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Prediction of mucositis risk secondary to cancer therapy: a systematic review of current evidence and call to action

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Prediction of mucositis risk secondary to cancer therapy: A systematic review of current evidence and call to action.

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Abstract

Purpose: Despite advances in personalizing the efficacy of cancer therapy, our ability to identify patients at risk of severe treatment side effects and provide individualized supportive care is limited. This is particularly the case for mucositis (oral and gastrointestinal), with no comprehensive risk evaluation strategies to identify high risk patients. We, the Multinational Association for Supportive Care in Cancer / International Society for Oral Oncology (MASCC/ISOO) Mucositis Study Group, therefore aimed to systematically review current evidence on that factors that influence mucositis risk to provide a foundation upon which future risk prediction studies can be based.

Methods: We identified 11018 papers from PubMed and Web of Science, with 197 records extracted for full review and 113 meeting final eligibility criteria. Data were then synthesized into tables to highlight the level of evidence for each risk predictor.

Results: The strongest level of evidence supported dosimetric parameters as key predictors of mucositis risk. Genetic variants in drug metabolizing pathways, immune signaling and cell injury/repair mechanisms were also identified to impact mucositis risk. Factors relating to the individual were variably linked to mucositis outcomes, although female sex and smoking status showed some association with mucositis risk.

Conclusion: Mucositis risk reflects the complex interplay between the host, tumor microenvironment and treatment specifications, yet the large majority of studies rely on hypothesis-driven, single candidate approaches. For significant advances in the provision of personalized supportive care, coordinated research efforts with robust multiplexed approaches are strongly advised.

Key words: mucositis, diarrhea, supportive oncology, risk prediction, precision medicine, personalized care

Introduction

Individualized care is a key strategic focus in precision medicine with relevance across almost all facets of care. In particular, methods of enhancing anti-cancer treatment efficacy have advanced rapidly, enabling patients to receive treatments specifically tailored to their genetic traits and tumor microenvironment[1,2]. Unfortunately, the importance of personalized supportive cancer care is less well recognized, with limited appreciation for the complex interactions that account for the significant heterogeneity seen in toxicity profiles of various anti-cancer agents.

Mucositis is a ubiquitous complication of almost all cancer therapies, with treatment-specific manifestations reflecting core pharmacological and biophysical actions of various agents and treatments[3]. Common to all therapies is the high degree of heterogeneity in the clinical manifestations of mucositis, with patients presenting along a spectrum – from mild mucosal irritation to severe, ulcerative lesions – despite equivalent tumor burden, demographic profile and treatment specifications[4].

In their mild forms, both oral (OM) and gastrointestinal mucositis (GI-M) can be adequately managed with existing supportive care measures[5-10]. When severe (NCI CTCAE III-V), OM and GI-M are catalysts for potentially lethal complications including infection, renal insufficiency and graft versus host disease[11-13]. In the setting of pelvic radiation, acute GI-M is by far the largest predictor of late GI injury[14,15]. When neutropenia is controlled, severe mucositis is the single largest factor defining the maximal tolerated dose of anti-cancer therapy and a significant driver of dose-reductions, interruptions/delays and treatment discontinuation[16]. Severe mucositis requires intensive in-patient supportive care such as the provision of intravenous fluids and electrolytes, parenteral nutrition and opioid analgesics and thus greatly impacts quality of life for weeks to months[17]. Early intervention is considered critical in managing the clinical burden of severe mucositis; however, it remains unclear who is at risk of developing severe symptoms. As such, there is a clear and currently unmet need to identify patients at risk of severe mucositis to enable methods of risk minimization and the provision of targeted supportive care.

To date, methods of predicting mucositis risk have focused on the individual and their treatment[2]. These approaches are limited as they are largely unmodifiable and highly dichotomous. Similarly, of the studies that have begun to illustrate the genetic nature of mucositis risk[18-20], the translation of these findings are plagued by substantial inconsistencies and disparities between the proportion of people that carry distinct mutations and those that develop severe mucositis. Given our understanding of mucositis pathobiology

has become increasingly sophisticated[3], new methods of risk prediction must acknowledge the variety of factors that determine mucositis risk and our siloed approach to personalized supportive care must be revised.

This systematic review, coordinated by the Multinational Association for Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO) Mucositis Study Group, represents an in-depth evaluation of the factors that contribute to mucositis risk. We aim to provide a clear overview of the factors identified to contribute to mucositis risk, discuss new approaches to risk prediction and provide a practical framework for future studies aiming to develop the next generation of risk prediction tools.

Methods

Search strategy, study selection and data retrieval

PubMed and Web of Sciences were searched for papers published using keywords listed in Table S1. Papers were screened for eligibility (HRW/JB) based on title and abstract. Clinical studies conducted between January 2000 and July 2019, in which the objective was the identification of 1) predictors of OM/GI-M or 2) associations between baseline characteristics and mucositis outcomes were included. Reviews, preclinical research, strictly interventional studies and case studies were excluded. Full details of the search strategy can be found in supplementary material.

