The road after cancer: biomaterials and tissue engineering approaches to mediate the tumor microenvironment post-cancer treatment

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Cancer affects tens of millions of the world's population each year with a stark
mortality rate. It is well established that in order to be effective in treating solid
tumor cancers, the current treatment methods used often sacrifice surrounding
healthy tissue and cause damage at the site of treatment, inducing changes to the
surrounding microenvironment. These changes to the microenvironment can
lead to adverse side effects as well as long-term damage which continues to have
a detrimental impact on the patient's quality of life, even after remission. It is
believed that by modulating the tumor microenvironment (TME) post-treatment,
not only may the efficacy of current treatments be improved, but such associated
negative side effects, as well as further complications arising from treatment,
including metastasis, have the potential to be reduced. Mediating the
microenvironment is also considered to aid in repairing the damaged site
post-treatment, subsequently making the conditions more favourable for
promoting regenerative processes. This review provides a brief overview of
the alterations in the TME resulting from the three main cancer
treatments—chemotherapy, radiation therapy and surgery—and the most
common tissue engineering methods currently used in an attempt to mediate
the TME post-cancer therapy. Furthermore, it investigates new emerging
technologies within this field and the progress of such methods in terms of
reaching the clinical setting.

KEYWORDS

cancer treatment, tumor microenvironment, chemotherapy, radiotherapy, surgery,
tissue engineering, repair, regeneration

1 Introduction

Cancer is a worldwide public health issue and, based on the most recent data collected
by the Global Cancer Observatory in 2020, just under 20 million new cases and 10 million
deaths were attributed to cancer worldwide (Chhikara and Parang, 2023). The three most
common treatment options for solid tumors are chemotherapy, radiation therapy and

surgical resection. The treatment regime that a patient subsequently receives is dependent on numerous factors, including the anatomical location of the tumor(s) and whether metastasis has occurred, as well as taking into consideration the age and general health of the patient. Whilst the three aforementioned treatment options are often largely effective in treating cancer, by causing adverse effects to the tumor and tumor microenvironment (TME), they can all cause damage to the surrounding healthy tissue, which can negatively impact a patient's quality of life. Importantly, these adverse effects can be experienced long after treatment has finished and the cancer has been cleared, leaving patients with long-lasting impairments, in some cases for the rest of their lives. This typically arises as a result of the treatment influencing surrounding healthy tissue; and whether as a direct or indirect result of the treatment, the tissue microenvironment surrounding the original cancer site becomes damaged. Not only can this altered, harsh microenvironment lead to adverse side effects, but it can also hinder the repair and subsequent regeneration of the surrounding tissue post-treatment. Indirect damage to the microenvironment is not limited to the area targeted by the treatment, and surrounding tissue is often also affected. Acute signs of damage to the TME include elevated levels of reactive oxygen species (ROS), inflammation, and cell death (Landskron et al., 2014; Barker et al., 2015; Yang et al., 2018), while chronic signs include fibrosis (Chandler et al., 2019). Developing a therapeutic strategy to mediate the TME during and after cancer treatment is a viable approach to improve the patient's quality of life. However, the treatment regime will also play a role in how the TME is altered, which will have a subsequent effect on the method in which the microenvironment can be mediated.

Current cancer treatments focus on clearing the cancer cells, with an emphasis on preventing recurrence. However, the damage caused to the surrounding microenvironment remains after treatment has ceased, even as the patient is in remission, and can cause life-long adverse effects. These post-remission effects are not often taken into consideration prior to and during treatment and there are limited treatment options currently available to target this severe consequence. However, there is some evidence that mediating the microenvironment to a state that closely resembles that of homeostasis could potentially improve the repair and regeneration processes within this 'damaged site' (Yao et al., 2019). In particular, focus on gaining an understanding of the changes that occur at the level of the tissue microenvironment will be crucial in designing successful interventions to benefit the patient.

