Unveiling the best predictive models for early-onset metastatic cancer: Insights and innovations (Review)

LIQING YU[1,2*], ZHENJUN HUANG[1*], ZIQI XIAO[2], XIAOFU TANG[2], ZIQIANG ZENG[3,4], XIAOLI TANG[5] and WENHAO OUYANG[1]

[1]Department of Medical Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, Guangdong 510120; [2]The Second Clinical Medical College; [3]Jiangxi Provincial Key Laboratory of Preventive Medicine; [4]School of Public Health and [5]School of Basic Medicine, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China

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Abstract. Cancer metastasis is the primary cause of cancer deaths. Metastasis involves the spread of cancer cells from the primary tumors to other body parts, commonly through lymphatic and vascular pathways. Key aspects include the high mutation rate and the capability of metastatic cells to form invasive tumors even without a large initial tumor mass. Particular emphasis is given to early metastasis, occurring in initial cancer stages and often leading to misdiagnosis, which adversely affects survival and prognosis. The present review highlighted the need for improved understanding and detection methods for early metastasis, which has not been effectively identified clinically. The present review demonstrated the clinicopathological and molecular characteristics of early-onset metastatic types of cancer, noting factors such as age, race, tumor size and location as well as the histological and pathological grade as significant predictors. In conclusion, the present review underscored the importance of early detection and management of metastatic types of cancer and called for improved predictive models, including advanced techniques such as nomograms and machine learning, so as to enhance patient outcomes, acknowledging the challenges and limitations of the current research as well as the necessity for further studies.

Correspondence to: Ms. Xiaoli Tang, School of Basic Medicine, Jiangxi Medical College, Nanchang University, 461 Bayi Avenue, Nanchang, Jiangxi 330006, P.R. China
E-mail: xltangmail@163.com

Dr Wenhao Ouyang, Department of Medical Oncology,Sun Yat-sen Memorial Hospital, Sun Yat-sen University, 107 Yanjiang West Road, Guangzhou, Guangdong 510120, P.R. China
E-mail: auyeung3@126.com; auyeung3@mail2.sysu.edu.cn

*Contributed equally

Key words: metastatic cancer, early-onset cancer, clinicopathological features, the predictable factors, the predictable models

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1. Introduction

The primary reason for cancer deaths is metastasis, which occurs when tumor cells from the originating site infiltrate into lymphatic veins, blood vessels or other passageways and are transported to other places for continued growth, resulting in tumors of the same type as the primary-site tumors (1-3) and the original tumors transform into metastatic ones. Metastasis is one of the defining characteristics of types of cancer (4). Lymphatic, vascular and implant metastases are some of the main transmission mechanisms (5). The majority of cancer cells enter the local lymph nodes (LNs) through lymphatic vessels and form intra-lymphatic metastasis to cause primary cell deaths (6). Once invading lymphatic vessels, the cancer cells may shed from tumors to form an embolus or proliferate in the vessels to form a continuous mass. As a result, cancer-related morbidity and mortality are primarily caused by metastatic diseases (7). Lungs, livers, bones and the brain are frequent sites for tumor metastasis (8).

The following is a summary of what is known of the characteristics of metastatic types of cancer: i) Metastatic cells are less stable and have a higher rate of spontaneous mutations than non-metastatic cells of the same origin. ii) Metastases can grow into invasive tumors even in the absence of a substantial initial tumor mass (9). iii) A number of primary solid tumors contain either localized or distant metastases and are physiologically diverse prior to detection (3,10). iv) The cells of a tumor are physiologically diverse (10). v) The primary factor for the treatment failure and deaths of patients with malignant malignancies is metastasis (11). vi) The phases of interacting with the microenvironment, invasion, migration, resistance to apoptosis and angiogenesis generation should be completed by tumor cells (12).

Several large cohort studies on patients (13) and studies using spontaneous mouse tumor models (14) demonstrate that metastases also occur in the early stages of types of cancer. In this context, Hüsemann *et al* (14) have refined the definition of 'early metastatic cancer' to signify that metastases might commence before the diagnosis of primary tumors, rather than being restricted to the advanced stages of tumor development. Furthermore, from some distal metastases of these patients, they could occur at a relatively early pathological stage (3,15). For these patients, there is a lack of effective clinical identification, as 'clinically-undetectable minimal residual lesions (MRDs)' are usually used (16,17). For this reason, only indirect knowledge of MRDs is available, so the prognosis of only ~20% of patients is improved through systemic (adjuvant) therapies (11), which, therefore, often leads to misdiagnosis while having a significant effect on patient survival and prognosis. In this context, it is suggested that the current understanding of early systemic types of cancer is not sufficient to prevent metastases (15). There is growing evidence that a number of types of cancer can have early lymphatic metastases, such as lung cancer (18), breast cancer (5,19), kidney cancer, brain cancer, prostate cancer and thyroid cancer (20). However, few articles are focused on early metastases or types of cancer, which warrants further investigation.