Eligible papers were delegated to independent reviewers who (in a single-fashion) extracted data using a standard electronic template to define study design, cancer type and stage, treatment specifications, patient demographics, mucositis outcome measure (OM or GI-M) and assessment scale/study endpoint, blinding, participant recruitment (consecutive/non-consecutive), statistical analyses and key findings related to mucositis prediction. Irrelevant papers were excluded before all data were synthesized by study leads (HRW/JMB).

Studies were stratified based on: 1) patient cohort (children (0-18 years), adults), 2) treatment modality (high dose chemotherapy/total body irradiation for hematopoietic stem cell transplantation, chemotherapy, radiotherapy, chemoradiation), 2) mucositis type (OM, GI-M) and 3) category of risk predictor (genetic, individual, tumor, treatment, comorbidities/medication use and miscellaneous). Information to assist with the interpretation of results was additionally extracted including, oncology cohort, tumor type, treatment specifications, sample size, drop-out rate, statistical approach(es) and mucositis assessment scale. Data were synthesised and organised into tables indicating evidence for each mucositis risk predictor. Factors were assessed for their association of OM and GI-M and assigned level 1 evidence when $\leq$3 high-quality studies identified an association with mucositis risk, level 2 evidence when 3-7 studies were identified and level 3 evidence when there were >7 studies. Inclusion of systematic review/meta-analysis data elevated the level of evidence. Importantly, these tables are intended to provide a simple and high-level overview of the factors identified to influence mucositis risk. They are intended to guide future research, **not** clinical practice.

Results

A total of 11018 papers were identified from our initial search strategy, 197 eligible for inclusion (Figure 1). After full text review, a further 85 papers were excluded largely due to mucositis not being a primary endpoint, no attempt of risk prediction, or case reports, leaving 113 papers for final inclusion. Studies included in this review were prospective observational, retrospective observational and secondary analyses of previously conducted randomized control studies. Most studies were conducted in adult patients, with only ten predicting mucositis in children.

The majority of studies evaluated a single risk prediction category (89/113) with cancer regimen-related factors the most common category. Studies evaluating genetic predictors were also common, and closely followed by those assessing factors related to the individual. The remaining studies evaluated the impact of tumor-related factors, biological parameters, medication and supportive care use, comorbidities, hygiene and the microbiota on mucositis outcomes.

Mucositis assessment

Almost all studies evaluated OM or GI-M in isolation, with only 24 of the 113 studies included evaluating both. There was significant diversity in type and quality of scales used to define mucositis presence and severity, with both clinical and patient-reported outcomes used. OM was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE; N=34, including studies that assessed OM and GI-M concurrently), Radiation Oncology Research Group (RTOG; N=23), the World Health Organization OM assessment scale (WHO; N=13), the Head and Neck Radiotherapy Questionnaire (HNRQ; N=1), the Oral Mucositis Assessment Scale (OMAS; N=1), the Oral Mucositis Index (OMI; N=4), the Oral Assessment Guide (OAG; N=1) and the Bearman's Oral Mucositis Scale (N=1). GI-M was assessed primarily using the NCI CTCAE (N=40, including studies that assessed OM and GI-M concurrently), however, other methods were also used including RTOG (N=4), WHO (N=3), the Inflammatory Bowel Disease Questionnaire (IBDQ); N=1), endoscopic evaluation (N=1), the bowel problem scale (N=1) [21] and intestinal wall thickness (N=1) [22]. In N=8 cases, mucositis severity was reported but the assessment scale used was not specified.

Treatment specifications define mucositis risk

The impact of treatment specifications, particularly dosimetric parameters, on OM and GI-M risk was evaluated in a variety of cohorts undergoing chemotherapy, radiotherapy and

chemoradiotherapy for a variety of solid and hematological tumors (summarized in Table 1). In all cases, “risk” is defined as an *increased* risk of mucositis unless specified. Clear dose-response relationships were identified for both OM and GI-M, with increasing doses of melphalan[23,24], methotrexate (MTX)[25] and radiation[26-30] predictive of OM, GI-M and late rectal morbidity (radiation only). Unsurprisingly, the volume of bowel exposed to radiation was a strong predictor of acute and late GI toxicity reported across several studies[31-38,21,39-41].