This review aims to introduce cancer and the TME, and to examine current cancer treatments for solid tumors, the effects that these treatments subsequently have on the surrounding microenvironment and methods in which these effects can be remedied. Various methods have been investigated in attempts to overcome the harsh microenvironment that arises from cancer treatments, primarily with the aim of preventing reoccurrence and regenerating functional tissue. Such methods include tissue engineering; primarily using biomaterials such as electrospun mats and hydrogel systems which can incorporate and introduce cofactors, drugs, or other small molecules into the microenvironment. An overview of the main methods described within the review, which both initiate damage to the TME and those
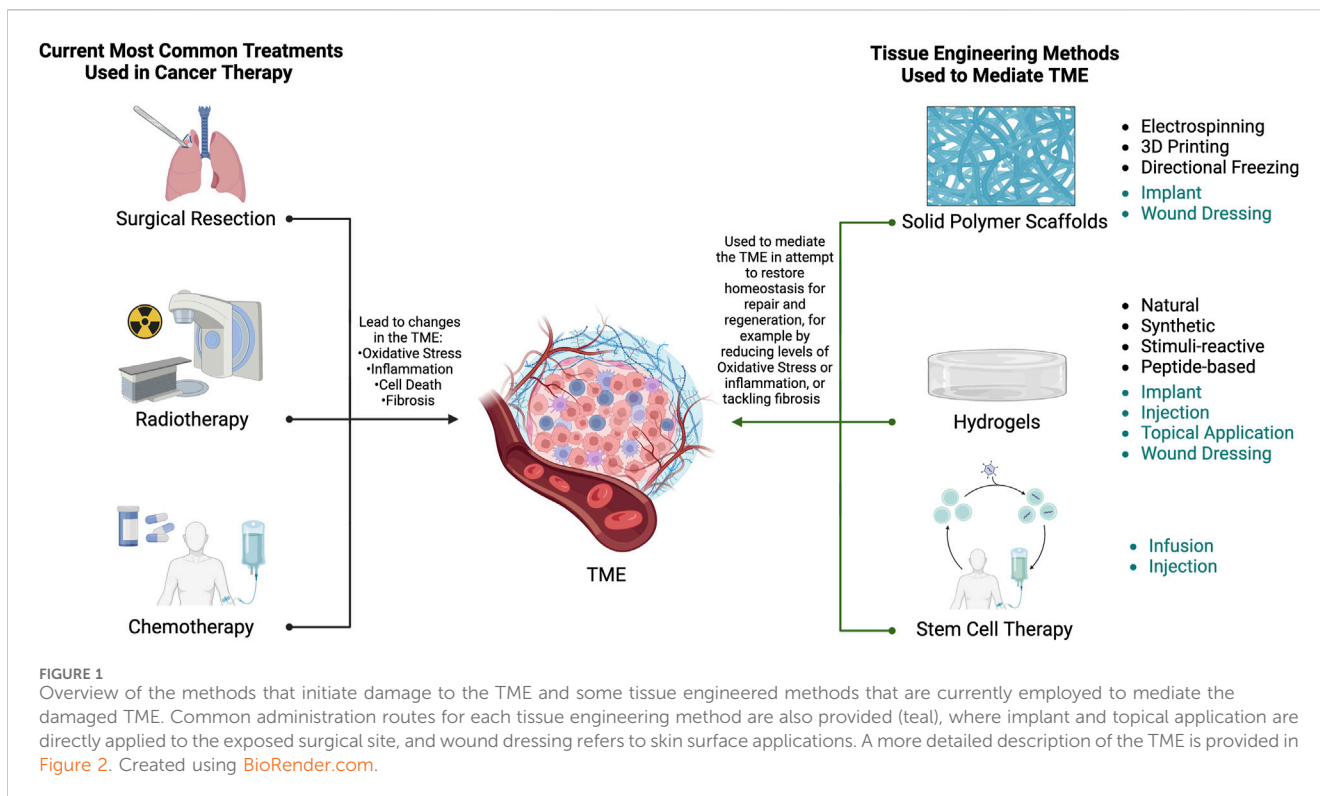
currently used to mediate the TME is shown in Figure 1. A summary of the methods used post-cancer for microenvironmental reversal can be found in the Supplementary Material S1. It is worthy to note that there is a plethora of literature that delves into alternative routes to both treat cancer and also mediate the TME, such as immunotherapy and nanomedicine, respectively, as well as neoadjuvant approaches (Aboulkheyr Es et al., 2018; Mendes et al., 2021; Gugenheim et al., 2022; Li et al., 2022; Sahu et al., 2022; Yan et al., 2022; Ou et al., 2023; Yang et al., 2023); however the purpose of this review is to evaluate, and give an overview of, the most common types of treatment (radiation, chemotherapy and surgery) and specifically tissue engineering approaches to mediate the damage of these treatments inflicted upon the TME.

Furthermore, for the purpose of this review, environmental change refers to any process in which an environment is altered, either as a direct result of, or indirectly from, the treatment.

2 Cancer and the tumor microenvironment (TME)

There are over 277 types of cancer, generally classified by the abnormal proliferation of immortal cells, by which the reproduction of normal cells becomes uncontrolled (Sarkar et al., 2013; Hassanpour and Dehghani, 2017). During the normal cell cycle, any cell which becomes damaged or "old" dies and is replaced by a newly generated cell. When this controlled process is disrupted, the aged or damaged cells are not replaced and instead they continue to survive and divide whilst new cells are still generated. This leads to a mass of cells which can promote the formation of a tumor.

The TME refers to the microenvironment around the tumor and all it encompasses (Figure 2), from the blood vessels to stroma, cancer stem cells (CSCs), epithelial cells, fibroblasts, immune cells (including macrophages and T cells) and other factors including growth factors, cytokines, the extracellular matrix (ECM), cell-matrix interactions, pH and oxygen concentration (Yang and Gao, 2017; Arneth, 2020; Bhattacharya et al., 2020; Blache et al., 2020). Compared to a healthy microenvironment, characteristics of a tumor microenvironment can include reduced oxygen concentration which ultimately leads to hypoxia, more acidic pH, remodelling of the ECM and the presence of a plethora of cells which activate inflammatory and immune responses, promote angiogenesis, and support the structure of the solid tumor (Fernando et al., 2021; Suwa et al., 2021). The distance between blood vessels and cells, which is maintained in a normal microenvironment, becomes disrupted within the TME. Generally, this distance expands to a point where regions become deprived of a sufficient blood supply, meaning there is a lack of oxygen and nutrients delivered to these areas. It is well known that the TME is also influenced by external factors, such as age, as discussed in a recent review (Fane and Weeraratna, 2020). Until recently, cancer research has focused on cancer cells alone, however more recent studies have found that tumors are intricately related to the TME, with tumor cells interacting closely in regard to their development, function and their response to treatments (Giussani et al., 2015; Hirata and Sahai, 2017). These constant interactions mean that the structure and growth of the tumor are continuously evolving (Hass, 2020). With the newfound understanding that the

FIGURE 1
Overview of the methods that initiate damage to the TME and some tissue engineered methods that are currently employed to mediate the damaged TME. Common administration routes for each tissue engineering method are also provided (teal), where implant and topical application are directly applied to the exposed surgical site, and wound dressing refers to skin surface applications. A more detailed description of the TME is provided in Figure 2. Created using BioRender.com.

TME is directly involved in events such as tumor progression and metastasis, and therefore plays a role in the efficacy of various treatments, it is important to consider not only the traits of cancer cells themselves but also the TME that they are found in, and whether it can be activated and used as a restorative agent (Hanahan and Weinberg, 2011; Barker et al., 2015).

