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Host - Tumor Determinants of Chemotherapy Toxicity and Resistance in the Postoperative Management of Geriatric Colorectal Cancer: A Mechanistic Scoping Review

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Abstract

Purpose

The postoperative management of elderly colorectal cancer (CRC) patients presents a persistent clinical dilemma in which efforts to optimize adjuvant chemotherapy efficacy are constrained by heightened vulnerability to treatment-related toxicity. Reliance on chronological age and body surface area–based dosing fails to account for substantial biological heterogeneity in older adults. This review examines whether treatment failure in elderly CRC patients reflects true therapeutic inefficacy or a mismatch between standard regimens and age-related biological factors.

Methods

We conducted a scoping review of peer-reviewed literature published between 2000 and 2025 using PubMed, Scopus, and Web of Science. Eligible studies included original human research, translational studies, and meta-analyses addressing immunosenescence, frailty, age-related pharmacokinetic alterations, tumor microenvironment changes, consensus molecular subtypes, and clinical outcomes following adjuvant chemotherapy in elderly CRC patients.

Results

The evidence demonstrates that immunosenescence, sarcopenia, frailty-related alterations in drug metabolism, and tumor microenvironment remodeling substantially influence chemotherapy tolerance and efficacy in older adults. In parallel, a higher prevalence of mesenchymal-like tumor phenotypes, particularly consensus molecular subtype 4, is associated with reduced therapeutic outcome. These interacting host and tumor factors frequently result in dose reductions, early discontinuation, and apparent chemoresistance, driven predominantly by host susceptibility rather than intrinsic tumor resistance.

Conclusion

Treatment failure in elderly CRC patients more often reflects biological mismatch than lack of drug efficacy. This review underscores that incorporating biological age, immune function, and tumor subtype into adjuvant decision-making may reduce toxicity-related attrition and improve survivorship. Integrating these insights allows clinicians to develop biologically informed, precision-based therapeutic strategies tailored to geriatric colorectal cancer care.

1 Introduction

The clinical treatment of colorectal cancer (CRC) in gerontology patients is typified by such a paradox: tumors in this population often evolve rapidly, yet therapeutic options are limited by frailty and comorbidities. As the world's demographics age (the so-called silver tsunami), CRC rates are expected to soar, underscoring the immediate need to re-evaluate treatment paradigms. Oncologists have the option

to balance between the cytotoxic activity of chemotherapy and the physiological vulnerability of the older population, in which toxic effects are likely to be observed mainly due to underlying diseases and polypharmacy (57, 85). Such a challenge requires an approach that neither ignores the interplay between treatment toxicity and host vulnerability nor remains insensitive to the disease's changing biology. CRC is one of the most common malignancies evaluated epidemiologically in individuals older than 65 years of age, which underscores the necessity of age-specific interventions to address it (12, 18). Old age not only increases cancer risk but also is associated with changes in tumor biology, with older patients often presenting with aggressive or late-stage disease, including increased rates of metastasis. Host frailty and tumor aggressiveness converge, making it harder to design an effective treatment regimen and highlighting the importance of precision in therapeutic decision-making. The rationalized therapy in this case requires a careful balancing of efficacy and harm reduction, especially for post-surgery patients entering a critical adjuvant period.

Post-operative survivorship is a critical stage in the management of elderly patients with CRC, where adjuvant chemotherapy choices and timing could be used to determine the recurrence rates and survival in greater detail. The pharmacokinetics and drug tolerance are altered by age due to factors such as immunosenescence, altered drug metabolism, and decreased organ reserve, which tend to increase systemic toxicity while also impairing therapeutic efficacy (15). Although these factors have clinical importance, there remains a significant gap in evidence-based practice for the elderly, as the older population is underrepresented in randomized trials. The main question discussed in this review is as follows: how is the combination of age-specific biological barriers, immunosenescence, altered pharmacokinetics, and mesenchymal tumor subtyping (CMS4) used to establish a trade-off between fatal systemic toxicity and acquired chemoresistance in the post-surgical adjuvant window? This comprehensive review will shed light on the mechanisms of therapeutic failure and resistance in older patients with CRC by combining recent discoveries in host physiology and tumor pathology. One of the unique contributions of the work is the focus on developing a conceptual framework to inform personalized treatment strategies that can positively influence treatment outcomes and reduce toxicity.

The clinical environment of geriatric cancer patients presents a challenge that can only be tackled by comprehending the overlap between the tumor biology, patient frailty, and the complex biochemistry of the disease and treatment. Focused studies in these areas, supported by joint clinical models, can address knowledge gaps and improve the treatment of this high-risk group. Finally, the establishment of the strategies that balance the fatal trade-off between the toxicity and chemoresistance will be crucial to the better survival and quality of life in the elderly survivors of the CRC. To support this synthesis, the literature search identified peer-reviewed articles published between 2000 and 2025 by reviewing large biomedical databases, including PubMed, Scopus, and Web of Science. Priority was given to original human studies, translational research, and high-quality meta-analyses that focused on age-related pharmacokinetic changes, immunosenescence, consensus molecular subtypes (especially CMS4), tumor microenvironment remodeling, and clinical outcomes of adjuvant chemotherapy in elderly colorectal cancer patients.

2 MATERIALS & METHODS

We conducted a scoping review to ensure a comprehensive mapping of the existing evidence in geriatric colorectal cancer studies. We adopted the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist to ensure rigorous reporting of the evidence landscape surrounding geriatric colorectal cancer (CRC). Our objective was to map the intersection of host frailty, pharmacokinetic (PK) variability, and mesenchymal (CMS4) tumor biology.