Treatment modality was also identified as an important mucositis predictor, with concurrent chemotherapy (in particular, cisplatin and cetuximab)[42,43] increasing the risk of OM and conventional 2D / 3D radiotherapy associated with more severe mucositis compared to intensity-modulated radiotherapy (IMRT)[44,41,45]. One study also reported higher risk of OM in only daily fractionated radiotherapy compared to altered fractionated schedules[46]. Fully ablative / myeloablative conditioning regimens (FAC/MAC) were consistently reported as predictors of mucositis in people with hematological malignancies, particularly when containing etoposide[47], high-dose melphalan[48,23,49], busulfan[50], doxorubicin[22] or total body irradiation[51]. Of interest, three studies also reported the potential effect of circadian rhythm on mucositis risk, with radiotherapy delivered in the evening associated with a higher degree of OM[52] and associated weight loss[53] in patients with HNC. This is in contrast to GI-M in women with cervical cancer, with overall diarrhea and grade III-IV diarrhea both significantly increased when radiation was delivered in the morning compared to the evening[54].

Genetic predictors of mucositis risk

Pharmacogenetic variants

Polymorphism affecting a variety of gene clusters were evaluated for their ability to predict mucositis risk (summarized in Table 2). Mutations in drug metabolizing pathways have been widely described for their influence on mucositis risk including methylenetetrahydrofolate reductase (MTHFR), cytochrome P450 (CYP), dihydropyrimidine dehydrogenase (DYPD), thymidylate synthase (TSMS), ATP-binding cassette (ABC) transporters and glucoronosyltransferase 1A (UGTA1) (for detailed description of these genes and their pathways please see[55]). Umbrella reviews support strong predictive power for *UGT1A1**6 and *28 for irinotecan-induced GI-M, *MTHFR* C677 for MTX-induced OM and GI-M, as well as *DPYD*- and *TYMS*-related SNPs for mucositis caused by fluoropyridimine and platinum-based therapies[56-58]. The impact of *MTHFR* mutations on MTX-induced OM were also confirmed in two large cohorts of allo-SCT recipients with the C677 TT genotype

associated with OM risk[59,51], as well as a cohort of pediatric patients undergoing chemotherapy for ALL[60].

Cell signalling variants

Genes related to cellular growth and DNA repair mechanisms were also evaluated for their impact on mucositis risk (Table 2). The *NBN* rs1805794 CC genotype, high RPM1 gene expression, *MDM2* (309 T>G) and *RB1* rs2227311 were all associated with a high OM risk in HNC patients[61-63,55]. *TGFBR25P* and *RAD51* G315C were associated with increased risk of GI-M in patients undergoing chemoradiotherapy for rectal and anal malignancies[64,65]. The largest study in this cohort also reported strong GI-M prediction based on the *VEGFR2* H472Q Q/Q rs1870377 genotype[66], however, this was not consistent across both cohorts included in the study. The *ERCC1* rs3212986 AA genotype was associated with a greater risk of late-onset GI-M in women with cervical cancer undergoing chemoradiotherapy[67]. Systematic review showed *XRCC1* rs25487 was strongly predictive of OM and GI-M risk in HSCT recipients[68], however this was not upheld in a smaller cohort of HNC patients[69]. XRCC1 polymorphic variants were also associated with OM risk in HNC patients treated with chemoradiation[70].

Immunogenetic variants

The third category of genetic factors evaluated for their impact on OM and GI-M were those related to inflammatory / immune pathways (Table 2). Immunogenomic studies report variants in pattern recognition receptor pathways, with *TLR2/TNFA* associated with heightened GI-M risk in people with gastric/colorectal cancers undergoing 5-FU-based chemotherapy[71]. TNF-related variants were also identified as predictors of GI-M, with the 1031 TT genotype (and *IL-1B-511* TC/TT) and baseline TNF mRNA expression associated with increased GI-M in patients undergoing chemoradiotherapy for GI[72] and oesophageal cancers[73], respectively. Similarly, *TNFRSR1A* -610T>G, *TNFA* -1211T>C (CC genotype) and *GHLR* -2531C>T were strongly associated with OM risk in HNC patients undergoing radiotherapy [74-76]. Radiation-induced oesophagitis was also linked mutations in a variety of inflammatory pathways, including *PSTG, TNF, IL6, IL4, and IL10*[43].

Uncategorised genetic predictors of OM risk also identified included the GT genotype in *EDN1* rs1800541[77], *ZNF24* rs11081899-A[78], *APEH* c.1521G>C (rs4855883 CC genotype)[75] and miR-1206 rs2114358 (homozygous GG)[79].

Individual traits linked with mucositis risk

Evidence from included studies for demographic and lifestyle predictors of mucositis was variable (summarized in Table 3). A strong and consistent outcome was female sex, which was linked to more severe chemotherapy-induced OM and GI-M across several studies[80-82,23,41,83]. Nonetheless, negative findings were also reported, with particularly robust evidence supporting no correlation between sex and OM in a study of 381 multiple myeloma patients[48]. Similarly, contradictory evidence supported male sex as a predictor of OM in HNC patients undergoing chemoradiotherapy[42].

