Use of population-based electronic databases for the identification of patients with synchronous colorectal cancer and liver metastases potentially eligible for a surgical trial

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Background: Some population-based recruitment methods, such as registries and databases, have been used to increase enrolment in clinical trials by identifying eligible participants based on baseline characteristics; however; these methods have not been tested in surgical trials, in which accrual occurs before surgery. We evaluated the use of population-based electronic databases to identify patients who potentially could be accrued to the Simultaneous Resection of Colorectal Cancer with Synchronous Liver Metastases (RESECT) trial and compared it to the traditional methods used to accrue patients (e.g., multidisciplinary rounds, letters to community surgeons) for that same trial during the same period.

Methods: An electronic database (ePath) was interrogated every 2 weeks for patients diagnosed with colorectal cancer from Feb. 1, 2017, to Mar. 30, 2019. A radiologic image database (OneView) was reviewed to identify those with liver metastases (level 1 screening). Reports were interrogated to identify potentially eligible patients for the RESECT trial (level 2 screening). A hepatobiliary surgeon reviewed radiology images to identify eligible patients for the trial (level 3 screening). The primary outcome was patient eligibility for the ongoing RESECT trial.

Results: The population-based method identified 90 (11.2%) of 803 patients diagnosed with colorectal cancer over the study period. Among the 90 patients, level 2 screening identified 60 (67%) potentially eligible patients for the RESECT trial. Of the 90 patients, 18 (20%) were eligible after radiographic image review (level 3 screening). Traditional accrual methods identified 38 patients with liver metastases, 27 (71%) of whom were identified as potentially eligible on level 2 screening, and 14 (37%) of whom were deemed to be eligible on level 3 screening. Twenty-six patients were identified by both methods. Twelve patients were identified by population-based methods alone, and 8 patients by traditional methods alone. Six eligible patients were identified by both methods. Baseline characteristics were similar between the 2 groups.

Conclusion: A population-based electronic database method of patient accrual was able to identify eligible participants for the RESECT trial. However, optimal accrual likely requires the use of traditional methods as well.

Contexte : Certaines méthodes de recrutement populationnelles, comme l'utilisation de registres et de bases de données, ont permis d'augmenter le nombre d'inscriptions aux essais cliniques en recensant des participants admissibles en fonction de certaines caractéristiques de base. Ces méthodes n'ont toutefois pas été éprouvées pour des essais chirurgicaux, pour lesquels l'inscription se produit avant la chirurgie. Nous avons évalué l'utilisation de bases de données électroniques populationnelles pour identifier des patients qui pourraient être admissibles à l'essai de résection simultanée du cancer colorectal avec métastases hépatiques synchrones (RESECT) et nous avons comparé cette approche aux méthodes conventionnelles utilisées pour recruter les patients (p. ex., tournées multidisciplinaires, lettres aux chirurgiens du milieu communautaire), pour le même essai et au cours de la même période.

Méthodes : Du 1er février 2017 au 30 mars 2019, une base de données électronique (ePath) a été interrogée toutes les 2 semaines pour repérer les patients avec un diagnostic de cancer colorectal. Une base de données d'images radiologiques (OneView) a ensuite été analysée pour repérer ceux atteints de métastases hépatiques (sélection de niveau 1). Des rapports ont été consultés pour identifier les patients potentiellement admissibles à l'essai RESECT (sélection de niveau 2). Un chirurgien hépatobiliaire a

examiné les images de radiologie pour déterminer l'admissibilité des patients à l'essai (sélection de niveau 3). L'issue primaire était l'admissibilité des patients à l'essai RESECT en cours.