Given the close proximity of the TME to cancer cells targeted by treatment, the TME is invertedly changed during cancer treatment. These changes, and other factors regarding the TME, such as the cell types present, need to be taken into consideration when designing a platform for its mediation. Some of the major influences of the TME are detailed in Figure 2 and described below.

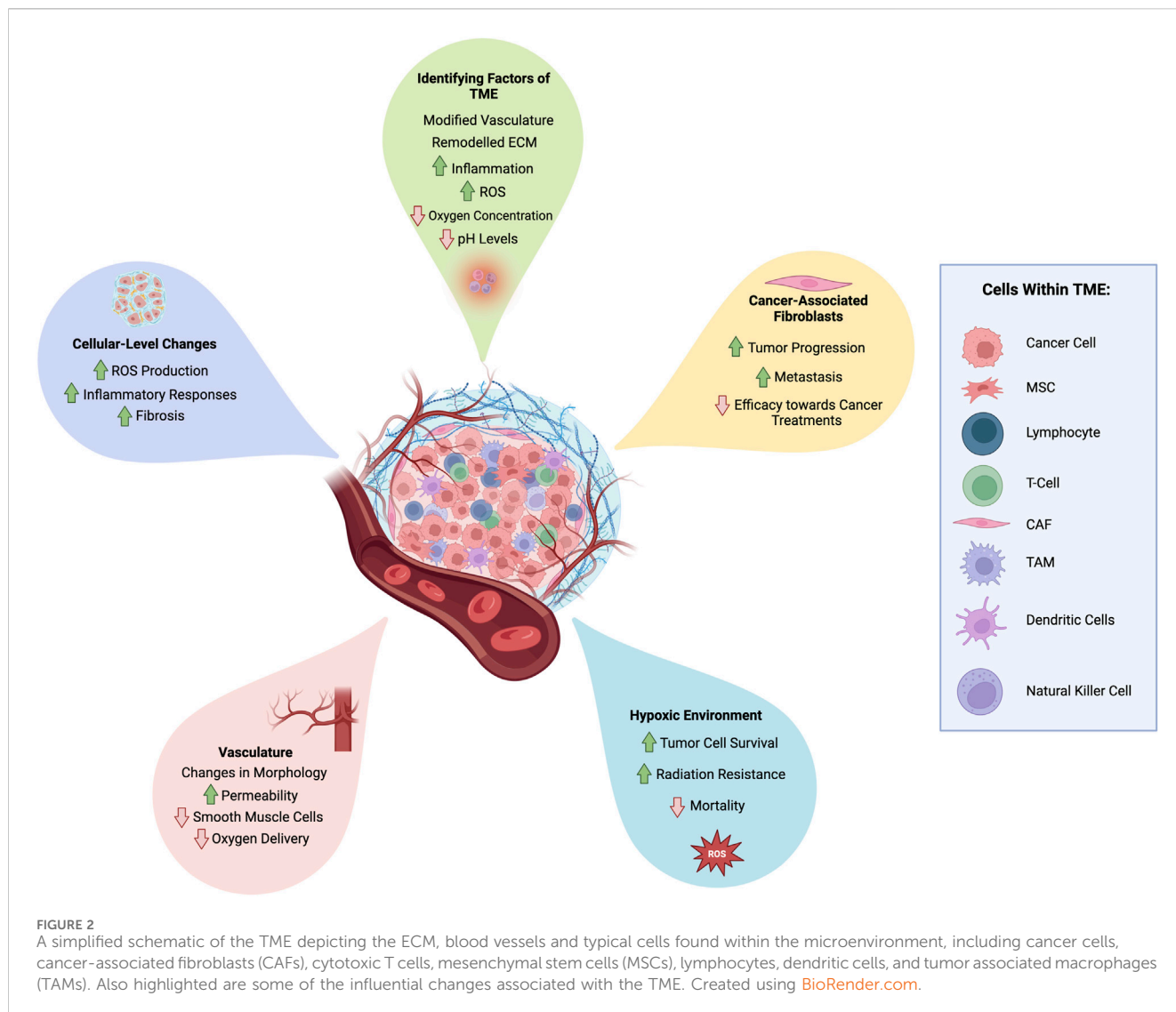## 2.1 Vasculature and nutrient delivery

Within the TME, tumor vasculature is altered and becomes geometrically abnormal. The shapes of the blood vessels change and become more permeable due to the development of an irregular endothelial cell lining and a decrease in smooth muscle cells (Graham and Unger, 2018). These changes to the structure of blood vessels have a negative impact on their function, hindering blood flow and subsequently reducing the delivery of oxygen to the area.

Regulation of oxygen levels is essential for homeostasis, therefore any deviation from this within the TME, particularly a reduction, can indicate phenomena such as hypoxia. Hypoxia within the tumor and its surrounding microenvironment is one of the hallmarks of cancer and has been found to be significantly influential in the effectiveness of treatment, likely due to its involvement in affecting multiple molecular pathways including

glycolysis, cell proliferation and angiogenesis (Hanahan and Weinberg, 2000; Sørensen and Horsman, 2020). It is found within all solid tumors and influences a patient's response to all treatments, with the exception of surgical resection. Consequently, hypoxia is the most researched parameter within the TME and is a major target in improving cancer treatments. There are multiple mechanisms involved in the development of a hypoxic microenvironment, and even within the same tumor the regions and levels of hypoxia are not always uniform (Graham and Unger, 2018). Hypoxia has been associated with an increased risk of mortality, enabling tumor cells to survive in typically unfavourable conditions such as low oxygen concentration, as well as increasing their resistance to radiation (Bhattacharya et al., 2020; Mughees et al., 2021).