2.1 Search Strategy

A comprehensive literature search was conducted across three primary biomedical databases: PubMed, Scopus, and Web of Science, to identify relevant studies published from January 2000 through December 2025. The search combined Medical Subject Headings (MeSH) with free-text keywords to maximize sensitivity and capture all pertinent publications relating to chemotherapy toxicity, resistance mechanisms, host determinants, and aging in colorectal cancer. Search terms included, but were not limited to, combinations and variants of *“colorectal cancer,” “chemotherapy toxicity,” “chemoresistance,” “pharmacokinetics,” “immunosenescence,” “aging,” “geriatric,” “tumor microenvironment,”* and *“consensus molecular subtypes.”* Boolean operators (AND, OR), truncation, and adjacency/search field limits were applied as appropriate for each database to refine retrieval while maintaining breadth.

2.2 Inclusion and Exclusion Criteria

Our approach included a broad spectrum of evidence to identify critical knowledge gaps.

Inclusion: We prioritized original human studies, translational research, and high-quality meta-analyses focusing on patients aged \ 65 years. Studies exploring the synergy between host physiology and tumor pathology were central to our selection.

Exclusion: Articles focusing exclusively on younger populations, non-English publications without available translations, and papers lacking a clear focus on the post-surgical adjuvant window were excluded.

2.3 Evidence Selection and Data Mapping

We captured emerging development in this study through a reference chaining approach, in which the reference lists of key publications were manually reviewed to identify studies that had not yet been indexed in major databases

2.4 Synthesis of Results

Data were synthesized into an Integrated Conceptual Framework. We moved beyond simple data extraction to create a "Decision Matrix" (see Fig. 3), which maps the Lethal Trade-off between systemic toxicity and acquired chemoresistance. This mapping provides a visual representation of the clinical gaps and the future therapeutic advancements required for personalized geriatric care.

3 Pharmacokinetic & Pharmacodynamic Barriers to Efficacy

3.1 Sarcopenia and Fallacy of Body Surface Area (BSA) Dosing

Body surface area (BSA) has traditionally been used as the standard for chemotherapy dosing. Although generally effective in younger age groups, BSA may easily overestimate pharmacokinetic requirements in the geriatric population, where sarcopenia, a progressive loss of skeletal muscle mass and strength, is common. Sarcopenia changes the balance between fat and lean mass, restructuring drug distribution and metabolism in ways that cannot be understood using BSA standard calculations (62, 75).

The use of BSA alone can be under and over-dosed to a pronounced degree, especially when patients have notable muscle wasting. In underdosing, the therapeutic effect can be compromised, and in overdosing, there is an increased risk of severe systemic toxicity. Population pharmacokinetic studies reveal that the precision of dose predictions in older adults improves when body composition measures, i.e., lean body mass and fat mass, are included (68, 52). This evidence confirms that there is a change in the individualization of dosing regimens that considers sarcopenia and other age-related physiological alterations.

3.2 Age-Related Decline in Renal Clearance and Hepatic Metabolism.

Several studies have shown that the ability of the body to clear drugs is naturally reduced with age. Renal dysfunction, such as decreased glomerular filtration rate and elevated serum creatinine, decreases the excretion of drugs through the kidneys, including oxaliplatin, thereby promoting drug accumulation and toxicity (2, 64). At the same time, hepatic metabolism is characterized by considerable age-related changes. A decrease in liver size, blood flow through the liver, and hepatic enzyme activity, specifically cytochrome P450, alters the metabolism of most chemotherapy agents (80, 82). Other metabolic pathways are inhibited, and others may even be counterintuitive, leading to erratic pharmacokinetic changes.

Long-term research indicates that older patients with CRC who have reduced renal or hepatic clearance may have increased dose-limiting toxicity compared to younger groups, and age-specific, systematic dosing schedules are required (99, 101). These findings highlight that traditional dosing regimens might be insufficient in models of the distinct pharmacokinetic environment in elderly people, underscoring the need for more accurate predictive models.

3.3 Mechanism of Lethal Systemic Toxicity: Grade 3–4 Neuro- and Cardiotoxicity

Among the most problematic adverse effects of chemotherapeutics in elderly patients are severe neurotoxicity and cardiotoxicity. Oxaliplatin and doxorubicin are agents with a high likelihood of grade 3–

4 toxicity, which is increased by age-related pharmacokinetic variations (35, 64).

The major causes of neurotoxicity occur with long-term systemic exposure to the effect of impaired renal and hepatic clearance, which results in the accumulation of drugs in the central nervous system. This accumulated exposure may initiate peripheral neuropathy and other neurodegenerative complications (68, 101). Another cause of cardiotoxicity is prolonged exposure and reduced cardiovascular reserve. The cardiotoxic agents can be maintained systemically, and this predisposes elderly patients to heart failure, arrhythmias, and other complications, which are increased by the presence of comorbidities (9, 54, 97). Taken together, these results provide a warning and require close attention during the prescription of such powerful agents to the elderly population, as they can no longer retain drugs and have an increased risk of experiencing severe toxicities.

3.4 Effect of Polypharmacy on Bioavailability of Adjuvant Chemotherapy

Polypharmacy is very common in elderly patients with CRC, and it is a major pharmacokinetic challenge. The use of multiple drugs simultaneously, such as antihypertensives, antidiabetics, etc., alters drug metabolism and transporter activity, thereby directly influencing the bioavailability and clearance of chemotherapeutic agents (2, 64, 99). In line with the general findings of various studies, interactions can either increase toxicity or reduce therapeutic efficacy, depending on the type of competing pharmacodynamic mechanisms or shared metabolic pathways. Indicatively, the interaction between drugs that interact with the same CYP450 enzymes or renal transporters may unintentionally modify the systemic exposure of chemotherapy, resulting in either underdose or life-threatening outcomes (35, 68, 80). Such complexities demand in-depth medication assessment, therapeutic drug monitoring, and personalised dose adjustments to achieve optimal outcomes in this group.