Résultats : Avec la méthode populationnelle, 90 patients (11,2 %) ont été repérés dans un bassin de 803 patients ayant reçu un diagnostic de cancer colorectal pendant la période de l'étude. Parmi ceux-ci, 60 patients (67 %) potentiellement admissibles à l'essai RESECT ont été identifiés par la sélection de niveau 2. Des 90 patients initiaux, 18 (20 %) étaient admissibles après l'examen des images radiographiques (sélection de niveau 3). Les méthodes de recrutement conventionnelles ont identifié 38 patients atteints de métastases hépatiques, parmi lesquels 27 patients (71 %) ont été identifiés comme étant potentiellement admissibles par la sélection de niveau 2. L'admissibilité de 14 patients (37 %) a été déterminée par la sélection de niveau 3. Au total, 26 patients ont été identifiés par les 2 méthodes : 12 par les méthodes populationnelles seulement, 8 par les méthodes conventionnelles seulement, et 6 par les 2 méthodes. Les caractéristiques de base étaient semblables parmi les 2 groupes.

Conclusion : Une méthode de recrutement des patients utilisant une base de données électronique populationnelle a été en mesure d'identifier les participants admissibles à un essai RESECT. Cependant, l'utilisation de méthodes conventionnelles est également nécessaire pour un recrutement optimal.

About half of surgical clinical trials fail to reach their target sample size.[1] A low recruitment rate is a major barrier to the completion of clinical trials. Owing to a variety of reasons (e.g., patients are in a rush to be treated, leaving little time to explore clinical trials), this recruitment issue is more evident in surgical trials for patients with cancer.[2] Although 70% of patients report an inclination to participate in clinical trials, less than 5% of patients being treated at cancer centres across North America are enrolled in a clinical trial each year.[3,4] Poor accrual is the main factor associated with early trial termination in up to 30% of clinical trials in cancer.[5–7] Traditional accrual to cancer surgery trials requires receipt of a patient referral by involved clinicians (e.g., surgeons), recognizing that a specific patient is trial eligible and approaching the patient for enrolment.

Alternative methods to recruit patients to clinical trials in cancer might decrease early trial termination, expediting trial completion.[8,9] Some population-based recruitment methods, such as registries and databases, have been used to increase enrolment in clinical trials by identifying eligible participants based on baseline characteristics.[10,11] These electronic registries are updated prospectively in real time and, as such, are feasible to use for enrolment purposes, requiring few additional resources from the research team as the database is already being used for other reasons. This approach also avoids relying exclusively on regional surgeons, oncologists or gastroenterologists to refer patients for clinical trial purposes, which is known to be an ineffective way to accrue patients (i.e., rate of enrolment of only 10%–20% of eligible patients).[12,13] Furthermore, population-based methods are attractive because of the availability of a large pool of potentially eligible candidates, especially for multicentre studies and those involving patients with rare diseases. These methods, however, have

not been tested in surgical trials, in which accrual occurs before surgery and, therefore, eligible patients must be identified within a limited amount of time, an issue that is even more relevant for patients with a diagnosis of cancer.

Surgery for patients with synchronous colorectal cancer and liver metastases can be performed via the traditional staged resection, whereby patients usually undergo primary tumour resection, followed weeks later by liver resection. Alternatively, patients may undergo the more recent simultaneous resection, involving a single operation to resect both sites (i.e., primary colorectal cancer and liver metastases[14,15]; however, this approach has not been fully researched. Our group designed a multi-institutional single-arm surgical trial, the Simultaneous Resection of Colorectal Cancer with Synchronous Liver Metastases (RESECT) trial,[16] to evaluate the feasibility of a larger randomized trial evaluating the efficacy of simultaneous resection of the primary tumour and liver among patients who present with resectable colorectal cancer with synchronous liver metastases. In the present study, we evaluated the use of population-based electronic databases to identify patients who potentially could be accrued to the RESECT trial and compared it to the traditional methods used to accrue patients for that same trial during the same period.[17]

METHODS

Study design and setting

The Hamilton Niagara Haldimand Brant Local Health Integration Network (LHIN; now Home and Community Care Support Services) (population 1.4 million) is 1 of 14 health administrative regions in the province of Ontario, Canada.[18] All hospital and clinic pathology reports related to cancer from each health administrative

region across Ontario are collected and codified in real time (i.e., as soon as the report is available in the patient's institution's medical record) to the ePath electronic pathology database at Cancer Care Ontario, the agency overseeing the quality of cancer services in Ontario.