Age was commonly reported as a predictor of mucositis, however there was no uniformity with both decreasing and increasing age reported as predictive of mucositis severity[84,41,25,85-87]. Similarly, the evidence was unclear regarding the impact of BMI on mucositis risk, with evidence indicating that low BMI[23,88] and a BMI of > 25[51] were predictive of OM risk. In contrast, whilst the evidence may be limited, there are consistent reports detailing baseline performance status, with low KPS[34] and ECOG performance status[24] predictive of OM and GI-M risk. Smoking was also identified as a predictor of OM in HNC patients and transplant recipients[69,88,89]. In contrast, one study also reported that non-smokers had a 2.7-fold increase in the risk of grade II-IV OM[90].

Several biological/laboratory parameters (assessed prior to therapy) were linked with mucositis risk (summarized in Table 3), including low colonic thymidylate synthase (TS) expression[91], ALT (>16Ul)[81], low urea[81], neutropenia[22], lymphopenia[42], low platelet counts[42], low hemoglobin levels[42], renal dysfunction[12] and serum creatinine[48], however the evidence was sparse and limited to a small number of stand-alone studies.

Comorbidities, medication use and previous therapy

There are limited data on the impact of comorbidities on mucositis outcomes (summarized in Table 3), with only one study reporting Inflammatory Bowel Disease (IBD) as a predictor of late-onset bowel injury caused by radiotherapy[28]. Similarly, the number of bowel movements at baseline was reported to predict GI-M risk[92]. Herpes simplex virus (HPV) was also reported to increase the risk of OM, with HPV+ patients reported to have a 6.8-fold increased risk of grade III-IV OM following chemoradiotherapy[90].

Few studies investigated the impact of medication use. One study reported multivitamin use prior to therapy as a predictor of lower OM scores[51]. Another study reported that antibiotic therapy for >10 days in the month preceding treatment was a predictor of GI-M (neutropenic colitis) in children with ALL[22]. This was also supported in a cohort of adult patients

undergoing conditioning chemotherapy for HSCT, with antibiotic use and GvHD prophylaxis with MTX predictive of OM[88].

Exposure to previous radiotherapy was reported as a predictor of OM in auto-SCT recipients[47], supporting reports of residual DNA damage as an independent predictor of OM risk[93]. Similarly, OM in previous chemotherapy treatment was reported to predict OM in HN patients undergoing adjunctive radiotherapy[85].

Tumor

Both tumor location[84,42], size[92] and stage[69] were reported as predictors of OM and GI-M, respectively in stand-alone studies (summarized in Table 4). A single study also reported a diagnosis of NHL (vs other hematological malignancies) as a predictor of OM[47]. In children, germinal tumors (vs non-germinal) and hematological malignancies vs CNS tumors (specifically Hodgkin's Lymphoma) were reported to increase the risk of HSCT-induced OM[50,94].

Areas requiring further investigation

While there were a large number of positive associations identified in our systematic review, we also identified negative studies or those that required further validation. For example, two studies reported no significant association between GI-M and *MTHFR* 677T mutations in patients undergoing chemoradiotherapy for rectal/anal cancer[95,96]. Similarly, two large studies (N=322, N=113) failed to identify any significant association between MTX transporter mutations and TYMS SNPs for OM risk in children with ALL[19,97] despite strong evidence supporting its role in adult cohorts[57]. While a systematic review of over 6500 patients supported a strong association between *XRCC1* (rs25487) and OM and GI-M risk in HSCT recipients[68], another reported no significant association in *XRCC1* mutations and OM risk in HNC patients[69]. Similarly, Lunberg et al., (2010) and Goutham et al., (2017) reported no significant effect of TGFB on OM despite a positive association identified for GI-M. Several studies, including a large prospective trial in 381 participants[98], also failed to identify any demographic influence on mucositis risk, including age, sex, BMI and race[99-101,24,48].

Discussion

This paper is the first to collect and synthesize factors identified to contribute to mucositis risk and symptom severity. The purpose of which is to provide a foundation for exploration of promising research pathways to optimize risk stratification tools. The panel reviewed 197 publications, with 113 eligible for assessment. The study inclusion period of 2000 - 2019 was chosen to reflect the rapidly changing face of cancer treatment and toxicity management with the advent of new technologies and supportive agents. Despite this, mucositis continues to be a major challenge in the delivery of effective care. It is critical that research efforts and resources are dedicated to identifying patients at risk of severe mucositis to mitigate the constellation of clinical, psychosocial and economic burdens with which it is associated, and potentially prevent long-term sequelae.