4 Molecular Landscape: CMS4 and the Aging Microenvironment

4.1 Mesenchymal (CMS4) Subtype Enrichment in Elderly Populations

Colorectal cancer has been found to be highly heterogenous with CMS4 subtype being a mesenchymal phenotype that is always characterized by poor prognosis and resistance to chemotherapy (10, 26). There is evidence that CMS4 tumours are disproportionately common in elderly patients, reflecting the cumulative effects of age-related genomic alterations and microenvironmental remodelling (96). This mesenchymal transition is induced by increased signalling via transforming growth factor-β (TGF -b) and interleukin – 6 (IL-6), which are often up-regulated in the elderly, resulting in a more aggressive tumour phenotype (47). These patterns of therapeutic response represent the clinical significance of CMS4 enrichment in older patients. Patients with CMS4 tumours tend to show limited response to conventional chemotherapeutic drugs, such as FOLFOX, partly because of the activation of epithelial-mesenchymal transition (EMT) pathways that increase survival and drug resistance (1). This evidence highlights the

importance of designing therapeutic approaches that are sensitive to the cellular and molecular conditions of mesenchymal tumours in the elderly, as standard dosages and regimens may not achieve sufficient efficacy (98). This review examines the consensus molecular subtype (CMS) landscape in elderly colorectal cancer and underscores the disproportionate impact of mesenchymal CMS4 tumors on therapeutic resistance and clinical outcomes in this population (Fig. 1).

4.2 The Senescence-Associated Secretory Phenotype (SASP) as a Driver of Resistance

The senescence-associated secretory phenotype (SASP) is a central pathway through which ageing enhances chemoresistance. The release of a range of pro-inflammatory cytokines, chemokines, and growth factors by senescent cells remodels the tumor microenvironment, making it immunosuppressive and pro-tumourigenic (71, 83). SASP factors, such as IL-6 and IL-8, in colorectal cancer play a direct role in maintaining tumor cell survival during chemotherapy, thereby facilitating tumor cell survival under cytotoxic stress (40, 83, 89). SASP is also involved in immune evasion and in strengthening stromal remodeling, forming positive feedback loops that increase chemoresistance. An example is tumor-associated macrophages, which have been shown to enhance IL-6-mediated survival signalling in tumour cells, thereby making them less vulnerable to apoptotic agents such as 5-fluorouracil (29, 98). These dynamics are vital to understand because the SASP can also affect the efficacy of immunotherapies, indicating that age-specific regulation of the tumor microenvironment can potentially maximize treatment responses. This section summarizes SASP-driven stromal and immunological remodeling as a central mechanism underlying acquired chemoresistance in the aged colorectal cancer microenvironment (Fig. 2).

4.3 Stromal Remodeling: How the Aging ECM Impairs Drug Penetration

In addition to molecular signaling, the physical structure of the tumor microenvironment (TME) strongly influences drug delivery. Age-related remodelling of the extracellular matrix (ECM) increases its density and stiffness, generating mechanical forces that prevent the uptake of chemotherapeutic agents in old age (93). Collagen and hyaluronic acid often reside in cross-linked assemblies composed of oligomers, which limit diffusion, especially of larger drug molecules (51, 88).

Stromal remodeling in aging is not merely a barrier to drug delivery; it is also a pro-survival process of tumor aggressiveness. The resident cancer-associated fibroblasts (CAFs) residing in the aged ECM release factors that promote epithelial-mesenchymal transition (EMT), survival signalling, and resistance to cytotoxic therapies (47, 83). These data highlight the importance of introducing measures to address the TME, e.g., CAF inhibition or ECM modulation, to restore chemosensitivity and improve outcomes in elderly patients with colorectal cancer (CRC).

4.4 Epigenetic Drift and Development of Acquired Chemoresistance

Progressive epigenetic drift, which plays a central role in the development of chemoresistance, is also a consequence of aging. Cumulative DNA methylation and histone alterations may also modify gene-expression programmes in CRC, allowing tumor cells to endure chemotherapeutic stress and re-enter the cell cycle, a process known as anastasis (59, 92).

Such epigenetic flexibility promotes tumor adaptability, helping it avoid the cytotoxic effects of a standard regimen. Notably, some epigenetic changes predispose reliance on a particular survival mechanism, which can be exploited as a therapeutic target. Epigenetic-target intervention in conjunction with standard chemotherapy could thus offer a solution to overcome resistance, especially in patients with CMS4 tumors who are older adults with widespread age-related epigenetic changes (16, 27). Collectively, these interventions converge on CMS4 enrichment, SASP-mediated immunomodulation, ECM remodelling, and epigenetic drift, defining a molecular environment in aged patients with CRC that predisposes to chemoresistance. This scenery underscores the need to adopt a tumor-intrinsic and microenvironment-based approach when developing therapies. By considering mesenchymal phenotypes, senescent signalling, and mechanical miniaturisation, the post-surgical adjuvant window can be reconceptualised as a window of systemic compromise or a window of opportunity for a precision-targeted intervention.

5 Immunological Barriers and Therapeutic Evasion

5.1 Immunosenescence: T -Cell Exhaustion and Decreased Surveillance Post Surgery

Age-related loss of immune competence, or immunosenescence, is a severe impairment of the capacity of T - cells to generate effective anti-tumor responses. Up-regulation of inhibitory receptors, including PD-1 and CTLA-4, and reduced proliferation and activation are constant features of ageing and T-cell exhaustion (8, 14). This impairment is especially critical during the post-surgical adjuvant treatment period, when efficient immune monitoring is necessary to identify and eliminate residual cancer cells.

Several studies have shown that older patients exhibit increased biomarkers of T-cell exhaustion, such as lower CD28 levels and higher PD-1 levels, which are associated with worse post-chemotherapy outcomes in CRC (8, 29, 41). This T-cell dysfunction impairs the host's response to cytotoxic agents, potentially leading to tumor recurrence. Notably, T cell exhaustion in elderly people does not depend solely on age; it is also driven by the TME, which enhances immunosuppressive conditions and further reduces T cell function (23, 36).

These results highlight the urgent need for interventions to restore or improve T-cell activity in the elderly, including immune checkpoint inhibition or methods to revitalize exhausted T-cell subsets. In geriatric patients with CRC, normal adjuvant chemotherapy would not reach its full therapeutic potential without treatment of this immunological inadequacy.