The Hamilton Niagara Haldimand Brant LHIN contains 11 hospitals along with about 50 surgeons who provide surgical care to patients with colorectal cancer.[19] All major liver surgery is performed at a single teaching site by 1 of 5 hepatobiliary surgeons. The RESECT trial recruited patients in Ontario from Feb. 1, 2017, to Nov. 30, 2019. The trial included 3 sites where surgery could be performed, 2 outside the Hamilton Niagara Haldimand Brant LHIN and 1 within the LHIN (Juravinski Hospital, Hamilton). The Juravinski Hospital is the only hospital within the Hamilton Niagara Haldimand Brant LHIN where major liver resection procedures are performed. We evaluated 2 methods to identify patients in the LHIN eligible for the RESECT trial over the truncated interval of Feb. 1, 2017, to Mar. 30, 2019: population-based accrual and traditional methods of accrual. Patients were accrued to the trial by means of traditional methods only. The institutional research ethics board approved this study.

Study population and accrual groups

Population-based electronic database accrual
A research assistant prospectively reviewed ePath every 2 weeks to identify patients diagnosed with colorectal cancer by endoscopic or percutaneous biopsy (about 20 new patients every 2 wk). Eligible histologic diagnoses included adenocarcinoma (including signet ring cell carcinoma), adenosquamous carcinoma, carcinosarcomas and mixed adenocarcinoma–neuroendocrine tumour (adenocarcinoma with neuroendocrine differentiation). The research assistant screened imaging reports in OneView (Hewlett Packard Enterprise) (an electronic repository of radiology reports and imaging [e.g., computed tomography (CT) and magnetic resonance imaging (MRI) scans] done at each Hamilton Niagara Haldimand Brant LHIN hospital) to identify patients with liver metastases (level 1 screening). This process took no more than 1 hour every 2 weeks.

Another research assistant then identified patients from the population identified in level 1 screening who were potentially eligible for the RESECT trial (level 2 screening; about 5 patients every 2 wk). This consisted of excluding pregnant patients, those with extrahepatic metastatic disease (other than lung) and those whose primary tumour had already been resected (before the biopsy was performed or after initial imaging because of bleeding or obstruction). Excluded patients were reviewed by a different research assistant to confirm that they met the exclusion criteria. We did not calculate a correlation κ value for this level, as the other research assistant reviewed only patients who were excluded. Agreement at

this level was obtained by consensus. Level 2 screening took no more than 30 minutes every 2 weeks.

In level 3 screening, a hepatobiliary surgeon reviewed OneView images in detail to identify patients eligible for the RESECT trial (2 patients per month). The surgeon excluded patients in whom assessment of the imaging scans indicated unresectable disease in the liver, the need for resection of more than 1 additional pelvic (other than rectum) or abdominal (other than liver) organ, and the presence of more than 3 metastatic deposits in the lung. Patients requiring 2-stage liver resection (owing to insufficient future liver remnant) were also excluded. The determination of resectability was a conservative measure; only patients with clearly resectable disease were considered eligible for the RESECT trial. Patients who would require neoadjuvant chemotherapy for downsizing were not considered eligible. Level 3 screening was done within 4 weeks of identification of the patient in ePath to allow for time to pass between the first biopsy and the first CT scan.

Traditional methods of accrual
The RESECT trial was advertised to surgeons, medical oncologists and radiation oncologists at weekly cancer centre multidisciplinary rounds, by hanging posters in surgeons' and oncologists' clinics, at national or regional surgical rounds, and via letters, emails and faxes to community surgeons, medical oncologists and radiation oncologists that explained the study and asked for prompt referral to the regional cancer centre when a potentially eligible patient was identified.

The population of patients with colon cancer and liver metastases was identified by screening all new patients referred to the surgical clinics at the Juravinski Hospital (5 hepatobiliary surgeons and 4 colorectal surgeons) and selecting those with a new diagnosis of colorectal cancer. Imaging reports of these patients were then reviewed to identify those with liver metastases (level 1 screening). A research assistant then identified potentially eligible patients for the RESECT trial by applying the inclusion and exclusion criteria of the trial (level 2 screening). The cases of potentially eligible patients were then reviewed by a hepatobiliary surgeon (P.S.) (level 3 screening) to confirm eligibility; this included a detailed review of the surgical aspects of the case (e.g., need for 2-stage liver resection, need for additional organ resection, presence of < 3 metastatic deposits in the lung).