2.2 Cellular responses

Initial events following radiotherapy and chemotherapy treatment that occur at the damaged site include double strand DNA breaks, production of reactive oxygen species (ROS), subsequently leading to an overall increase in ROS levels, and general stress responses. These factors induce damage to the cells, which can lead to a number of detrimental outcomes, including apoptosis, senescence and mitotic catastrophe, as well as inducing inflammatory responses and fibrosis at the tissue level (Gao et al., 2018). Following surgical resection of a tumor and its associated microenvironment, a number of wound healing responses are activated, including COX-2 enzyme (inflammatory response) and transforming growth factors (Predina et al., 2012). However, research has found that these factors can actually promote

FIGURE 2
A simplified schematic of the TME depicting the ECM, blood vessels and typical cells found within the microenvironment, including cancer cells, cancer-associated fibroblasts (CAFs), cytotoxic T cells, mesenchymal stem cells (MSCs), lymphocytes, dendritic cells, and tumor associated macrophages (TAMs). Also highlighted are some of the influential changes associated with the TME. Created using BioRender.com.

the survival of any remaining cancer cells, causing subsequent recurrence (Predina et al., 2012).

2.2.1 Inflammatory cells

Through interaction with pro-inflammatory cells, such as macrophages, neutrophils, and lymphocytes, as well as non-cellular components, cancer cells aid in the production of the inflammatory TME. This results in chronic inflammation which is a key factor in cancer development, as well as promoting tumorigenesis, as detailed in other literature (Greten and Grivennikov, 2019; Wen et al., 2022).

2.2.2 Cancer-associated fibroblasts

Under healthy tissue conditions, the function of fibroblasts is to inhibit tumor growth and maintain homeostasis within the tissue. However, when in close proximity to tumorigenic cells, the healthy fibroblasts are influenced by the signals emitted from these cells and undergo irreversible morphological changes, producing cancer-associated fibroblasts (CAFs). A detailed description of CAFs and

a comparison to normal fibroblasts, as well as how the interact with the TME has previously been published (Liu et al., 2019). CAFs have been shown to promote tumor progression, metastasis and importantly, CAFs are known to reduce the efficacy of the naturally occurring tumor immunity found within the microenvironment, subsequently reducing the efficacy of existing cancer treatments, in particular, chemotherapy (Farhood et al., 2019; Joshi et al., 2021).

2.2.3 Cancer stem cells

One particular aspect of the TME worthy of note is the presence of cancer stem cells (CSCs) and their plasticity–a property that enables cells to change their phenotypic expression as a result of environmental cues, without causing any genetic mutation. CSCs have been found to exhibit enhanced self-renewal, differentiation and tumorigenesis in multiple cancer types (Kruyt, 2023; Salem and Salo, 2023). For these reasons, complete obliteration of CSCs is a major factor that should be considered when looking for effective therapy methods.

2.3 Other considerations

Not only does the TME influence the evolution of the tumor, but it also has an effect on its response to cancer therapeutics (Hirata and Sahai, 2017). This can be utilised to provide new avenues for therapeutic treatments, including improving the results of currently available treatments as well as novel treatment methods. The most significant challenges to tackle when developing new therapeutics in cancer treatment is tumor recurrence and metastasis (Zhao and Cui, 2020). Even in cases where chemotherapy and/or radiotherapy are given post-operatively following surgical resection of solid tumors, recurrence occurs in up to 40% of patients (Predina et al., 2013). Additionally, the unspecific targeting nature of current treatments, such as chemotherapy, often leads to reduced efficacy, resistance to treatment and subsequent cancer recurrence. The immunosuppressive nature of the TME is another influencing factor that appears to act as a protective barrier, defending the tumor from therapeutics and allowing it to thrive (Jin and Jin, 2020; Parayath et al., 2020). However, methods of overcoming such issues are currently being studied in the area of tissue engineering. One of the drawbacks in using tissue engineering to repair, and ultimately restore and regenerate the microenvironment, is that many of the factors used to promote these processes can also facilitate tumor survival, growth and metastasis, such as is the case with factors targeting improving angiogenesis (as reviewed in Zimmerlin et al., 2013).

Such changes to the TME and the microenvironments of surrounding healthy tissues and organs are attributed to the unpleasant side effects, notoriously associated with current cancer therapies. These side effects range from short term effects experienced during treatment to long term side effects which are experienced for a prolonged period of time post-treatment, ranging anywhere from months or years after treatment to the rest of the patient's life. Most of these side effects have enough of an impact to affect the person's day-to-day activities, leading to poor quality of life, as well as impacting their health and wellbeing. Currently, there are limited treatments available for such impairments, and most options only offer palliative, surface level care. If a detailed understanding of how the TME responds to the various cancer treatments can be established then interventions can be developed to overcome these post-treatment side effects, and thus improve the patient's quality of life after cancer.

3 An overview of common tissue engineering approaches for post-cancer repair

Tissue engineering is an emerging technology concept discussed in detail throughout literature which primarily utilises specifically engineered constructs to aid the repair of damaged tissue, using combinations of biomaterials, cells and biochemical cues to mimic the healthy normal tissue (Yoo et al., 2014; Lombaert et al., 2017; Micek et al., 2020; Unnikrishnan et al., 2021). A variety of tissue engineering methods have been applied to cancer research, not only to support repair but also to mimic the native TME for *in vitro* modelling, including using patient-derived cells to obtain more clinically relevant data (Unnikrishnan et al., 2021), drug screening and toxicity studies for radiotherapy and chemotherapy (Xu et al., 2014).