5.2 Inflammaging: The Role of Chronic Inflammation in Tumor Recurrence

Another critical impediment to effective treatment in older patients is chronic, low-grade inflammaging, so-called inflammaging. It is a systemic inflammatory condition resulting from accumulated age-related stressors and facilitates tumour progression and resistance to treatment (7, 21). Age-related increases in key inflammatory mediators such as IL 6 and TNF-alpha are consistently linked to mechanisms that prefer tumor survival and recurrence (24, 78). Clinical evidence indicates that increased inflammatory phenotypes correlate with worse outcomes in older patients with CRC. Indicatively, high IL-6 stimulates epithelial-mesenchymal transition (EMT) to sustain residual tumor growth and recurrence following adjuvant chemotherapy (31, 36, 95). Although inflammation may, in certain situations, boost anti-tumor immune responses (53, 78), in geriatric populations, pro-tumor effects predominate. Consequently, defining the dual role of inflammation in ageing and cancer may lead to the development of targeted interventions that reduce chronic inflammation and enhance anti-tumour immunity.

Inflammation remains a prime target in adjuvant therapy, and by targeting inflammaging, the supportive niche that tumor cells with residual survival capacity utilize may be diminished, allowing immune-mediated clearance to become effective. Combining anti-inflammatory measures with chemotherapy or immunotherapy may restore the post-surgical microenvironment, thereby increasing response rates in older patients with CRC.

5.3 Impairment of Immunogenic Cell Death (ICD) in the Geriatric Host

Immunogenic cell death (ICD) is a critical mechanism through which cancer therapies trigger systemic anti-tumor immunity. Nonetheless, ICD appears to be impaired in elderly hosts, preventing the use of effective agents such as 5-fluorouracil (5FU) (39, 44). This defect is predetermined by intrinsic defects in cell-death pathways in addition to impaired peripheral immune responses, which are required to recruit and activate dendritic cells (94). Age-related changes in damage-associated molecular pattern (DAMP) expression also cause inhibitory effects on ICD, suppressing antigen presentation and T-cell activation (32, 94). Moreover, the non-physiological cytokine milieu characteristic of aged patients can disrupt ICD induction, reducing the immunogenicity of chemotherapy. Some studies indicate that these effects can be partly offset by changes in timing and dose, and here, contextualised treatment approaches are likely to be of crucial importance in geriatric CRC management (77, 100).

Although the role of ICD in therapeutic success has been established, T-cell senescence, inflammaging, and ICD have not been studied comprehensively. This is an extremely critical knowledge gap to address. Closing this gap is important to develop adjuvant regimens that are not only cytotoxic but also able to harness residual immune function to prevent recurrence. Individualized strategies that consider the remodeling of the aging immune system can turn a potentially susceptible phase of post-surgical care into a remission-inducing phase.

6 The “Lethal Trade-off”: Trial Critiques and Clinical Realities

6.1 Overtreatment vs. Undertreatment: Dose De-escalation Impact on Survival

There is a sharp clinical paradox with the issue of chemotherapy dosing decisions in elderly patients with CRC. Aggressive treatments are used to ensure that the tumors are as much as possible controlled, although they tend to exceed the ability of weak elderly persons, leading to drastic toxicities. There is now an emerging body of evidence that dose de-escalation, when used wisely, can reduce toxicity without impairment and, in certain instances, even improve overall survival (76, 81). Recent meta-analyses indicate that less intensive regimens can improve quality of life without compromising survival in the chosen elderly cohort (43, 44). Optimally de-escalated treatments prove the fact that personalized treatment can be equally efficient with reduced side effects, and it is time to stop treating everyone in the same way (67). Nevertheless, there is no unified set of criteria for increasing or decreasing the dosage, which makes it difficult to make clinical decisions, and physicians have to rely on their own judgement of frailty (22).

Conversely, inappropriate dosing can result in overtreatment of vulnerable patients still undergoing active treatment. The full-intensity therapy applied to geriatric patients with low physiologic reserve may contribute insignificant benefit and cause severe harm. The boundaries between what requires treatment and what is excessive are not always clear and depend on clinicians' perceptions and institutions' practices (73). Consequently, establishing robust clinical protocols to guide dose adjustments is critical, ensuring that the trade-off between efficacy and toxicity favors patient-centered outcomes (86).

6.2 Limitations of Current Evidence: The Underrepresentation of Frail Cohorts

A persistent limitation in CRC research is the underrepresentation of frail elderly patients in clinical trials. Most studies enroll younger, healthier participants, leaving a gap in understanding how standard chemotherapy protocols perform in the frail population (38, 90). Consequently, current evidence may overestimate efficacy and underestimate toxicity in real-world elderly cohorts. The pharmacokinetic and pharmacodynamic differences introduced by age also make treatment more challenging, as standard regimens such as oxaliplatin and 5-fluorouracil are more toxic to older adults (19, 47, 76). Neurotoxicity, myelosuppression, and cumulative adverse effects are common, but there is limited evidence advocating how these risks can be reduced. Lack of specific studies in frail populations with colorectal cancer (CRC) has also been a major omission, and therefore, regulating agencies like the FDA have highlighted the necessity of age-and-vulnerability-specific research in this group (6, 63–65).

To produce evidence-based adjustments that address the needs of frail cohorts, their inclusion is imperative to generate information that will lead to appropriate changes in therapeutic regimes for

ageing CRC. Without this focus, trial outcomes risk misrepresenting both the safety and utility of adjuvant chemotherapy in geriatric patients.