Data collection and variables

Variables collected from ePath included patient demographic characteristics (age, sex and institution where the biopsy took place), histologic findings and location of the primary colorectal tumour. Variables collected from OneView included type of imaging performed (CT or MRI), location within the liver (laterality), number and size

of liver metastases, type of liver resection required (minor or major[20]), type of colorectal resection required (i.e., need for additional organ resection other than the location of the primary tumour), presence of 3 or fewer lung metastases and presence of extrahepatic metastases other than lung. The same variables were collected for patients identified by means of traditional methods; however, they were extracted from the hospital's medical record system.

Primary outcome

The primary outcome of this study was patient eligibility for the ongoing RESECT trial.[16] For the 2 accrual methods, we calculated the proportion of patients identified by dividing the number of patients identified by 1 method by the total number of patients identified by both methods, without overlap. We calculated the population identification ratio for eligible patients by dividing the number of patients identified prospectively by means of population-based methods alone by the number of patients identified through traditional methods alone.

Statistical analysis

We reported patient demographic characteristics as absolute counts and proportions, or median and range when

appropriate. For eligible patients, a population identification ratio of 1.3 or greater was considered to be clinically significant before the initiation of the RESECT trial (arbitrary measurement). We conducted all analyses using R (R Foundation for Statistical Computing, version 3.5.0).[21]

RESULTS

Accrual groups

Population-based electronic database accrual
The ePath search identified 803 patients diagnosed with colorectal cancer from Feb. 1, 2017, to Mar. 30, 2019, of whom 90 (11.2%) had primary colorectal cancer with imaging on OneView suggestive of liver metastases (level 1 screening) (Figure 1). Body imaging was performed a median of 15 (range 5–37) days from the biopsy date. Of the 90 patients, 60 (67%) were classified as potentially eligible for the RESECT trial on review of the OneView radiologic reports on level 2 screening. On level 3 screening, 42 patients were excluded, leaving 18 patients (20%) eligible for the RESECT trial. Most patients were excluded because of the presence of more than 3 metastatic deposits in the lung (16 patients) or unresectable hepatic lesions (10 patients) (Table 1). Of the 18 eligible patients, 4 were found to have undergone colorectal resection within
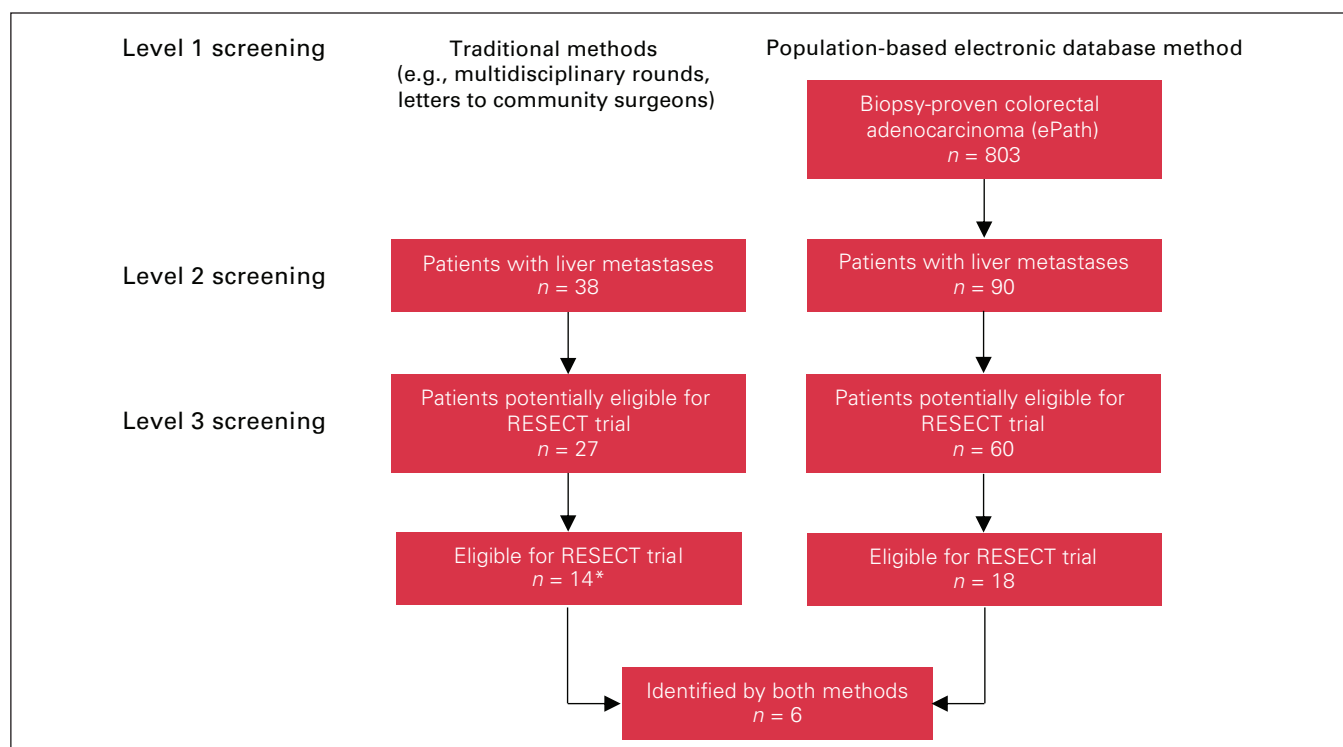