2. Early-onset metastases of different types of cancer

A number of studies have verified that early-onset metastases can occur in a number of types of cancer such as gallbladder cancer (21), lung cancer (18), breast cancer (5,19), urothelial carcinoma of the bladder (22), esophageal cancer (23) and colorectal cancer (CRC) (24,25), which are often biologically aggressive. In particular, in gallbladder cancer, early distant metastases have been demonstrated in 16% of resected T2 lesions (26). Similarly, the rate of LN metastases among all patients with T1-2 CRC ranges from 2-8.4% (24). In addition, compared with a 5-year survival rate of >90% among T1-2 patients without Stage I LN metastases (LNMs) in CRC, the survival rate of T1-2 patients with positive Stage III LNMs is <70% (24), suggesting that the high incidence of Stage I LNMs, including T1 and T2, leads to a higher TNM mortality and staging (25,27). Bone metastases in the fallopian tubes, peritoneum and ovary with advanced bone diagnosis have little prognostic effect, whereas early bone metastases have a significant impact. These findings suggest that distant metastases play an active role in the progression of early types of cancer and it can be concluded that if detected early, cancerous patients can show good survival rates. However, some type of cancer, such as esophageal squamous cell carcinoma, despite having been detected early and resected completely, the 5-year survival rate remains low with the prognosis remaining poor (28). Therefore, predicting the status of LN metastases of patients with early-stage types of cancer (T1-2) is essential for observing the clinicopathological characteristics and prognosis of patients while determining the type of treatment they should receive, which will be discussed later.

3. The clinicopathological and molecular features of early-onset metastatic types of cancer (Table I)

Various types of cancer exhibit distinctive characteristics concerning early metastases. For instance, in breast cancer, patients with primary tumors located in the caudal axilla or invasive ductal carcinoma are more likely to test positive for LNMs (19). Conversely, in terms of colon cancer, the propensity is often towards the left side (24). Furthermore, the TNM staging of early tumor metastases differs. In breast cancer, LN positivity tends to be higher among T1 patients compared with T2 patients (19). In summary, early-onset metastatic types of cancer typically manifest multifactorial clinicopathologic features. For early-onset gastric cancer (GC), bowel type, T1b stage and tumor size emerge as the risk factors of LNM development, with T1b and LNMs positivity serving as risk factors for their survival (29). These findings suggest a systematic and distinctive distribution of early-onset metastatic types of cancer across both time and space.

4. Factors affecting the metastases of early-onset metastatic types of cancer

Numerous studies have underscored that early-onset metastatic types of cancer are subject to a myriad of factors, with their demographic distribution exhibiting distinct characteristics. Younger patients exhibit a higher propensity for developing LNMs in comparison with their older counterparts (18,19,30). This observation implies that an early detection at the initial stage may enhance the survival outcomes of patients (31,32). Additionally, there is a noteworthy disparity based on race (33). Furthermore, the primary sites of different metastatic types of cancer vary due to differences in the sites of metastases. For instance, a predominant site of liver metastases among patients with pancreatic cancer is the tail of the pancreas (30), underscoring the substantial influence of tumor location on metastases. Moreover, individuals with detrimental lifestyle habits, such as smoking and alcohol abuse, exhibit a heightened susceptibility to developing early-onset metastatic types of cancer (34). In conclusion, the occurrence of early-onset metastatic types of cancer is intricately linked to tumor characteristics, demographic factors and lifestyle habits.

5. Biochemical characteristics of early-onset metastatic types of cancer

Early-onset metastatic types of cancer are usually associated with abnormalities in signal transduction pathways. Elevated

Table I. An overview of the pattern of manifestation of early-onset metastasis in various types of cancer, highlighting how early-onset metastatic types of cancer exhibit distinct characteristics in different individual types.

Type of cancer	Main site of metastasis	Main features	Characteristics of majority of cases	(Refs.)
Breast cancer	Axillary lymph node.	Biologically aggressive phenotypes	Younger (age <45); Black ethnicity; T1C, grade III, larger tumor size. Primary site: Central portion and axillary tail. Histological type: Invasive ductal carcinoma	(19,92,93)
Gallbladder cancer	Peritoneum, liver and lung; liver: accounting for >50% of patients	Aggressive cancer	Caucasian females, adenocarcinoma, grade II, TNM stage, T2/N0, larger tumor size	(21,94,95)
Urothelial carcinoma of the bladder		75% non-muscle-invasive	Larger tumor size (≥3 cm), multiple tumors, hydronephrosis and lymphovascular invasion	(22)
Colorectal cancer	Liver metastasis in 27.3% of patients	Aggressive cancer	Younger (age <60), Caucasian females, larger tumor size, poor tumor grade, distal colon, higher frequency of T2 status	(24,43,96)
Gastric cancer		Aggressive cancer	Male, poorly differentiated, larger tumor size, submucosal tumors, location: middle (pT1b). Histological type: Pure undifferentiated-type. Predominant macroscopic tumor type: Flat/depressed,	(42,48,97,98)
Esophageal squamous cell carcinoma	Liver, lung, nonregional lymph nodes and adrenal gland. Mostly found in lung	Aggressive cancer Early regional tumor progression, extensive lymph node networks and early lymph node metastases.	Caucasian males. Distribution of tumor locations: Middle esophagus. Tumor differentiation: G2. Depth of tumor invasion: T1b	(23,99-102)
Oral squamous cell carcinoma	Hard palate, buccal, lip, floor of mouth, tongue and other places. Mostly found in tongue	Distant metastasis, highly aggressive with local invasion and in early stages of the disease.	Larger tumor size. Clinical T classification: T2. Primary Site: margin. Histologic grade: Moderately differentiated. Pathologic nodal status: Negative. Muscle infiltration: Positive. Neural infiltration negative.	(41,82)
Lung Adenocarcinoma	Bone, brain, liver and the adrenal gland	Aggressive cancer	Male, frequently in smokers. Tumor side: Right. T stage: Equally distributed in T1 and T2. EGFR mutation.	(18,103)
Papillary thyroid carcinoma		Non-invasive	Female, younger (age ≤55), larger tumor size. Tumor location: Most are upper, middle and inferior. Multifocality: Absent, mostly without chronic lymphocytic thyroiditis	(20)
Cervical cancer			Younger (age <51, especially those aged <46 years), larger tumor size, large percent of squamous cell carcinoma antigen (SCC-Ag). Menstrual status: Most are premenopausal	(85)