6.3 Biological Age vs. Chronological Age: Moving Toward Comprehensive Geriatric Assessment (CGA)

Reliance on chronological age alone has proven inadequate in guiding therapy for elderly CRC patients. Biological age, encompassing comorbidities, cognitive function, nutritional status, and immunologic reserve, provides a more precise metric to inform treatment intensity (3, 69). Functional capacity, rather than years of life, will help clinicians more effectively customize regimens that are both therapeutically effective and non-harmful. This approach is operationalized through comprehensive geriatric assessments (CGA) and structured tests that integrate physiological, cognitive, and psychosocial factors into treatment planning (72). It has been shown that CGA-directed therapy is effective in enhancing patient outcomes by classifying patients to receive the correct dose intensity and supportive measures to allow the safe use of cytotoxic therapy (70).

Although there are undisputable advantages, CGA implementation has practical challenges. Its common practice is hampered by time constraints, resource limitations, and perceived complexity in oncology clinics (48). However, systematic application of CGA in trial design may yield vital information, enabling protocols to compensate for biological variability and maximise life without causing unnecessary adverse effects. Together, the twin issues of overtreatment and underrepresentation of frail populations highlight one of the main contradictions in geriatric oncology: how to manage tumors without compromising the physiological limitations of the ageing population. Future research must prioritize frailty-informed dosing frameworks and integrate CGA to guide individualized therapy, thereby reconciling the "lethal trade-off" between efficacy and toxicity in this vulnerable population

7 Synthesis and Integrated Conceptual Framework

7.1 Interactions between Host Physiology and Tumor Pathology

The dynamic interaction between host physiology and tumor pathology defines therapeutic outcomes in elderly patients having colorectal cancer (CRC). Aging of the immune system, or immunosenescence, impairs the ability of T cells to develop effective anti-tumor immunity, whereas persistent low-grade inflammation amplifies systemic vulnerability and increases susceptibility to chemotherapy-induced toxicity (14, 41). At the same time, the shift in tumor biology among older individuals often involves more aggressive phenotypes, especially the mesenchymal CMS4 subtype, which is typified by invasion-, metastasis-, and chemoresistance-promoting signalling pathways (3, 72). These combined weaknesses form a positive feedback loop: the breakdown of host defenses promotes tumor growth, whereas tumor aggressiveness further impairs immune surveillance and increases therapeutic risk (37). The Colorectal Cancer Subtyping Consortium highlights the need to use integrative models that explain treatment

response variability, accounting for both host and tumor features (17). The CMS-specific differences are clinically relevant: e.g., CMS2 tumors are generally more favourable and chemosensitive than CMS4 tumors, which explains the importance of contextualising tumor biology alongside the patient's physiological reserve (33, 46). Therefore, only with knowledge of these interactions can treatment decisions be framed, especially during the post-surgical adjuvant period, when the efficacy-tolerability balance is paramount.

7.2 Proposed Decision Matrix for Personalized Adjuvant Therapy in the Elderly

Building on the synthesis of biological and clinical insights, a structured decision matrix emerges as a tool for guiding adjuvant therapy in elderly CRC patients, as shown in Fig. 3. This framework integrates chronological age, biological age (assessed via comprehensive geriatric assessment), tumor subtype, and comorbidities, providing a roadmap for individualized treatment planning (38 69).

1. **Assessment of Biological Age**: Comprehensive Geriatric Assessment (CGA) should be employed to evaluate functional status, comorbidities, and nutritional parameters. This assessment enables tailored dosing strategies that reflect the patient’s physiological tolerance, rather than relying solely on chronological metrics.
2. **Tumor Classification**: Integrate consensus molecular subtyping into initial diagnosis. Patients with CMS4 tumors, for example, may warrant alternative regimens targeting mesenchymal signaling pathways, such as TGF-β modulation, or therapies designed to circumvent EMT-driven chemoresistance (13, 28).
3. **Dose Adjustments**: Develop individualized protocols for dose de-escalation guided by CGA and tumor subtype. In frail patients, prioritizing tolerability can prevent severe toxicities without compromising therapeutic effect, aligning survival benefits with quality of life considerations (12).
4. **Monitoring and Adaptation**: Implement continuous clinical and radiographic monitoring to adjust therapy in real time. This iterative feedback loop allows clinicians to respond to changes in patient status or tumor behavior, optimizing outcomes while minimizing adverse effects.
5. **Multidisciplinary Integration**: Foster collaboration across oncology, geriatrics, pharmacology, and palliative care. A coordinated approach ensures that diverse expertise informs decision-making, addressing the multidimensional challenges inherent in treating older CRC patients (3, 72).

By operationalizing this decision matrix, care teams can navigate the complex interface of host frailty and tumor aggressiveness, ensuring that adjuvant chemotherapy is both safe and effective. This framework emphasizes precision oncology in the geriatric setting, moving beyond age-based heuristics to strategies that account for individualized risk profiles.

Ultimately, this integrated approach reframes post-surgical management in elderly CRC patients. By explicitly linking host and tumor characteristics to clinical decision-making, the matrix provides a roadmap for optimizing survival, minimizing toxicity, and preserving functional independence. As the

aging population grows, such structured, evidence-informed frameworks will be essential in transforming geriatric oncology from reactive management toward proactive, patient-centered care.

8 Future Perspectives and Conclusion

The future of CRC treatment in the elderly population lies in incorporating biological age, tumor biology, and the patient's specific vulnerabilities to create more accurate, effective, and tolerable treatment plans. The key aspect of this change is the application of an age based on biological markers, providing a more humanized evaluation than chronological age alone. The use of Epigenetic clocks, which are based on patterns of DNA methylation, indicates they are potential tools for measuring physiological reserves, offering actionable data for chemotherapy selection and dosing in frail patients (5, 55). In complement to this method, liquid biopsies enable dynamic, non-invasive monitoring of tumor-derived biomarkers, allowing clinicians to assess tumor evolution, treatment response, and emerging resistance during treatment (30). The combination of these tools might make the post-surgical adjuvant period a more precision-directed, effective, and tolerable intervention in elderly individuals.