The most common factors investigated for their influence on mucositis were treatment-related factors, with dosimetric parameters evaluated across several oncology cohorts. Unsurprisingly, the strongest level of evidence was achieved for the volume of target organ (gastrointestinal tract and oral cavity, to lesser extent) exposed to irradiation[35,32,38,98,36,40,39,31]. Similarly, increasing doses of melphalan[23,24] and methotrexate[25], myeloablative conditioning therapy[102,103,88] and conventional RT (vs IMRT)[45] were all robustly demonstrated to increase an individual's risk of mucositis. However, these parameters provide little benefit in terms of risk as they are largely unmodifiable, and the concept that increasing exposure of the alimentary mucosa to cytotoxic therapy increases mucositis risk reflects what is already well understood from a pathobiological perspective. It is also important to note that while female sex was consistently linked with increased mucositis risk, this may not be a direct effect and is likely mediated through altered dosimetric parameters. Of the studies included that identified female sex as a risk factor, dosimetric parameters were not considered and in one case, females were reported to receive higher doses due to the way in which chemotherapeutic drugs are administered unadjusted for sex-dependent anthropometry[24].

Multi-parameter risk prediction modelling was uncommon in the studies included for review, with most hypothesis-driven focusing on a single parameter in a strictly defined cohort, and a compartmentalized/siloed viewpoint when it comes to treatment outcomes. While this provides focus to many studies, single candidate gene studies fail to address the complexities of mucosal injury and are limited by the overriding risk of false negatives, given the large number of participants required to obtain sufficient power[104]. Similarly, they are impacted with greater ease by confounding factors such as cohort heterogeneity, and gene-drug dose interactions need to be considered. As such, it is unsurprising to see such

inconsistency in the literature. Pathway analyses and genome-wide association studies (GWAS) have the potential to offer greater insight both pathobiologically and predictively[4], however they are rare, presumably due to the high logistical demand of patient recruitment, biospecimen collection and mucositis assessment, as well as cost. It was for this reason that we decided to include both association and risk prediction studies to provide a comprehensive overview of the current landscape regarding mucositis prediction/risk factors. So, while association studies provide a solid foundational knowledge of the factor that are likely to govern risk, they fail to provide tangible benefits in the provision of personalized supportive care. Future studies must therefore aim to prospectively develop multiplexed predictive strategies that are developed in training cohorts and validated in an independent manner. There has already been promising early work identifying clustered predictors and algorithms that predict high risk patients and their response to intervention[105-107]. Moving forward, coordinated efforts, appropriate infrastructure and consistent/comprehensive data collection across multiple locations with access to biobanks would drastically improve our ability to identify meaningful risk predictors, which will lay the foundation for personalized supportive care in which toxicity, efficacy and cost can be prioritized based on the individual's needs (Figure 2).

Critical to such efforts is the recognition of non-genomic risk predictors, which are likely to offer great predictive power when combined with treatment- and genomic-factors. This has been adopted in gerioncology, with a risk stratification tool developed using geriatric assessment variables, laboratory tests, patient-, tumor- and treatment variables [108,109]. While authors used a multiplexed approach, the variables included were primarily related to the performance status of the individual and treatment specifications, and thus could be improved by inclusion of modifiable biological and genetic parameters. An emerging area of personalized risk prediction, with relevance to geriatric oncology and the broader field is the microbiota. While this has primarily focused on immunotherapy-induced colitis, evidence suggests pre-therapy microbial composition dictates mucositis caused by both chemotherapy and radiotherapy, with early microbial changes predictive of ulcerative OM development[110,111]. While an area of increasing interest due to the modifiable nature of the microbiota, this is a relative new area of risk prediction and thus, few studies were included in this systematic review. Given the profound influence the microbiota has on both local mucosal and immune function, the influence of the gastrointestinal and oral microbiota is likely to be significant. Future biobanking efforts to evaluate pre-therapy microbial predictors and clinically-feasible methods of characterizing the microbiota (e.g. FAIMS) are therefore warranted.

With the development of multi-parameter risk prediction models and appropriate recognition of systems medicine approaches to analysis, risk prediction serves to not only identify high-risk patients, but also guide the development of next-generation interventions. These are likely to be unique to specific oncology cohorts and will almost certainly differ between adults and children. Disappointingly, in the 113 papers included in our analysis, only 10 addressed the topic of risk prediction in children. Developing risk prediction tools for children undergoing cancer therapy is of particular relevance as mucositis (and its associated manifestations) not only pose an acute impact on their quality of life, but are increasingly recognized for their influence on late effects in survivors of childhood cancer[112,113].

Risk prediction in children is also critical as many factors recognized for their influence on mucositis development in adults are likely to be poorly extrapolated to children (e.g. comorbidities, smoking status, medication use). Similarly, microbial communities are well recognized to differ between adults and children[114], hindering efforts to predict pediatric mucositis based on microbial enterotypes identified in adults. A growing body of evidence also suggests that mucosal barrier injury and microbial injury are catalysts for other late onset conditions (seen in both adults and children), including cardiac toxicity[115], graft versus host disease[13], fatigue[116] and neurocognitive impairment[117]. As such, a new frontier in risk prediction will be the interaction between acute and chronic toxicities, and the ability to mitigate chronic morbidity via the personalized prevention of acute injury.