rates of P53 mutations among individuals with an early-onset breast cancer impede the expression of the growth-arrest-specific 7 (GAS7) gene, which has notably been identified as a potent inhibitor of breast cancer metastases, exerting its effect on the cytoplasmic FMRP-interacting protein (CYFIP1) and WASP-family verprolin-homologous 2 (WAVE2) complex to obstruct CYFIP1 and Rac1 protein interactions, actin polymerization as well as the β1-integrin/FAK/Src signaling pathway. Rac1, an activated GTP form, stimulates actin polymerization by binding to a WAVE2 subunit. However, the interaction of GAS7 isoform b (GAS7b) with CYFIP1 thwarts this process, concurrently inhibiting the β1-integrin/FAK/Src signaling pathway, ultimately impeding breast cancer metastases (35).

Similarly, the metastases of early-onset prostate cancer, a specific molecular subtype, are primarily governed by the transmembrane protease, serine 2, a gene with the erythroblast transformation-specific-related gene (TMPRSS2-ERG fusion gene). To a lesser extent, alterations in the androgen receptor, speckle-type POZ protein and additional sex comb-like 1 also contribute to the regulatory landscape of this process (36). Meanwhile, the BRCA1 gene assumes a pivotal role in the metastases of early-onset colon cancer. Functioning as an antioncogene involved in diverse biological processes, variations in the BRCA1 gene have been associated with a five-fold increase in the risk of CRC development (37). Furthermore, the early expression of BRCA1 gene mutations is closely linked to a poor prognosis of CRC (37). These findings underscore the significance of biochemical characteristic alterations as contributory factors for the initiation of early metastatic types of cancer.

6. Predictable factors and indicators of early-onset metastatic types of cancer

The clinical features of various types of cancer are important prognostic indicators of patients with cancer. The survival rate of patients with distant metastases is very low (38,39). It has been established that the degree of vascular invasion and differentiation is an independent prognostic indicator of the overall survival after 5 years (40). In oral tongue cancer, the large tumor volume (≥20 cm^3) is significantly associated with the 5-year disease-specific survival (41). In addition, the sequence of insurances, radiotherapy, surgeries and chemotherapy compared with surgeries is another important independent prognostic factor (23).

Clinical features. The evidence that a number of molecular characteristics can influence the metastases of types of cancer has been explored in numerous studies and some indicators are usually taken into account, such as age, race, tumor size, tumor location, tumor number, histological grade, pathological grade and T-status (19,21-23,41-43). In most cases, these factors, which have a strong effect on types of cancer, usually consist of predictive models. For example, in gallbladder cancer, histologic grade has the highest discrimination (44) and a poor grade is the strongest indicator of distant metastases (45). In squamous cell carcinoma, age has been found to be significantly associated with distant metastases (46). In different types of cancer, each tumor has its own specific criteria for detection. In addition to the aforementioned indicators, the nerve terminal invasion and clinical assessment of LNMs (cLNMs) are two other biomarkers of colorectal tumor metastases to LNs (24). Similarly, lymphovascular invasion (LVI) can help diagnose uroepithelial carcinoma of the bladder (22), as well as axillary node metastases in breast cancer (47) and gastric cancer (42,48,49). Similarly, in gastric cancer, the exclusive features predicted compared with other types of cancer are ulcerative findings, and the LN status is reported through computed tomography (48-50).

7. Association of early-onset metastatic types of cancer with gene mutation profiles

The phenomenon of metastases in early-onset types of cancer is closely related to genetic factors. A previous study on the early-onset metastatic CRC indicate that younger patients (<50 years old) have a significantly shorter progression-free and overall survival compared with older patients, showing a disparity that can be attributed to distinct genomic profiles influencing treatment-related adverse events (51). At the same time, the precision provided by the next-generation sequencing (NGS) technology and the knowledge of circulating tumor DNA (ctDNA) offer new insights as well as possibilities for the diagnosis and treatment of types of cancer.

8. NGS

NGS technology has emerged as an indispensable tool for research on types of cancer, providing unprecedented insights into the genetic factors that may contribute to the phenomenon of early-onset metastases. A previous study (52) highlights the use of NGS in identifying mutations within the SF3B1 gene associated with an increased risk of early metastases among patients with uveal melanoma. This groundbreaking work illustrates the ability of NGS to uncover specific genetic alterations that could serve as predictive biomarkers for metastases, offering a more nuanced approach to patient stratification and prognosis.