3.1 Biomaterial-Based scaffolds

Biomaterials have commonly been used to support the repair, and in some cases regeneration, of damaged sites. This is due to the similarities that can be observed within their structure and composition to the natural extracellular matrix. As a result, biomaterials can mimic the natural cellular environment, creating new microenvironments capable of enabling cell attachment, growth, and proliferation, by providing mechanical support to control factors such as cell phenotype and behaviour. Electrospun scaffolds in particular show great promise as therapeutic agents as they are used to mimic the native ECM, with high drug loading capabilities which makes them suitable for both drug delivery systems for local cancer therapy, which can further be tuned to release the drug in a stimuli-responsive manner, and also to influence tissue regeneration (Hinderer et al., 2016; Liu et al., 2018; 2021; Blache et al., 2020). Electrospinning is the process of applying a high voltage electric field to a polymer solution to create a fibrous mat, known as an electrospun scaffold. Numerous parameters, such as temperature and humidity, voltage, solvent used to dissolve the polymer, and parameters within the electrospinning setup itself, are all vital in controlling the fabrication process. Altering any one, or combination, of these parameters enables control over many characteristics of the produced fibre scaffold, including fibre diameter, surface topography, porosity and fibre alignment. All of these subsequently affect the relationship between the cells and the scaffold, and can therefore be tailored to the desired application of the scaffold. One feature of electrospun scaffolds suggested to be beneficial in cancer therapeutics is an appropriately designed electrospun mat with well-interconnected porosity, which can have the potential to trap cancer cells, preventing them from cell migration and thus reducing metastasis (Samadzadeh et al., 2021). Electrospun fibres in particular are advantageous in that they have a large surface area to volume ratio which aids drug release, and they are also able to be physically implanted during surgical resection procedures. Studies have also found that electrospun scaffolds can be used to promote angiogenesis, which is essential for successful implantation and acceptance of the graft in the body (Montero et al., 2012; Gigliobianco et al., 2015). However, promotion of angiogenesis should be avoided until it is certain that there are no remaining cancer cells present. Similarly, hydrogels are another form of biomaterial that can be employed. Hydrogels are cross-linked polymer networks that are prepared and then surgically implanted, and have the potential to be used in a variety of applications, including repair and regeneration, as cell or drug delivery systems, attributing their biomimetic properties and multifunctionality (Zhang et al., 2016). Over fibrous scaffolds, hydrogels have the advantage of the ability to create the material in a liquid form that can respond to environmental stimuli to form a gel *in situ*. This allows a non-invasive delivery method for the precise delivery of either drugs or cells, which reduces the risk of post-surgical infection, as well as reducing trauma to surrounding tissue (Zhang et al., 2016). Modification of the synthesis of the polymer

TABLE 1 Common polymers used in biomaterials, their biomaterial forms, and compound types commonly added to the biomaterial.

Name	Polymer type	Applications		References
		Electrospinning	Hydrogel	
Alginate	Natural	✓	✓	Mokhena and Luyt, 2017; Taemeh et al., 2020; Lu et al., 2021
Chitosan	Natural	✓	✓	Antaby et al., 2021; Anisiei et al., 2023; Zhang et al., 2023a
Collagen	Natural	✓	✓	Tang et al., 2016; Rao et al., 2018; Mei et al., 2019; Hernández-Rangel and Martin-Martinez, 2021
Fibrin	Natural	✓	✓	Al Kayal et al., 2020; Zhang et al., 2020a; Nelson and Gilbert, 2021; Talukder et al., 2021
Gelatin	Natural	✓	✓	Ajmal et al., 2019; Beikzadeh et al., 2021; Koch et al., 2022
Hyaluronic Acid	Natural	✓	✓	Castro et al., 2021; Ding et al., 2023; Han et al., 2023; Zhang et al., 2023b
PCL	Synthetic	✓		Khalf and Madihally, 2017; Chen et al., 2020; Kalantary et al., 2020; Pinzón-García et al., 2021; Westwood et al., 2023; Blanquer et al., 2024
PEG	Synthetic	✓	✓	Deng et al., 2019; Majumder et al., 2020; Tsekoura et al., 2021; Song et al., 2022
PLGA	Synthetic	✓	✓	Pereira et al., 2021; Samadzadeh et al., 2021; Yang et al., 2021
PTFE	Synthetic	✓		Kolesnik et al., 2021; Yu et al., 2022; O'Meara et al., 2023

allows properties of the hydrogel, including water content, mechanical properties and drug release profiles, to be tailored for each individual application. Additionally, hybrid scaffolds of electrospun scaffolds and hydrogels can also be fabricated. Recently, there has been an increase in hybrid scaffolds, where electrospun fibres and hydrogels, such as PCL and alginate, respectively, are used to promote the effects seen by each individual material to yield improved results (Chen M. et al., 2019; Koch et al., 2022).

A list of polymers commonly used to fabricate biomaterials is provided in Table 1. As shown, most polymers are used in the fabrication of both electrospun scaffolds and hydrogels; however, PCL and PTFA are two synthetic fibres that have only been used in the electrospinning process and only exist in hydrogels when used as a polymer backbone to support a gel in hybrid systems. There are many reasons for selecting particular biomaterials, including their indented applications and for their functions within the TME. The advantage of using biomaterials is that, whilst there are some more suited to other functionalities than others, they can be tailored to suit both the purpose and application of their intended use. For example, PLGA, a synthetic polymer, can be fabricated into both electrospun fibres and also hydrogel systems. The same holds true for natural biopolymers such as alginate, collagen and gelatin (Xue et al., 2019). These can be used alone or in combination with other biomaterials–combinations are commonly used to enhance the properties of the existing biomaterials. For example, studies have found that coating alginate fibres with molecules such as glutaraldehyde or chitosan improves the mechanical properties of the alginate fibres (Najafiasl et al., 2020). Alginate is already a popular choice of biomaterial due to its easy gel formation and its ability to perform as an effective carrier and delivery system for drug and biomolecule compounds, including genes. Using combinations to improve other properties of the material, such as chitosan to improve tensile properties, makes an appealing biomaterial choice even more attractive. Hyaluronic acid (HA) is another popular biomaterial most commonly used post-operatively,