In addition to its influence on late-onset toxicities, mucositis is well established to cluster with other significant toxicities, including fatigue, pain and blood stream infection, suggesting common molecular pathways[118,116,119,120]. It is therefore intuitive to suggest that symptom clusters also have common, or at least complementary, risk predictors. This has already been highlighted with the microbiota now recognized to predict multiple toxicities. Similarly, overlap exists in predictors of mucosal and hematological toxicities, reiterating the importance of targeting ubiquitous mechanisms of injury and inflammation with relevance to the broader field of regimen-related toxicities. These approaches will likely be based on multiplexed approaches, with weight given to certain parameters with particular relevance to organ-specific toxicities.

Despite a large number of positive studies included in this review, we also identified several negative studies that require further investigation or validation. While the number of negative studies is likely to be higher than those identified, biased by the pressure to produce positive findings, these studies also emphasize the challenges faced in conducting rigorous risk prediction studies. We identified a number of studies that had very low patient numbers, used non-validated assessment scales and poorly defined patient populations that were

undermined by high heterogeneity. Future studies must be appropriately powered and be guided by validated principles for mucositis assessment. The increased utilization and appropriate use of biobanking and shared data may help overcome the difficulties of recruitment to predictive supportive care studies and increase power. The involvement of bioinformatic and statistical experts to develop uniform methods of risk prediction analysis in the field of supportive care are also critical to success.

While this paper represents an important step in laying a foundation of knowledge regarding mucositis risk, it is not without its flaws. Firstly, we cast a large net to capture the breadth and variability of studies addressing mucositis risk prediction. This resulted in a large number of studies *or varying relevance* that were identified in our initial search strategy. With no uniform terminology relating to mucositis, particularly GI-M (i.e. diarrhea, gut toxicity, colitis), there is also the possibility that papers were not identified in our search strategy when they were not indexed using our defined terminology criteria. This highlights the need to standardize reporting of mucositis in clinical trials. Similarly, variable assessment scales and outcome measures prevented meta-analyses being performed, and severely compromised our ability to draw parallels between studies.

In conclusion, mucositis risk prediction is becoming increasingly recognized for its role in the provision of individualized cancer care. Despite identification of distinct factors associated with mucositis risk, we remain limited in our ability to identify high risk patients with current evidence undermined by inconsistencies, siloed approaches and unpowered studies. For significant advances in our ability to provide personalized supportive care, large and coordinated research efforts with innovative data sharing and input by statistical support personnel are required. These approaches should focus on multiplexed approaches that address related toxicities to provide a comprehensive risk evaluation of an individual with specific weighting reflecting their unique oncological scenario and personal requirements.

Take home messages and call to action

1. Personalizing supportive cancer care is critical and requires a solid foundational understanding of the factors that govern individual risk.
2. Multi-parameter risk prediction efforts with appropriate statistical approaches must be prioritized over restrictive, hypothesis-driven studies.
3. Risk prediction strategies identified in adults are not easily translated to children, and as such, specific risk stratification methods must be identified for pediatric cohorts.
4. Oral and gastrointestinal mucositis must be approached more holistically with risk prediction methods developed in parallel given the commonalities in pathobiology.
5. Validated assessment scales and outcome measures should be prioritized and used consistently.
6. Coordinated, international biobanking of patient biospecimens coupled with comprehensive data collection related to patient demographics, treatment specifications and outcomes are desperately required to enable more robust risk prediction efforts with greater power and clinical influence.
7. Future efforts in risk prediction should focus on multiplexed approaches that transcend a single toxicity and aim to predict clusters of related symptoms

Conflict of interest

No authors have any conflicts of interest relevant to the current work.
I (Hannah Wardill, corresponding author) and Joanne Bowen have full control of all primary data and agree to allow the journal to review data is requested.

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Tables

Table 1: Treatment-related factors associated with *increased* mucositis risk		
Factor	Mucositis type	Level of evidence
Cumulative dose	OM	++
	GI-M	+
Irradiation volume / area	OM	+
	GI-M	+++
Duration of therapy	OM	+
Concurrent chemotherapy	OM	++
Conditioning therapy containing TBI, busulfan, melphalan, etoposide)	OM	+
Conditioning therapy containing doxorubicin	GI-M	+
Myeloablative or fully ablative (vs non-myeloablative) conditioning	OM	++
	GI-M	+
Altered fractionated RT (vs once daily)	OM	+
3DCRT (vs IMRT)	GI-M	++
Infusion (vs bolus)	OM/GI-M	+
Evening radiotherapy	OM	+
Morning radiotherapy	GI-M	+