In research on breast cancer (35), NGS has been pivotal in elucidating the role of the GAS7b gene, which is found to be underexpressed in early-onset cases. This study demonstrates the potential of NGS to reveal complex gene-expression patterns and interactions that are critical for understanding the metastatic process, thus opening up possibilities for early intervention and treatment customization based on the genetic profile of the patient. Previous research (53) has shown the significant impact of NGS on enhancing the prognosis accuracy of CRC. By analyzing a broad array of single nucleotide polymorphisms, it identified specific genetic markers associated with metastasis timing. The study exemplifies the power of NGS to discern subtle genetic variations that could inform the development of personalized treatment plans, greatly enhancing the ability to predict and manage early-onset metastases for patients with CRC (54-57).

By integrating the results of these studies, it has been found that NGS has become critical for identifying genetic factors associated with early-onset metastases. Each study brings to light the promise of NGS in enabling the detection of genetic markers that can predict the course of types of cancer more

accurately than ever before, marking a significant advancement towards personalized oncology with improved patient outcomes.

9. ctDNA

The understanding of ctDNA is rapidly evolving in research on modern oncology. A previous study has shown its great potential for early cancer diagnosis, treatment monitoring and minimal residual disease assessment (58). Particularly for CRC treatment, ctDNA analysis assists in accurately categorizing the prognoses of patients and guiding personalized adjuvant chemotherapy. However, challenges such as the handling of liquid biopsy samples, the variability of assay sensitivities and specificities as well as technological limitations remain in the clinical application of ctDNA analysis.

Further advancements in oncology encompass various cancer types, with significant developments in treating blood and solid malignancies, groundbreaking immunotherapies for rectal cancer, novel engineered cell therapies as well as clinical trials for pancreatic cancer and other solid tumors. The progresses in targeting the tumor microenvironment as well as developing drugs and cancer vaccines, along with ctDNA research, are revolutionizing the situation of cancer diagnosis and treatment, offering new hopes and strategies for combating this complex disease.

10. Cytokines

In some cases, cytokines are an important factor in tumor progression. First, blood counts are a routine part of the preoperative examination. Studies have indicated that inflammation-related factors and hematological parameters are also responsible for LN metastases and tumor progression in different types of cancer (59,60). Previous studies have shown that the neutrophil-to-lymphocyte ratio, the platelet-to-lymphocyte ratio (PLR) and fibrinogen are important hematological predictors of LNMs (61,62). For example, neurospecific enolase, PLR, carcinoembryonic antigen (CEA), lactate dehydrogenase (LDH) and cytokeratin 19 fragment are independent hematological parameters associated with distant metastases in lung adenocarcinoma. Similarly, CEA is a biomarker of distant metastases in colorectal tumor (25), while the pre-CEA level is a biomarker of predict LNs (24). In addition, the statuses of human epidermal growth factor receptor 2, progesterone receptor and estrogen receptor are other important predictors of breast cancer (19). Similarly, the statuses of tumor LDH and serum LDH are two hematological parameters of triple-negative breast cancer (63), implying that different clinical factors have an important impact on early-onset metastatic types of cancer.

Accordingly, univariate and multivariate logistic regression analysis and identification were used to screen out influential factors (64-67). After the exclusion of unknown data, the remaining factors were selected to build a prediction model to detect distant metastases (Fig. 1). After building an appropriate model, in order to assess the impact of each factor, it was easy to calculate the total score by summing up each particular score, and by processing the total score to a lower criterion, it is possible to predict the probability of LNMs.

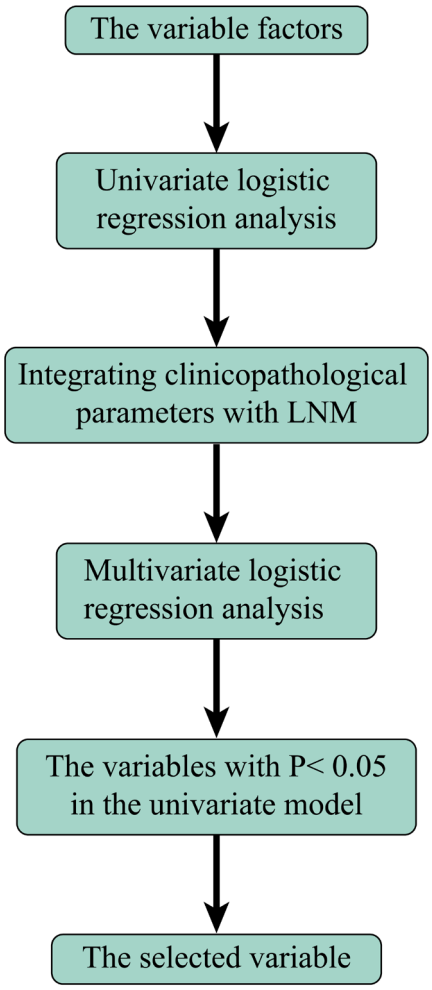

Figure 1. Recruitment pathway chart of multiple variable factors analysis selection. LNM, lymph node metastases

11. Risk analysis and assessment of early-onset metastatic types of cancer (Table II)

At present, several methods including imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT) (68,69), quantitative comparative proteomics and histological analysis (70) have been used to identify factors influencing the prediction of distant metastases. In urological tumors, positron emission computed tomography/CT using radionuclides such as 11C-choline has become one of the routine imaging tools (71,72), whose advantage is that it allows the assessment of the prostate bed and reduces the urinary excretion of patients (73).

