemorrhoidal disease in kidney transplant recipients. Although colonoscopy is not a standard diagnostic tool for the detection and evaluation of hemorrhoids, a prompt diagnosis while undergoing baseline colonoscopy, as well as proper management in the pre-transplant period, is of value in preventing proctology emergencies after kidney transplantation.

Our rate of 2.3% of endoscopic features of ulcerative colitis is lower than reported by Schnitzler et al. (4.74%) [68]. However, there were some patients with non-ulcerative colitis detected in baseline colonoscopy. It was found that the incidence of ulcerative colitis after transplantation is higher than in the general population. Moreover, ulcerative colitis in patients after organ transplantation is associated with higher morbidity and management difficulties due to possible interaction between immunosuppressive therapy and IBD therapy [68,69]. About 30% of patients with previously diagnosed ulcerative colitis develop recurrence after transplantation and are at higher risk of colectomy [68,70].

The strength of our study is that it is a broad review of endoscopic findings in kidney pre-transplant patients. It is not limited (as in previous reports) to polyps, adenomas, or advanced adenomas. The results of analysis of age subgroups suggests screening colonoscopy would also be beneficial for patients under the age of 50, as one of the patients (4%) had advanced adenomas removed (the group of patients at high risk of CRC). All the adenomas removed in this group of patients were advanced.

The limitations of the study are the retrospective design of this study and potential incompleteness of the transplant registries. Additionally, it has to be considered that the patients might have already had clearance colonoscopies before, and the ADR for the studied population might thus be underestimated. In addition, colonoscopies were performed in 29% of candidates (43.97% of candidates ≥50 years of age and 12.38% of candidates under age 50). It is therefore possible that colonoscopy findings in this selected group might not be entirely representative of all kidney transplant candidates. Despite a relatively large study group, subset analyses might be underpowered for conclusive evaluation.

Conclusions

Colonoscopy as part of the pre-transplant work-up in successful kidney transplant candidates enables not only detection and removal of precancerous lesions, but also detects other benign conditions, enabling pre-transplant management. All

candidates meeting the criteria for the general population screening recommendations should be screened. Patients under the age of 50 years who are not included in the general population screening programs could also benefit from colonoscopy as part of the pre-transplant work-up. Therefore, we suggest that baseline colonoscopy should be included in pre-transplant work-up guidelines for all patients, regardless of age. However, further studies are needed to confirm this recommendation.

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Conflict of interest

None.

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