RT: radiotherapy; CRT: conventional radiotherapy; IMRT: intensity modulated radiotherapy; TBI: total body irradiation

** indicates presence of conflicting data*

Table 2: Genetic factors associated with *increased* mucositis risk		
Gene	Mucositis type	Level of evidence
Drug metabolizing/efflux pathways		
MTHFR	OM	+++
	GI-M *	+++
UGT1A1	GI-M	++
DPYD	OM	+++
	GI-M	+++
TYMS	OM *	++
	GI-M	++
DPYS	OM	+
IVS1	GI-M	+
CYP2B6	OM	+
ABCC1	OM	+
Cell growth/repair pathways		
NBN	OM	+
TGFB	GI-M	+
ERCC1	GI-M	+
RAD51	GI-M	+
VEGFR2	GI-M	+
ATM2/2	GI-M	+
RPM1	OM	+
MDM2	OM	+
CCND	OM	+
XRCC1	OM *	++
	GI-M	++
RB1	OM	+
Inflammatory and immune pathways		
IL1B	GI-M	+
PTSG	OM (oesphagitis)	+
IL4	OM (oesphagitis)	+
IL10 / IL10RA	OM (oesphagitis)	+
TNF	OM	++
	GI-M	+
TLR2	GI-M	+
GHLR	OM	+
Miscellaneous		
EDN1	OM	+
ZNF24	OM	+
APEH	OM	+
miR-1206	OM	+

** indicates presence of conflicting data*

Table 3: Patient-related factors associated with *increased* mucositis risk		
Factor	Mucositis type	Level of evidence
Demographic and lifestyle factors		
Female sex	OM *	++
	GI-M *	+
Age (extremities)	OM *	+
Smoking	OM *	++
Low BMI	OM *	+
Performance status	OM	+
	GI-M	+
Clinical/laboratory factors, comorbidities and medication use		
Low colonic TS	GI-M	+
ALT > 16UL-1	OM	+
	GI-M	+
Urea < 4.8 mmolL-1	OM	+
	GI-M	+
Neutropenia < 500 mm^3	GI-M	+
High serum creatinine	OM	+
Low DPD activity	OM	+
	GI-M	+
Leukopenia/lymphopenia	OM *	+
Hemoglobinaemia	OM	+
Low platelets	OM	+
Renal dysfunction	OM	+
HPV diagnosis	OM *	+
IBD / high number of daily bowel movements	GI-M	+
Recent antibiotic use	OM	+
	GI-M	+
Use of tongue immobiliser	OM	+
Lack of oral care protocol	OM *	+
Oral feeding (vs tube)	OM	+

BMI: body mass index; HPV: herpes simplex virus; IBD: inflammatory bowel disease; DPD: dihydropyrimidine dehydrogenase

** indicates presence of conflicting data*

Table 4: Tumour characteristics and diagnostic features associated with *increased* mucositis risk		
Factor	Mucositis type	Level of evidence
Orally-located tumour	OM	+
Stage	OM	+
Volume	OM	+
Germinal (vs non-germinal) tumor	OM	+
Haematological (vs CNS) malignancy	OM	+