A series of experiments have demonstrated that conventional MRI diagnostic models based on shape and size do not reflect the true state of distant metastases (74,75), which, even with the most advanced imaging techniques, are still difficult and expensive to be accurately predicted (69,76,77). Therefore, we should explore a more accurate model for clinical diagnosis based on combining analytical factors such as epidemiological features, pathological features and inflammatory indicators to accurately identify the metastases of cancer.

Nomograms, developed in the multivariate logistic regression mode, are popular visual graphs used to show the

Table II. In the context of various early-onset metastatic types of cancer, common clinical diagnostic methods were evaluated.

Cancer type	Common clinical diagnostic methods	Effect evaluation	(Refs)
Breast cancer	SLNB	Standard procedure in the past. Disadvantages: it can only examine the axillary sentinel nodes	(104,105)
	Nomograms	AUC in both primary and validation cohorts: 0.733 and 0.741. C-index in both primary and validation cohorts: 0.720 and 0.718. Calibration curve demonstrating a good agreement. Advantages: The patients can be stratified into different groups and it can predict any lymph nodes	(19,92)
Gallbladder cancer	Nomograms Based on Nomograms, PET-CT or staging laparoscopy: for patients at higher risk of M1	AUC and the calibration plot: Advantages: it is verified that the prediction is effective	(21)
Urothelial carcinoma of the bladder	Nomograms	AUC curves: 0.8-0.9. Hosmer-Lemeshow test: Suggesting a non-significant statistic. Harrell's C-index: 0.8-0.9 in the primary cohort while 0.8-0.9 in the validation cohort. Advantage: It is verified powerful to have a good fit and differentiate LN metastasis	(22)
Colorectal cancer	Nomograms for predicting lymph nodes metastasis	The calibration curve showing a predictive accuracy effectively. C-index: 0.6-0.7. Analysis of DCA and CIC: Showing that the probabilities between 0 and 0.3 are the most beneficial prediction. Advantage: Indicating a good agreement between observations and predictions	(25)
		The calibration curve is highly consistent with the standard curve, meaning a high reliable prediction ability. AUC between 0.65-0.72 in training, external validation and internal validation cohorts in T1 patients, indicating that the nomogram has favorable discrimination. DCA showing a higher net benefit. Advantage: Showing the best predictive discrimination ability.	(24)
	Nomograms for predicting distant metastasis	Calibration plot showing a satisfactory predictive accuracy. C-index: 0.8-0.9, showing an effective spreddiction Analysis of DCA and CIC showing that the probabilities between 0 and 0.3 are the most beneficial prediction	(25)
	LASSO-Based machine learning algorithm	AUC: 0.765 in the validation set, demonstrating better predictive accuracy. DCA showing a positive net benefit. Advantage: A classifier that can maximize its predictive power effectively and improve the accuracy of prediction potentially	(106)
	Machine learning: The RF model	Achieving a high accuracy, specificity and sensitivity. AUC: 0.991. Advantage: Showing the best precision, accuracy, F1 score, AP score, and Matthews correlation coefficient value.	(96)

Table II. Continued.

Cancer type	Common clinical diagnostic methods	Effect evaluation	(Refs)
	Machine learning: The ANN model	AUC: 0.78 in the training cohort while 0.83 in the validation cohort, indicating a higher predictive power. Advantage: Having strong fault tolerance which indicates that it can be widely used for analysis and prediction of a number of types of data.	(107)
Gastric cancer	Nomograms	AUC: 0.8-0.9 Hosmer-Lemeshow test: 0.8-0.9 in the training set and 0.6-0.7 in the validation set, suggesting that the model is well fitted. C-index: 0.78 to 0.86 in the primary cohort and 0.60 to 0.94 in the validation cohort, showing it has good discriminations. Advantage: Has a high probability	(42)
	Risk-scoring model	AUC: 0.82-0.86 in the training set and 0.75-0.88 in the validation set, suggesting model's potential usefulness. Advantage: Easier to compare LNM risk and surgery-related risk and to administer more individualized care for patients.	(48)
Esophageal squamous cell carcinoma	Nomograms	AUC: between 0.7 and 0.9, showing superior discrimination ability. Calibration curve demonstrating that it has a good agreement. DCA: showing satisfactory net benefits. NRI values and the NRI values: Improved accuracy	(23,77)
Oral squamous cell carcinoma	SLNB	Detection rates: 95%, sensitivity: 0.93. NPV: 0.88-1. Advantage: Reliable method with high accuracy. Disadvantages: Hard to demand plenty of experience and professional technology of the performing the procedure.	(108)
	For prediction of preoperative lymph node metastasis. ML model: The random forest model	AUC: between 0.7 and 0.9; sensitivity: 85%; specificity: 75%. Advantage: The performance is superior to anyone of conventional statistical methods and predictors	(82,109)
	For prediction of delayed lymph node metastasis. ML model: Support vector machine model.	AUC: 0.956; sensitivity: 100%; specificity: 87.5%. Advantage: Performance is superior to conventional statistical methods and predictors.	
Lung adenocarcinoma	ML models: RFC	AUC=0.890. Decision curve: Presenting better net benefits. Advantage: Combining radiographical features and clinical characteristics. The performance is superior to anyone of conventional statistical methods and predictors	(110)
	Nomograms	C-index: 0.792, meaning that it has high accuracy Calibration curve: close to the standard curve and there is no significant difference, meaning that the model is close to the actual outcome. AUC: between 0.7-0.9, showing that the model was more effective than the clinicopathological risk factors alone. DCA: Presents more net benefits at 0-81% threshold probability. Advantage: Performs well and possesses reliability and satisfactory accuracy.	(18,111)

Table II. Continued.