Fig. 1. Results of population-based electronic database method versus traditional methods of identifying and screening eligible patients for the Simultaneous Resection of Colorectal Cancer with Synchronous Liver Metastases (RESECT) trial. *Eight patients were not found by the population-based method: 1 was missed, 2 were diagnosed outside the Hamilton Niagara Haldimand Brant Local Health Integration Network, 2 had biopsy findings that showed high-grade dysplasia, not invasive carcinoma, and 3 had biopsy of the colorectal tumour outside the study period.

Table 1. Reasons for excluding potential RESECT trial participants identified via population-based electronic database and traditional methods of accrual

Reason	Population-based methods alone $n = 51$	Both methods $n = 9$	Traditional methods alone $n = 18$
Unresectable liver lesions	10	1	2
Benign liver lesions	1	0	4
Extrahepatic disease*	16	0	0
Not fit for surgery	3	0	0
Urgent colon resection	9	0	1
Prior liver resection	0	1	1
Need for 2-stage liver resection	0	0	1
Local excision†	0	0	1
Pregnancy	0	1	0

RESECT = Simultaneous Resection of Colorectal Cancer with Synchronous Liver Metastases.
*Extrahepatic metastases other than fewer than 4 sites in the lung.
†Primary tumour treated with local transanal excision.

Table 2. Baseline characteristics of eligible patients

	Accrual method; no. (%) of patients*		
Variable	Population-based method alone $n = 18$	Traditional methods alone $n = 14$	Total $n = 26$†
Age, median (range), yr	64 (35–91)	57 (35–76)	61 (35–91)
Female sex	9 (50)	4 (29)	10 (38)
Distance from hepatobiliary cancer centre,‡ median (range), km	20 (0–53)	0 (0–53)	3 (0–53)
Primary tumour site			
Right sided	5 (28)	4 (29)	9 (35)
Left sided	9 (50)	4 (29)	10 (38)
Rectum	4 (22)	6 (43)	7 (27)
Imaging			
CT	9 (50)	4 (29)	11 (42)
MRI	2 (11)	3 (21)	3 (12)
CT and MRI	7 (39)	7 (50)	12 (46)
No. of liver metastases, median (range)	2 (1–8)	2 (1–9)	2 (1–9)
Bilobar liver metastases	10 (56)	7 (50)	12 (46)
Major liver resection	11 (61)	10 (71)	18 (69)
Additional organ§	3 (17)	2 (14)	3 (12)
Size of metastases, median (range), mm	23 (6–70)	36 (7–82)	26 (6–82)

CT = computed tomography; MRI = magnetic resonance imaging.
*Except where noted otherwise.
†Six patients were identified by both methods.
‡Centre where the colorectal biopsy was performed.
§Additional abdominal organs involved with the primary colorectal cancer.