CNS: central nervous system

** indicates presence of conflicting data*

Figures and figure legends

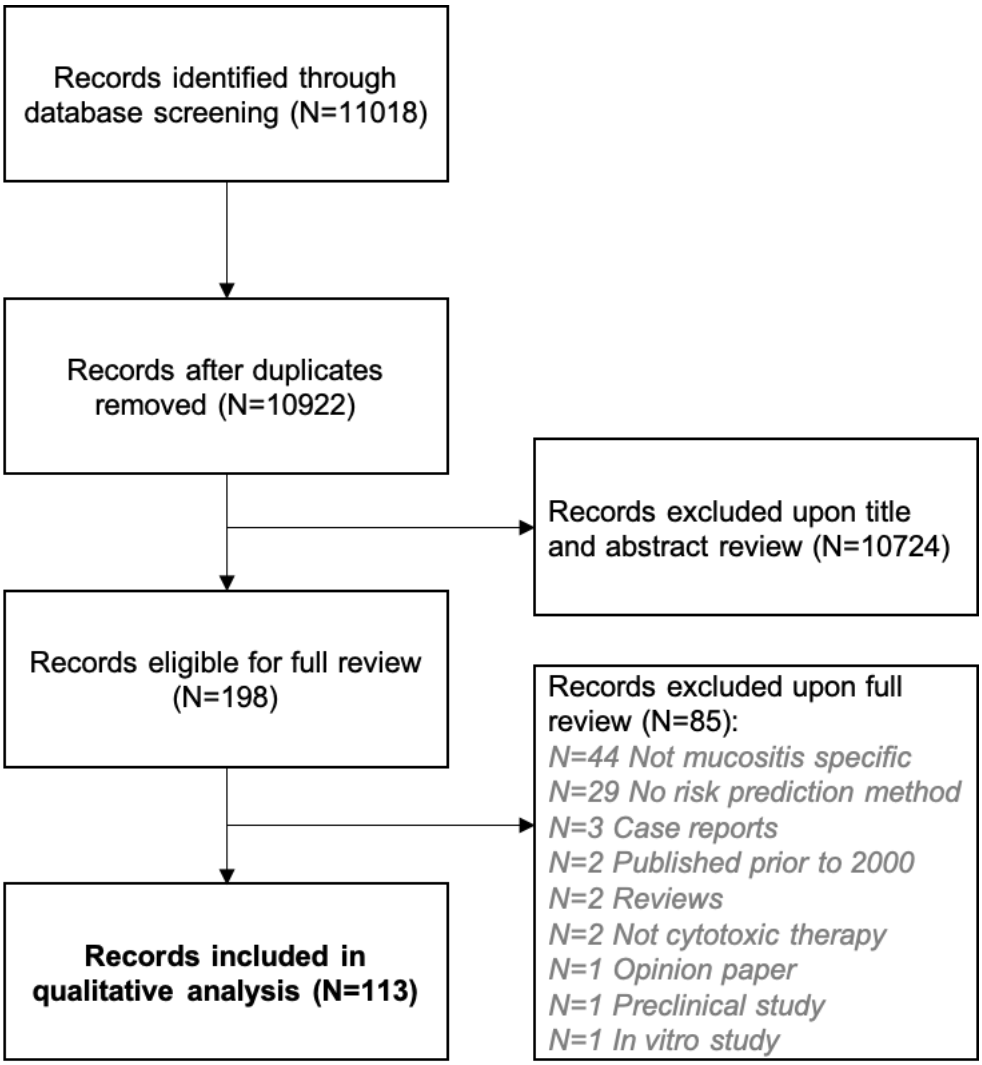

Figure 1: PRISMA flow chart.

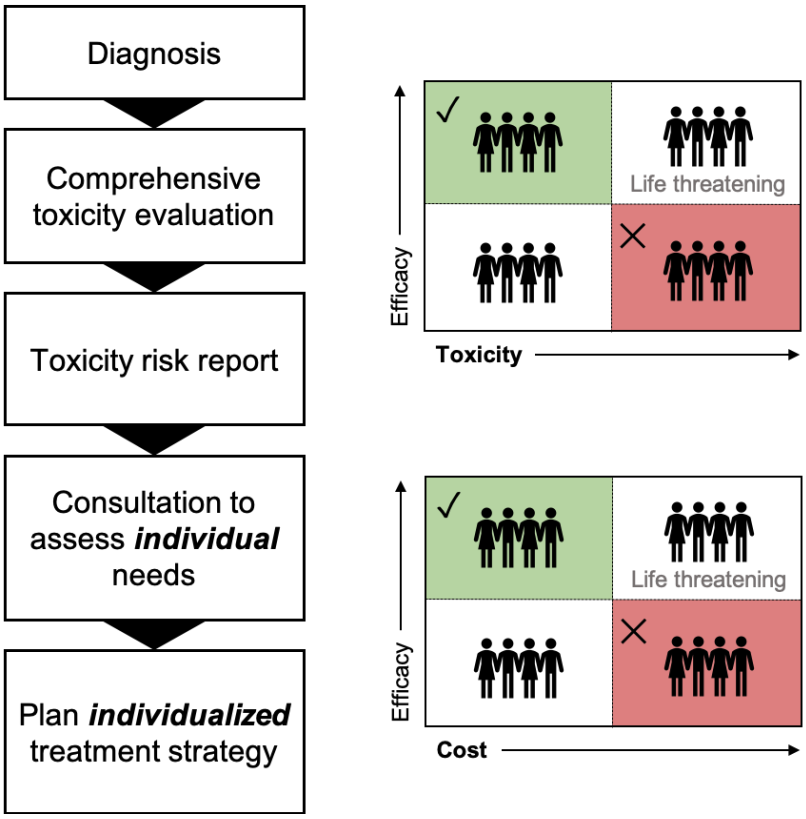

Figure 2: Conceptual framework for implementing personalized cancer therapy that optimizes efficacy, toxicity and economic outcomes based on comprehensive risk evaluation and individual needs of the patient. Multiplexed risk evaluation tools should provide risk stratification for all toxicities/side effects, providing the option to preferentially avoid toxicities considered most impactful for the individual whilst optimizing efficacy and reducing cost. Proactive and tailored supportive care can be directed to high risk patients, while low risk patients can avoid unnecessary interventions and be treated in an out-patient setting with confidence. Clear risk evaluation also provides patients with greater clarity regarding treatment outcomes which can be used to guide decision making particular in end-of-life care when quality of life may be prioritized over quantity.

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