Cancer type	Common clinical diagnostic methods	Effect evaluation	(Refs)
Papillary thyroid carcinoma	XGBoost model of ML	AUC: 0.750, demonstrated the highest performance of predicting CLNM among the six algorithms models (LR, GBM, RF, DT, NNET and XGBoost) Advantage: Differentiating between benign and malignant	(20,112, 113)
Endometrial endometrioid carcinoma	KGOG-2014	Advantage: Identifying serum CA-125 level and MRI as a combination and achieving accurate identification of low LNM risk. Disadvantage: Including non-endometrioid histology patients	(114)
	SLN	Advantage: Improving surgeons' detection ability in small-volume disease and reducing intraoperative and postoperative morbidity Disadvantage: demanding of the surgeon are crucial and most critically, it is performed during surgery	(115)
	A five-gene biomarker panel associated with LNM	AUC: 0.898. The accuracy, negative, and positive predictive values are all high. The sensitivity and specificity are 88.9 and 84.1%, respectively.	(116)
Cervical cancer	Histopathologic examination	Advantage: Gold standard for LN status assessment. Disadvantage: Invasive and expensive with a high risk of complications.	(85,117)
	MRI	Advantage: Providing more information for evaluation access and leading to more treatment decisions. Disadvantage: It is unable to accurately identify LNM, especially for small metastatic LN.	
	Radiomics nomogram	ROC-related AUC: between 0.7-0.9, a nonsignificant Hosmer-Lemeshow test statistic. Advantage: Providing a visualization tool for clinicians and SCC-Ag, a useful marker, combined with the radiomics model achieving predictive efficacy	

Biomarkers exhibiting an AUC value between 0.7-0.9 are associated with higher diagnostic accuracy, indicating a notable level of distinction. Additionally, the Consistency Index (C-index), which ranges from 0.5, denoting no discriminative ability, to 1, representing perfect discrimination, serves as a crucial metric; a higher C-index value correlates with superior predictive performance of the model. SLNB, sentinel lymph node biopsy; AUC, area under receiver operating characteristic curve; PET, positron emission tomography; CT, computer tomography; DCA, decision curve analysis; CIC, clinical impact curve; LASSO, least absolute shrinkage and selection operator; ANN, artificial neutral network; NRI, net reclassification index; NPV, negative predictive value; ML, machine learning; RFC, random forest classifier; SVM, support vector machine; XGBoost, extreme Gradient Boosting; CA-125, carbohydrate antigen-125; SLN, sentinel lymph node; CLNM, central lymph node metastasis; LN, lymph node; MRI, magnetic resonance imaging; SCC-Ag, squamous cell carcinoma antigen; LR, logistic regression; GBM, gradient boosting machine; RF, random forest; DT, decision tree; NNET, neural network.

predicted probability of an event for decision support while achieving greater clinical benefits (78). This model also allows clinicians to screen patients at a high risk of distant metastases for closer follow-ups and adjuvant therapies (Fig. 2).

Machine learning (ML) is a model of artificial intelligence in which various probabilistic, optimization and statistical techniques are used, allowing computers to learn summarized information from historical data and make predictions from new data (79,80). Several studies have shown that ML can surpass human judgments in a number of aspects in predicting patient outcomes or cancer risks (81-84). In contrast to traditional statistical methods that rely on predetermined models such as logistic regression (LR), ML can be used to detect deeply the interactions among variables and update algorithms by learning from iterations on the data. In addition, the ML technique can help clinicians to provide new ideas for more personalized patient care (Fig. 3).

Radiomics, as another detection system, can also help identify patients with LN metastases. In combination with patient/tumor characteristics, radiomic features can be utilized