particularly in the form of a hydrogel, and can be combined with both natural molecules as well as synthetic polymers (Abatangelo et al., 2020). However, care must be taken when using HA, as it has been shown to regulate the TME and promote the malignant phenotype of cancer cells, and lead to multidrug resistance (Markowska et al., 2023). So, whilst HA is beneficial in applications such as wound repair, studies have shown that it can also effectively feed the cancer, causing it to grow and spread.

Biomaterial scaffolds can also be combined with other therapies, such as stem cell and immune therapy to heighten or produce multiple simultaneous/subsequent effects (Zhao and Cui, 2020). This can also be achieved by incorporation of additional compounds, such as drugs or growth factors, to elicit various beneficial responses within the TME. For example, Quercetin is one commonly used compound that is often incorporated within both electrospun fibres and hydrogel systems. Quercetin has been shown to display multiple beneficial properties: as an antioxidant to suppress oxidative stress through free radical scavenging; inhibiting inflammatory enzymes such as COX to act as an anti-inflammatory agent; reduces fibrogenesis; and also acts as an anticancer by decreasing expression of CSCs and myofibroblast markers, suppressing proliferation and mitosis and has also been shown to reduce drug resistance (Ajmal et al., 2019; Asgharian et al., 2021; Reyes-Avendaño et al., 2022). Growth factors are also commonly added to scaffolds as a means to repair and restore the environment back to normal–VEGF is one example which has been incorporated into different scaffold systems and has been shown to act on both the vasculature of the local environment but also directly with cells and other molecular components of the surrounding environment. Studies have suggested that using polymer scaffolds as a means of growth factor delivery can play a vital role in aiding regeneration in where the vasculature of the environment has been damaged through means including enhancing angiogenesis, increasing blood vessel density and vascular perfusion, as well as displaying capacity to increase bone formation (Kaigler et al., 2006).

3.2 Stem cell therapy

Another method is stem cell therapy, which uses a wide variety of techniques, often in conjunction with the aforementioned biomaterials, to improve the efficacy of the biomaterial construct or to tackle multiple concerns simultaneously. Stem cells are extremely versatile and have several properties which make them special, including self-renewal, differentiation, migration and tissue repair (Dalerba et al., 2020). Stem cell therapy is most commonly used for regenerative purposes and has significant potential and a large amount of interest in terms of cancer treatment. Specifically, due to their involvement in several processes which aid the development of tumors, targeting CSCs could improve the efficacy of cancer treatment (Duan et al., 2021).

3.3 Drug delivery systems

Whilst not specifically a tissue engineered approach, drugs are often incorporated into such constructs and used in the remodelling of the TME (Ye et al., 2019). Biomaterials are commonly used as drug delivery systems and to improve properties such as bioavailability and solubility in anticancer drugs which on their own, perform poorly, with the additional benefit of being able to cleverly control the release kinetics. By designing systems with features such as release only under certain conditions means that greater control and more specific targeting can be achieved. This approach is extremely common, as will be shown throughout the review where tissue engineering approaches are used to create biomaterials-based modalities for delivering treatment without causing the extensive damage caused via traditional treatment options.

4 Current approaches for cancer therapy, their impact on the TME, and post-cancer treatment

4.1 Chemotherapy

Chemotherapy is typically used for advanced cancers, particularly when metastasis has occurred. It can be used as a curative measure, both by itself and in combination with other treatments such as radiotherapy or surgery (both pre and post), as well as for palliative treatment. Chemotherapy works by using cytotoxic drugs, including paclitaxel, doxorubicin, or fluorouracil, to inhibit the growth of and destroy cancerous cells; however, it is not selective and as such, also targets healthy cells.

Most conventional chemotherapy drugs are administered as part of a 'cocktail mix' of drugs, typically delivered intravenously. The administration periods and cycles vary on an individual basis. Recent research has looked at alternative methods of delivering chemotherapy agents, including tissue engineered biomaterial scaffolds, hydrogel systems and other alternatives, and in some cases novel, drug delivery systems. These alternative methods of administration have the advantage of being able to incorporate additional agents to deliver to the site, which can provide benefits such as mediating the TME. Chemotherapy is often combined with

surgical resection of tumors; therefore, research has looked at ways in which chemotherapeutics can be inserted into the tumor resection site. This is often achieved using biomaterials such as electrospun scaffolds or hydrogel systems. It is commonly seen in polymer fibres loaded with a drug that there is an initial burst release of the drug followed by a period of sustained release which can range from 14 days to 80 days (Ranganath and Wang, 2008; Samadzadeh et al., 2021). With typical drug administration routes, it is common for drugs to only become effective once they have reached therapeutic concentrations within the body, which in some cases can take up to several months. Such results indicate that having the ability to directly implant the desired dose of drug into the target site could offer the possible benefit of reducing the time taken for the drug to produce its therapeutic effect. Another advantage of using a biomaterial scaffold as opposed to traditional administration routes such as IV is that the drug delivery is more localized, meaning that there is less accumulation of the drug in areas other than directly at the tumor site, constituting less damage to healthy tissue and thus reducing adverse effects (Chen et al., 2020).