In addition to perfecting the method of patient evaluation, emerging treatment approaches to address age-related obstacles have huge potential. Chemoresistance in elderly CRC patients is mediated by the senescence-associated secretory phenotype (SASP) and stromal remodelling. Chemosensitivity can be restored and immune-based tumor control enhanced by interventions that reduce SASP mediated inflammation or manipulate the tumor microenvironment (42). An example of these is the use of pathway inhibitors that are often overexpressed in senescent tumor cells, such as NF-κB and TGF-b which have demonstrated preclinical activity in reorganizing tumor stroma interactions and causing tumor resistance to therapy (4, 60). Modifying the impact of tumor-associated fibroblasts and other stromal components may also enhance drug penetration, reduce systemic toxicity, and improve overall treatment response (91).

To combine these biological and therapeutic understandings into practice, it is necessary to have organized, patient-based systems. Personalized treatment paradigms integrating CGA-based biological age measurements, tumor molecular imaging, and personalized dosing regimens could provide a roadmap for safer, more efficient interventions. These methods enable clinicians to classify patients by physiological reserve and tumor aggressiveness, thereby optimizing dose, making timely adjustments, and preventing preemptive toxicity. Notably, this paradigm focuses on maintaining functional status and quality of life, rather than conventional survival indicators, because geriatric oncology care has multifaceted objectives.

The decision matrix described above outlines how these concepts could be operationalized. This framework provides a pragmatic tool to inform clinical decision-making by associating patient frailty, tumor subtype, and pharmacokinetic vulnerabilities with specific treatment algorithms. In combination with improved biomarker surveillance and emerging anti-SASP or stromal-targeted therapies, it offers a

way to truly personalized care that recognizes the multifactorial interactions among host, tumor, and therapy.

Finally, the general issue of treating elderly survivors of CRC requires ongoing studies on the biological barriers across all ages and the clinical outcomes of these findings. The need to translate these insights into practice is both an ethical and a clinical imperative, given the rising incidence of CRC in ageing populations. Together with accurate assessment instruments, new treatment plans, and systematic treatment models, clinicians will be able to balance efficacy and toxicity, enhancing the survival and quality of life of older patients.

In conclusion, advancing care for elderly CRC patients requires a paradigm shift from age-based heuristics to biologically and clinically informed decision-making. Harnessing biomarkers of biological age, targeting microenvironment and senescence-driven resistance mechanisms, and implementing structured, multidisciplinary frameworks can transform the post-surgical adjuvant phase into an opportunity for personalized, effective, and compassionate care. As demographic pressures from an aging population intensify, these innovations represent not only a moral responsibility but also a strategic approach to improving treatment outcomes for a patient group that has been historically underrepresented in clinical research. By prioritizing tailored interventions that account for both patient and tumor-specific factors, the field of geriatric oncology can move decisively toward a future in which elderly CRC survivors receive optimized, evidence-informed treatment and care that respects both longevity and quality of life.

Abbreviations

CRC
Colorectal Cancer
BSA
Body Surface Area
CMS
Consensus Molecular Subtype
CMS4
Consensus Molecular Subtype 4 (Mesenchymal)
PRISMA-ScR
Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
PK
Pharmacokinetic
MeSH
Medical Subject Headings
TGF-b / TGF-β
Transforming Growth Factor-β
IL-6

Interleukin-6

EMT

Epithelial-Mesenchymal Transition

CMS1

Consensus Molecular Subtype 1 (Immune)

CMS2

Consensus Molecular Subtype 2 (Epithelial)

CMS3

Consensus Molecular Subtype 3 (Metabolic)

SASP

Senescence-Associated Secretory Phenotype

IL-8

Interleukin-8

TME

Tumor Microenvironment

ECM

Extracellular Matrix

CAFs

Cancer-associated fibroblasts

DNA

(refers to DNA methylation and patterns)

PD-1

(described as an inhibitory receptor and biomarker of T-cell exhaustion)

CTLA-4

(described as an inhibitory receptor)

CD28

(described as a biomarker of T-cell exhaustion)

TNF-alpha

(described as an inflammatory mediator)

ICD

Immunogenic Cell Death

5FU

5-fluorouracil

DAMP

Damage-associated molecular pattern

FDA

(refers to the Food and Drug Administration)

CGA

Comprehensive Geriatric Assessment

G8 / VES-13

(identified as geriatric frailty screening tools)

GA-PK-CMS4

Geriatric Assessment-Pharmacokinetic-Molecular (Workflow)