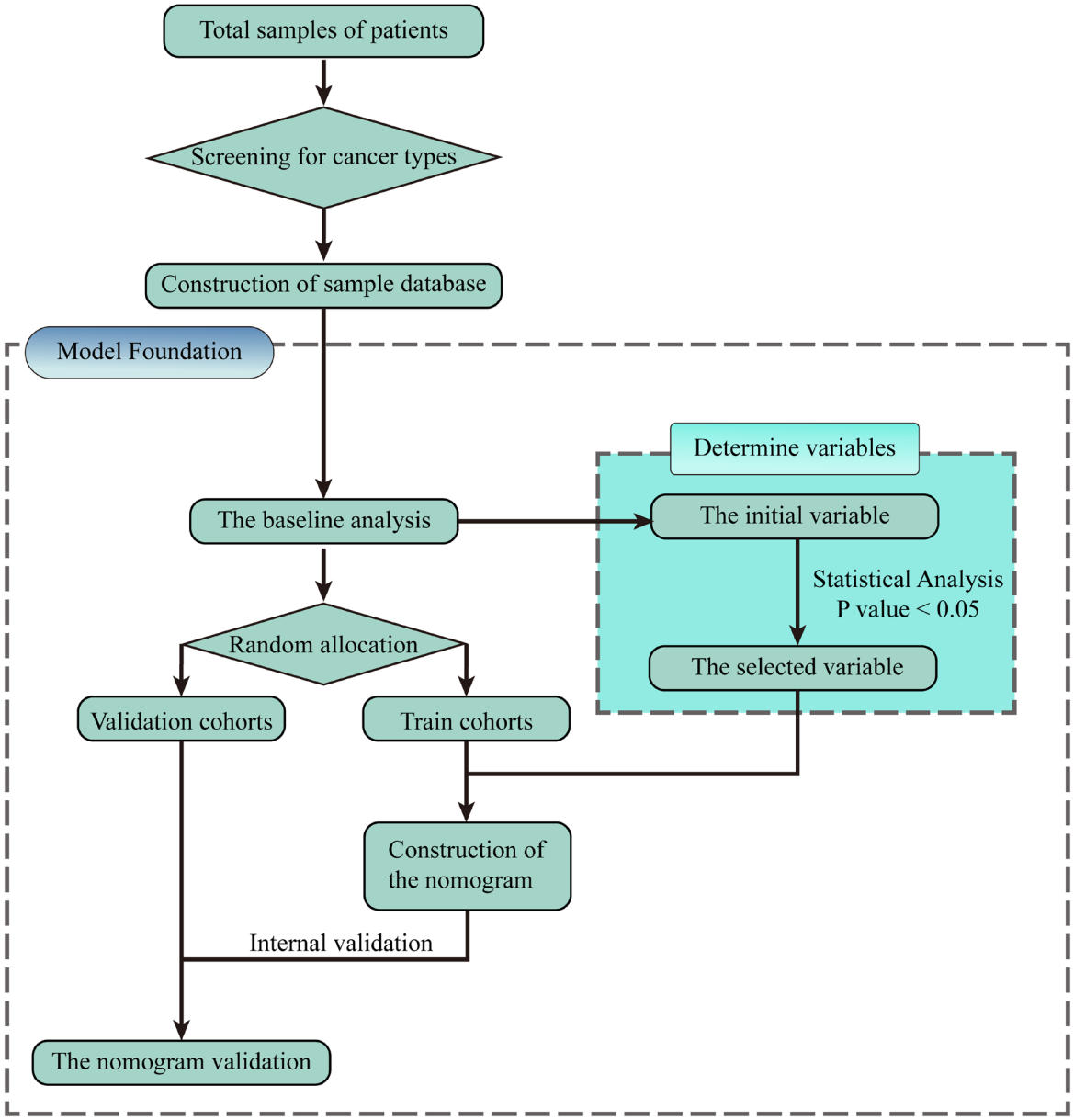

Figure 2. Nomogram displaying the traditional approach for identifying predictable factors.

through clinical decision support systems to make medical decisions and ensure diagnostic accuracy. For example, in terms of cervical cancer, a radiomics model has been developed, which incorporates the squamous cell carcinoma antigen level and has shown good predictive results (85).

Notably, there are some methodological indications of the established models. Based on a receiver operating characteristic curve (ROC) analysis, calibration curves and the C-index, these models have improved performance compared with traditional methods such as CT and MRI. Therefore, these modeling techniques will play an important role in the analysis of medical datasets. In addition, decision curves are used to assess clinical utility, such as in esophageal squamous cell carcinoma (23). In addition, the Cox univariate regression analysis is a method to assess predictable independent prognostic factors (23), which means that it offers a novel approach to assess the clinical value of various testing models.

12. Discussion and conclusion

Cancer metastasis refers to the spread of diseases from one part of the body to another that is not directly related to it. With the development of extensive data analysis and retrospective studies, it has been found that cancer metastases can also occur in the early stages of types of cancer, and the definition of 'early metastatic cancer' was refined by Hüsemann *et al* (14) A study demonstrated that cells from early low-density lesions express more stem cells, which have more migratory and metastatic functions than cells from advanced large-density tumors (15), implying that early-onset metastatic types of cancer may play an important role in cancer progression, causing great harm to the human body. In order to grasp the distant metastases and characteristic distribution of various types of cancer such as breast, gallbladder, bladder urothelial, colorectal and gastric cancer, the present review systematically evaluated