4.1.1 Impact of chemotherapy on the TME

Chemotherapy drugs target many aspects of cell physiology, including DNA replication, RNA synthesis, cell structure and metabolism. The cytotoxic nature of chemotherapeutic agents can lead to numerous side effects including nausea, anemia, fatigue, immunosuppression, and alopecia. In long-term studies, researchers discovered that children who had received chemotherapy also suffered from long lasting side effects, including fertility issues, organ disfunction and cognitive impairment (West et al., 2009; Demaria et al., 2017; Goossens et al., 2020). The wide range of side effects is the result of chemotherapeutics targeting a wide range of cell-cycle dependent mechanisms, and often specifically rapidly dividing cells. This includes cells found in hair follicles, bone marrow, the digestive tract and reproductive system (Prieto-Callejero et al., 2020). Cellular senescence inhibits cell pathways and halts cell proliferation, therefore suppressing cancer. During chemotherapy, the action of the drugs can induce cellular senescence, creating therapy-induced senescence cells, which remain in the microenvironment and can trigger inflammation. A study by Demaria et al. revealed that there was a direct relationship between the removal of these therapy-induced senescent cells and a reduction in several side effects (Demaria et al., 2017). The results of the study indicated that the presence of these cells contribute to the side effects observed with chemotherapy, thereby making them a desirable target in improving anticancer treatments (Demaria et al., 2017). Senolytics have been developed to selectively target senescent cells as an alternative therapeutic approach, and have been found to successfully clear senescent cells whilst also reducing cancer relapse and improving the treatment-damaged environment (Demaria et al., 2017; Barazzuol et al., 2020). However the removal of senescent cells also impacts regeneration in a number of tissues so a fine balance will be necessary in order to be beneficial (Elder and Emmerson, 2020).

The efficacy of chemotherapy can be affected by many factors, such as vasculature of the tumor, which impacts drug delivery. Chemotherapy drugs are designed to damage the rapidly dividing cancer cells, inducing tissue damage through mechanisms such DNA damage and ROS production, but other surrounding

TABLE 2 Approaches for mediating the TME post chemotherapy treatment.

Type of therapeutic				Site specific approach		Result	Reference
Stem cell therapy	Scaffolds	Hydrogels	Free drug	Environmental	Regeneration		
✓				✓		Increased repair of ovarian injury post chemotherapy, improved the degree of apoptosis in the tissue and improved endocrine function	Shen et al. (2020)
✓				✓		Enhanced the repair effect of MSCs on chemotherapy damaged ovarian tissue, reduced apoptosis of MSCs in the local environment, improved ovarian structure and endocrine function	Chen et al. (2018)

healthy cells also succumb to the same damage (Gao et al., 2018). This can potentially lead to activation of pathways/events which can protect tumor cells from DNA damage, but also protect cancer cells against the cytotoxic action of chemotherapy drugs. For example, research has shown that chemotherapy agents can promote hypoxia in the TME, which drives the activation of hypoxia-inducible factors (HIFs), in particular HIF-α. This in turn, through a series of events, can influence not only growth and progression of cancer, but also metastasis and chemo-resistance (Li et al., 2016; Budi and Farhood, 2023).

4.1.2 Treatment approaches post-chemotherapy

New approaches to delivering chemotherapy agents can bring forth many new concepts, such as delivering agents capable of mediating the TME, including growth factors, which not only better the efficacy of chemotherapy but also provide these additional benefits. Methods which have been used to reverse damage to the TME following chemotherapy are outlined in Table 2, which highlights whether the approach aims to modify the environment, or initiate or aid regeneration. Both studies provided used mesenchymal stem cells to promote ovarian function restoration post-chemotherapy. One example is a combined chemo-photodynamic therapy which is directly injected into the tumor to trigger a series of anti-tumor immune responses. However, during their studies, G. Yang et al. also discovered that this injection was able to relieve hypoxia and unexpectedly also found that, when used in combination with checkpoint blockade therapy, tumors at distant sites were reduced, meaning that this treatment also has promising potential for tumor metastasis (Yang et al., 2017). Chemotherapy drugs are often regarded as a double-edged sword, as whilst they are cytotoxic to cells, they can also activate reaction pathways and other processes which subsequently result in off-target effects. Another important consideration regarding chemotherapeutics is that the cells can quickly become resistant to the cytotoxic effects. However, some studies found that using a synergistic combination of chemotherapy drugs and other small molecules can reduce the accumulation of tumor promoting activity and enhance the tumor response to the chemotherapeutic (Kemp et al., 2016).

As shown in Table 2, there is currently a limited amount of investigation and proposed tissue engineered treatment approaches in mediating the microenvironment post-chemotherapy. While this is not a comprehensive overview of all studies it acts to highlight the

most clinically relevant avenues which are showing good potential in post-chemotherapy care.

4.2 Irradiation therapy

Radiation therapy is one of the key treatment options for cancer, with approximately 50% of all cancer patients receiving radiotherapy as either a stand-alone treatment or in combination with surgery or chemotherapy (Barazzuol et al., 2020). Depending on the type and stage of the cancer, radiation therapy can be used as a cure for cancer, prevent recurrence, halt its growth or spread, as well as for palliative reasons to ease symptoms. It is predominantly used when the cancer is in its early stages and can be delivered in many different ways, with its main purpose being inducing DNA damage within the cancer cells. The most well-known method of administration is external radiotherapy, where a dose of radiation is beamed directly onto the target area and passes through the body. Alternatives include radiotherapy implants or injections where a radioactive material is administered into the body where it remains for anywhere from minutes to days, with some small implants being permanently placed. The treatment is usually given as fractionated doses, where the total amount of radiation to be delivered is divided into small amounts over a number of days. Fractionated radiation not only maximizes the effect that the radiation has on the cancer cells, but also to reduce the amount of damage caused to healthy cells, with some studies showing that tumor cells are more susceptible to fractionated radiation than healthy cells (Baskar et al., 2014; Wang J.song et al., 2018). The dose given is specifically calculated for each patient.