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Figures

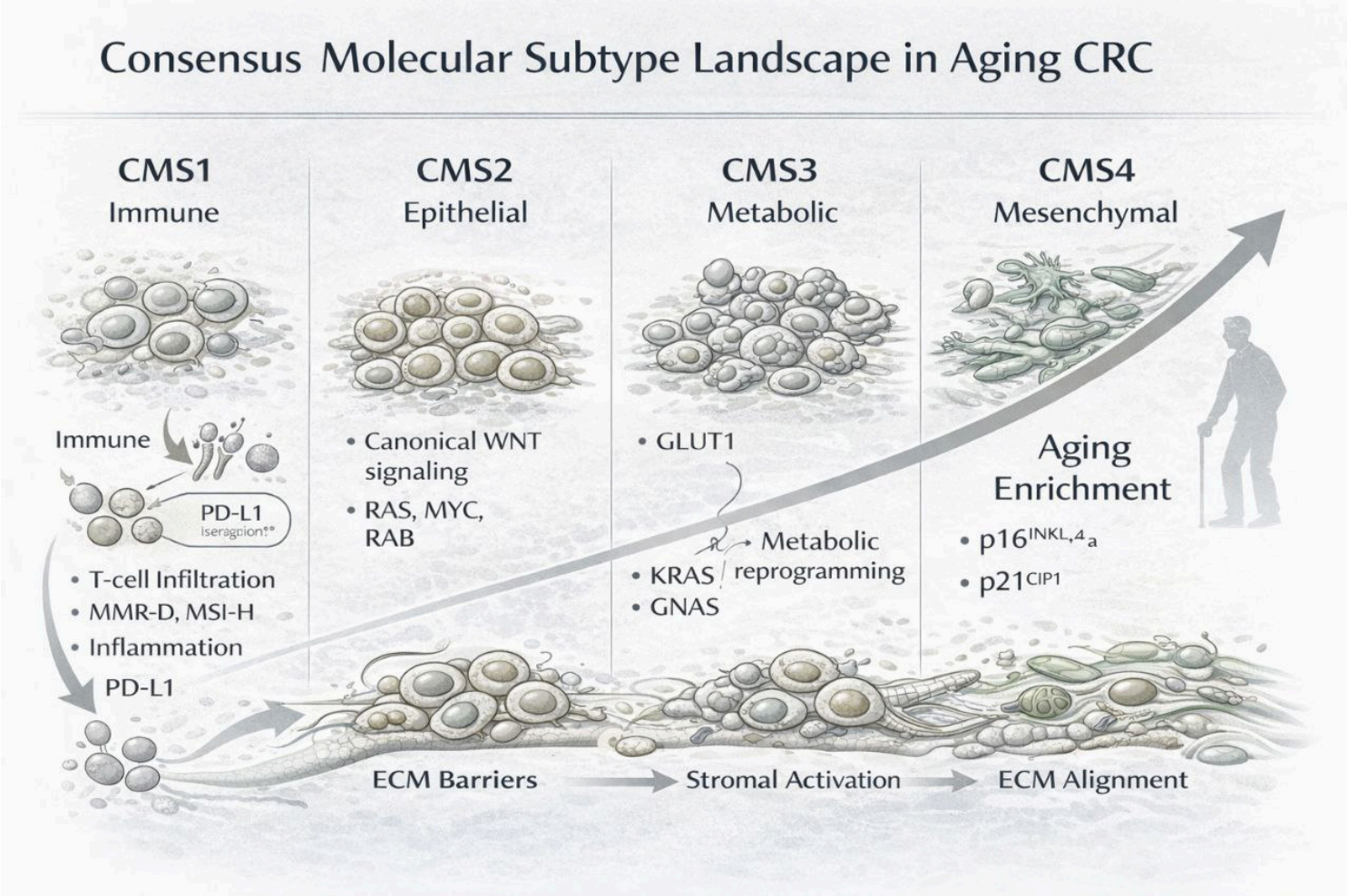


Figure 1

Consensus Molecular Subtype (CMS) Landscape of Aging Colorectal Cancer. The diagram demonstrates four types of CMS, CMS1 (immune), CMS2 (epithelial), CMS3 (metabolic), and CMS4 (mesenchymal). Ageing enrichment overlay indicates the CMS4 tumors dominance in the elderly patients which are chemoresistant stromal rich tumors. The most important mechanistic characteristics such as ECM barriers, stromal stimulation, ECM rotation, and metabolic reprogramming are labelled to demonstrate how tumor biology changes with age to offer a conceptual framework that characterizes therapy resistance in older adults. Created in BioRender.