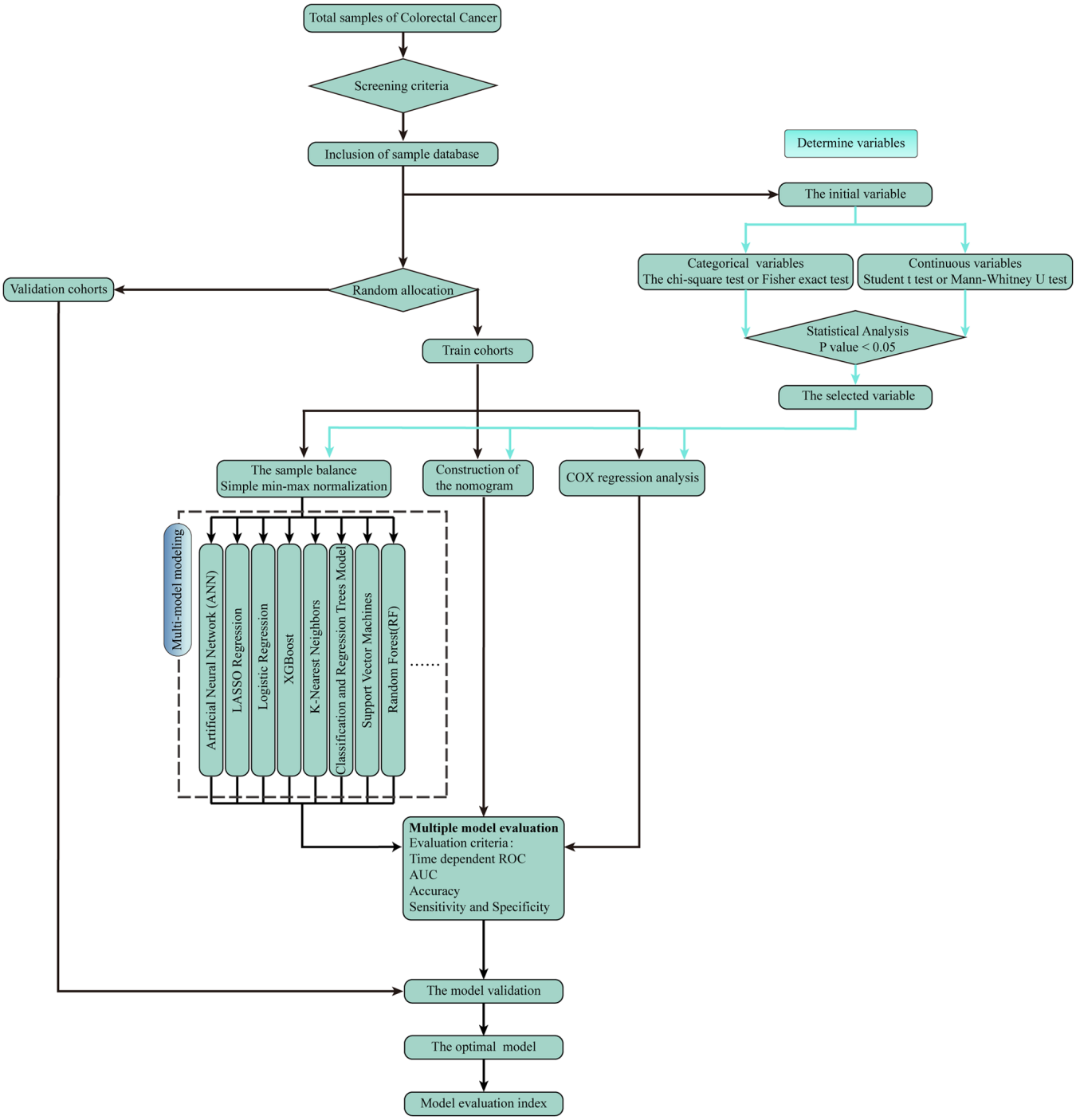

Figure 3. Application of machine learning in the context of colorectal cancer, employing advanced methodologies and public trends to compare various technologies and identify the optimal model. ROC, receiver operating characteristic curve; AUC, area under curve.

and discussed the clinicopathological features of different early-onset metastatic types of cancer while summarizing their epidemiological characteristics. In detail, the early onset of metastases was associated with a large number of clinicopathological features. Predictors vary from tumor to tumor, but tumor size, tumor location, tumor number, histologic grade, pathologic grade and T-status are usually the most common indicators. In addition, some biochemical features can be other important predictors. In different types of cancer, the predictors are specific. It has been found that early-onset metastatic types of cancer are associated with the poor prognosis of cancerous patients. Depending on different factors, a number of studies have validated that a number of new models can be developed to effectively predict whether early-onset metastatic types of cancer occur (86,87). The area under curve (AUC) associated with ROC represents the accuracy of detection and decision curve analysis can be used to assess the clinical utility and ensure the reliability of model prediction significantly. Nomograms and ML have become common models compared with traditional imaging techniques, which are relatively advanced and effective. A few studies (88-91) have also been conducted using new approaches, such as radiomics, through

which some accuracy can also be achieved. Due to fewer studies, these models cannot be widely used. Taken together, the development of these models suggests that it may become an important detectable prognostic factor for patients (41). However, the present review had a number of shortcomings. First of all, the sample size of all reference studies was small, which was associated with information biases and unavoidable selection biases and the present review was unable to extract more representative conclusions. Second, the validation cohorts of some predictable models had low AUCs, which might affect the accuracy of the models. Finally, all the data was from delineated patient subgroups; an external validation of the models remains necessary. Most importantly, various studies have shown that early-onset metastatic types of cancer play an important role in cancer development. Therefore, it is hoped to build models to predict it as soon as possible, so as to take clinical treatments and therapies for cancerous patients.

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Authors' contributions

XLT and WO conceived and designed this review. LY, ZX, XFT, ZZ and ZX contributed in the writing of the manuscript. LY, ZH and ZX was involved in article revision. LY and ZH surveyed the literature and provided suggestions. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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