2 weeks of being determined eligible for the study when the pathology report of their colorectal tumour was found in later reports in the ePath database.

Traditional methods of accrual

Thirty-eight patients with colon cancer and liver metastases were identified via traditional patient accrual methods, of whom 27 (71%) were determined to be potentially eligible for the RESECT trial on level 2 screening (Figure 1). Nine of the 27 patients were also found via the population-based electronic database method. Among the 38 patients, level 3 screening identified 14 (37%) who were eligible for the RESECT trial. The most common reason for exclusion on level 3 screening was the finding that the liver lesions were benign and not metastases (4 patients), followed by unresectable liver lesions (2 patients) and the need for 2-stage liver resection (1 patient) (Table 1). Of the 14 eligible patients, 6 were also found via the population-based electronic database method. The reasons why 8 patients were found by means of traditional methods only, and not via the population-based method, were biopsy not reported by ePath and therefore missed (1 patient), biopsy showed high-grade dysplasia, not invasive carcinoma, and therefore the case was not reported to ePath (2 patients), patient diagnosed outside the Hamilton Niagara Haldimand Brant LHIN catchment area (2 patients) and patient had undergone biopsy of the colorectal tumour outside the study period (3 patients).

Baseline characteristics of eligible patients

Patients identified by means of population-based and traditional methods of accrual were similar in age (median 64 yr v. 57 yr) (Table 2); however, patients identified via the population-based method alone (excluding those identified by both methods) were more likely to be older than patients identified via traditional methods alone (median age 69 yr v. 49 yr). Patients identified by means of the population-based method alone were also more likely to have had a biopsy procedure farther away from the hepatobiliary cancer centre (median 20 km v. 0 km). The location of the primary tumour, the number and size of liver metastases, the extent of liver disease (1 lobe v. both lobes) and the need for major liver resection were similar between the 2 groups. A few patients (3/26 [12%]) were identified as requiring resection of an additional abdominal or pelvic organ other than the primary tumour; the additional organs included the spleen, pancreas and abdominal wall.

Population identification ratio

After level 3 screening, there were 26 eligible patients identified by both accrual methods, with 20 patients identified without overlap (Table 3). The population identification ratio for eligible patients was 1.5 (12/8) (Table 3). Of the 14 eligible patients identified by traditional methods (8 by traditional methods alone and 6 by both methods), 10 (71%) were enrolled in the study. The remaining 4 patients were not enrolled because the patient declined

Table 3. Population identification ratio based on patients potentially eligible and eligible for the RESECT trial*

	Accrual method; no. (%) of patients*				
Screening level	Population-based method	Both methods	Traditional methods	Total (either method alone)	Population identification ratio
1 (population size)	803	—	—	—	—
2 (potentially eligible)	51 (74)	9 (13)	18 (26)	69	2.8
3 (eligible)	12 (60)	6 (20)	8 (40)	20	1.5

RESECT = Simultaneous Resection of Colorectal Cancer with Synchronous Liver Metastases.
*Data presented as count and proportion of the total number of patients identified by either method alone, excluding patients identified by both methods.

to participate (1 patient), because of surgeon's preference (2 patients) or owing to progression of metastatic disease (1 patient). Of the 18 eligible patients identified by the population-based method, 6 (who were also identified by traditional methods) were enrolled in the RESECT trial. The remaining 12 patients were not approached to participate in the trial and were not referred to the hepatobiliary cancer centre before they underwent colorectal resection.