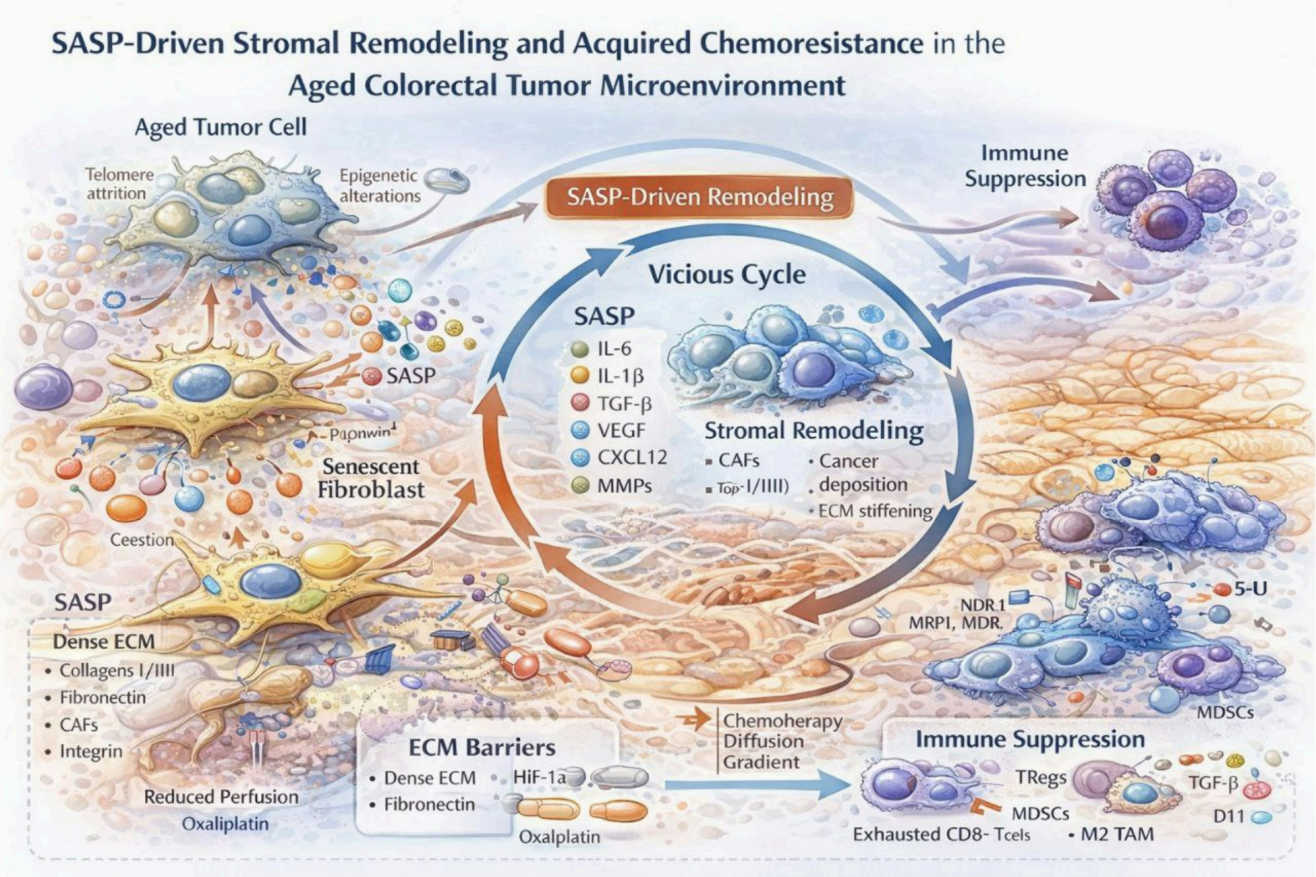


Figure 2

SASP-modulated stromal and immunological remodeling as a key modulator of acquired chemoresistance in an aged colorectal tumor microenvironment. This schematic shows that therapy-induced and age-linked senescence of cells facilitates the release of the senescence-associated secretory phenotype (SASP), such as pro-inflammatory cytokines, growth factors, and enzymes of matrix-remodeling. These mediators induce stromal activation, reorganisation of the extracellular matrix, immune suppression and tumourstroma crosstalk, which together create a permissive tumor stroma niche. The resulting remodeling in microenvironment degrades drug penetration, increases tumor-cell plasticity, and enables immune evasion, leading to the acquired resistance to chemotherapy in colorectal cancer patients of old age. Created with Biorender.com

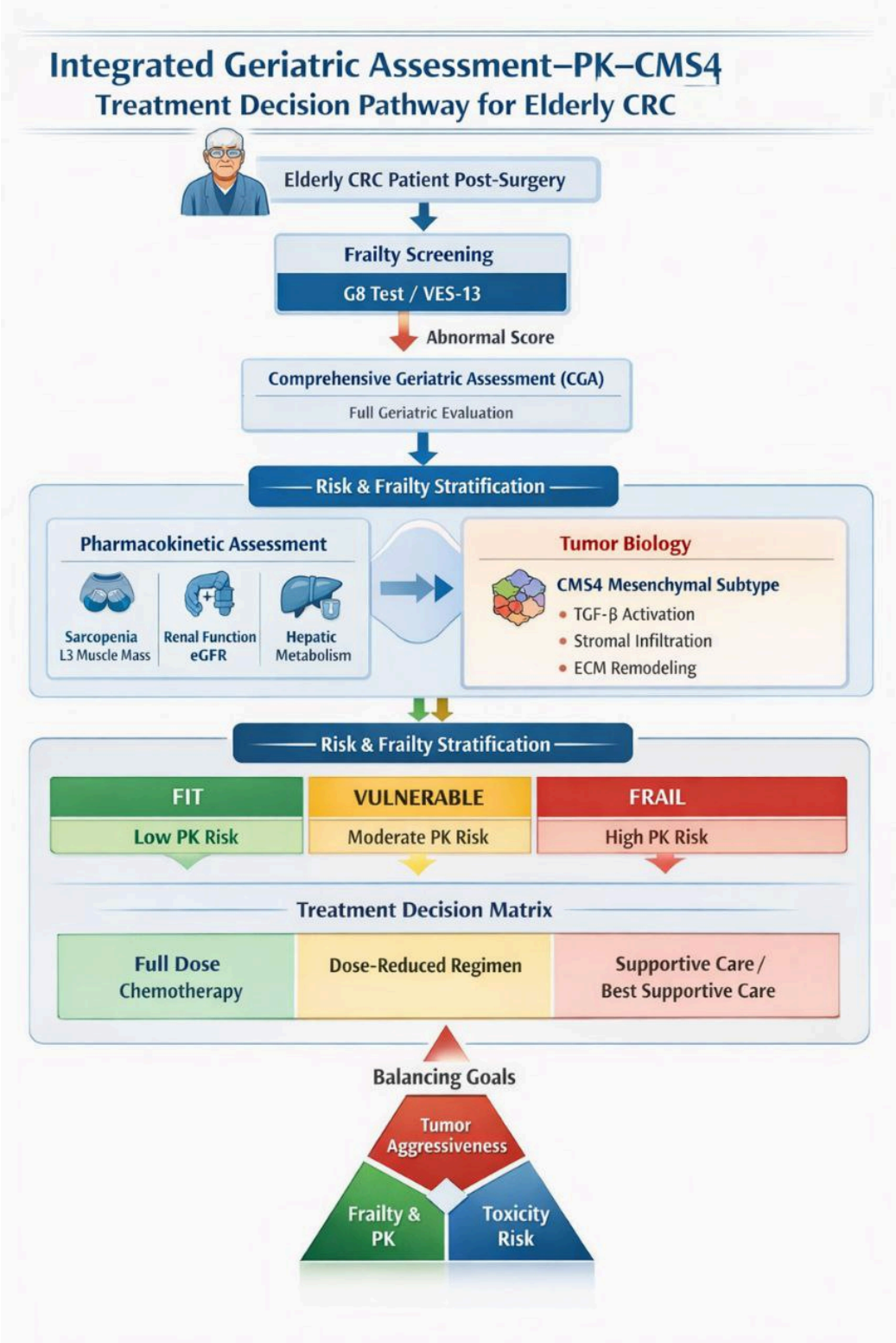


Figure 3

Combined Geriatric Assessment-Pharmacokinetic-Molecular (GA-PK-CMS4) Workflow of Personalizing Adjuvant Chemotherapy in Elderly Colorectal Cancer. This model is a combination of geriatric frailty screening (G8/VES -13), comprehensive geriatric assessment, pharmacokinetic risk profiling (sarcopenia, organ clearance, pharmacogenomics) and tumor molecular subtype classification (CMS1 -4). The combination of host resilience, drug tolerance and tumor aggressiveness stratifies patients to

either full-dose therapy pathway, dose-attenuated therapy, or supportive care pathway. Created in BioRender