Discussion

In this study, the use of a population-based electronic database method identified almost 3 times as many potentially eligible patients and 50% more eligible patients for the RESECT trial compared to traditional methods of accrual. Eligible patients identified by means of both methods had similar baseline characteristics, with the exception that patients identified via the population-based method were being treated at a region farther away from the hepatobiliary cancer centre. Considering that 71% of eligible patients identified via traditional methods were eventually enrolled in the RESECT trial, it is possible that many more patients could have been enrolled with the use of population-based accrual methods.

Population-based cancer registries are not commonly used to identify patients eligible for surgical trials. For most cancers, surgical resection should happen relatively soon after diagnosis and confirmation of resectability; therefore, population-based methods to screen and approach patients should have the capability of identifying eligible patients in a timely manner (i.e., within a few weeks of diagnosis). The short time window between biopsy and imaging means that our research team would have been able to contact the treating surgeon within a reasonable amount of time before considering surgical resection of the primary tumour. It is important to remember that the liver lesion in patients with synchronous colorectal cancer and liver metastases is not always upfront resectable; sometimes these patients require neoadjuvant treatments. Our group is designing the protocol for a randomized controlled trial (RESECT-RCT), and, given the success of the present study, we plan to trial the use of population-based methods to increase accrual.

We identified few studies that aimed to increase accrual of patients with colorectal cancer to surgical clinical trials. A systematic review by Tan and colleagues[22] showed that cancer registries are the most frequent population-based databases used to recruit potential participants to clinical trials: of the 25 citations found, 14 were from cancer registries. However, only 1 of the 14 studies included patients with colorectal cancer, and that study aimed to recruit family members of probands with colorectal cancer for screening.[23]

The proportion of potentially eligible patients who were found to be eligible for the RESECT trial after review by a hepatobiliary surgeon was lower in the population-based accrual group than in the traditional methods accrual group (20% v. 37%). Most patients were deemed ineligible because of the presence of extrahepatic disease (i.e., > 3 metastatic deposits in the lungs) not previously mentioned in the radiology report or unresectable liver disease. It is possible that a research coordinator can be taught to identify such patients, which would lead to a more streamlined use of resources. It is also conceivable that machine learning could be used to identify potentially eligible patients for the trial based on the radiologic report description (i.e., mention of liver metastases).

Limitations

The small number of patients who are eligible for the RESECT trial makes comparisons between groups difficult, and therefore the applicability of population-based methods to different clinical trials with broader patient eligibility is unknown. In addition, this study aimed to test only the feasibility of ePath and OneView to identify potential participants for a clinical trial; we did not attempt to contact treating physicians (directly involved with patients' circle of care) to approach patients to participate in the study. Therefore, we do not know whether the proportion of patients enrolled by means of the population-based method would be the same as the proportion enrolled through traditional methods. It may be that tumour characteristics (e.g., rectal primary), surgeons' or patients' preferences, or even geographic location (i.e., distance from the hepatobiliary cancer centre) are important barriers to patient enrolment,[24] which would make the true δ between the 2 methods smaller than what we found in the present study. Also, a substantial number of eligible patients (4/18 [22%]) identified by means of the

population-based method underwent colorectal resection within 2 weeks of being determined eligible for the study, which left a small window to potentially attract them to the RESECT trial. It is also not known whether a population-based method of identifying patients for a clinical trial would be useful in other jurisdictions, as the databases used are unique to Ontario.

CONCLUSION

In this study, the use of a population-based electronic database accrual method identified almost 3 times as many potentially eligible patients and 50% more eligible patients for the RESECT trial compared to traditional methods of accrual. With adequate training, population-based methods seem to yield a patient population very similar to that accrued with traditional methods. Population-based methods are easily accessible with the use of existing resources; therefore, they can keep the cost of accrual down and the effort of the research staff to accrue patients low. However, these methods may miss patients who would otherwise be captured by traditional methods (e.g., those with biopsy showing high-grade dysplasia, patients whose biopsy procedure was performed outside the catchment area, and patients who require downsizing neoadjuvant chemotherapy or portal vein embolization); therefore, both methods of accrual are likely necessary for optimal recruitment.

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