4.2.1 Impact of Irradiation therapy on the TME

Radiotherapy damages cancer cells by using radiation to damage the DNA within the cells, hindering their growth and causing cell death. This does not happen immediately; therefore, a course of radiation treatment is provided to give enough radiation to initiate this process and to continue destroying cancer cells for a duration of time after. Due to its reduced blood supply, the TME can impair the efficacy of radiotherapy as this reduces the accessibility of radio-sensitizers to the area (Koukourakis and Giatromanolaki, 2020; Sørensen and Horsman, 2020).

Penetrating radiation causes cellular stress as a result of several responses including the activation of the damage repair cascade in

TABLE 3 Approaches for mediating the TME post irradiation treatment.

Type of therapeutic			Administration route		Site specific approach		Result	Reference
Stem cell therapy	Scaffolds	Hydrogels	Implant	Injection	Environmental	Regeneration		
		✓		✓	✓		Relieved tumor hypoxia, downregulated expression of HIF-α, improved radiotherapeutic efficacy, suppressed tumor growth and prolonged survival	Yang et al. (2021)
	✓					✓	Enhanced vascularization and bone regeneration	Kaigler et al. (2006)
		✓				✓	Showed that $\alpha_1\beta_1$-integrin is essential in the formation and organization of human stem/progenitor cell microstructures, subsequently played a key role in the structure and function of human salivary gland	Wu et al. (2019)
✓		✓		✓	✓		Restored ECM and enhanced growth factor activity – increased cell attachment and survival, aided epithelial regenerative process	Moussa et al. (2019)
✓		✓			✓	✓	Increased α-amylase activity, reduced levels of adult ductal stem/progenitor cell markers, recovered of basic epithelial tight junction markers to levels similar to SG tissue; provided appropriate microenvironment for cell survival and cytodifferentiation for regenerative therapy	Shin et al. (2019)
✓				✓	✓		Reduced inflammatory cytokine and senescence-related gene expression; reversed oxidative stress; prevented irradiation-induced cellular senescence	Dong et al. (2021)

normal tissues. This begins with DNA damage, the production of ROS, subcellular organelle damage (incorporating the mitochondria and endoplasmic reticulum) and autophagy (Kim et al., 2019). Whilst these responses are all actively involved in cancer cell death, the activation of damage-repair and survival signaling responses can be activated in a small number of the cancer cells present, ultimately resulting in cancer cell survival and tumor resistance to radiation (Kim et al., 2019). This can then lead to tumor regrowth and/or recurrence, hindering the overall effectiveness of radiotherapy. Following exposure to irradiation,

TABLE 4 Approaches for mediating the TME post surgical resection.

Type of biomaterial			Site specific approach				Target		Result	Reference
Implant	Injection	Other	Environmental	Regeneration	Drug delivery system	Stem cell therapy	Primary resection/ Local site	Metastasis		
✓			✓					✓	Displayed cytotoxicity to cancer cells, enhanced intracellular ROS, inducing apoptosis in cancer cells, significantly altered expression of genes related to apoptosis	Samadzadeh et al. (2021)
✓					✓		✓		Effective drug delivery administration, displayed cytotoxic effect against cancer cells, improved tumor inhibition	Ranganath and Wang (2008)
✓			✓		✓		✓	✓	Inhibited local recurrence of the tumor and metastasis, enhanced the distribution of CAR-T cells within the damaged site, subsequently triggered platelet activation in the inflammatory microenvironment	Hu et al. (2021)
		✓	✓				✓	✓	Inhibited local tumor recurrence and could potentially prevent metastasis	Chen et al. (2019b)
	✓		✓				✓	✓	Controlled release of gemcitabine and anti-PD-L1 blocking antibody evoked immunogenic tumor phenotype, promoted immune-mediated tumor regression and prevented tumor recurrence at the primary resection site	Wang et al. (2018a)
✓			✓	✓			✓	✓	Established an immune environment that inhibited tumor formation and inhibited tumor growth	Wolf et al. (2019)
✓			✓				✓		Sustained release, reduced viability and growth of cancer cells *in vitro*. Induced generation of ROS and cell cycle arrest, also attributed to the death of cancer cells	Jain et al. (2016)
✓					✓		✓	✓	Apoptosis resulted in decrease in viability of cancer cells, produced antitumorigenic and anti-metastatic effects	Zhan et al. (2013)
✓						✓	✓		Increased stem cell survival when delivered to the surgical site, reduced tumor volume and increased survival in mice	Sheets et al. (2020)
✓						✓	✓		Increased retention of stem cells within the surgical site, reduced viability of cancer cell spheroids, reduced tumor volume, increased time until recurrence and prolonged median survival in mice	Bagó et al. (2016)

(Continued on following page)

TABLE 4 (*Continued*) Approaches for mediating the TME post surgical resection.

Type of biomaterial			Site specific approach				Target		Result	Reference
Implant	Injection	Other	Environmental	Regeneration	Drug delivery system	Stem cell therapy	Primary resection/ Local site	Metastasis		
✓			✓	✓			✓		Significantly reduced cancer cell viability, promoted viability and proliferation of healthy cells; modulated neutrophil recruitment to the damaged site within 24 h of surgical resection	Sarkar and Bose (2020)
✓			✓		✓		✓	✓	Promoted wound healing post-resection; scaffold responded to the TME to deliver sustained drug release which inhibited growth and recurrence of the tumor, reduced drug toxicity, was not cytotoxic to healthy tissue	Shi et al. (2020)
✓			✓				✓	✓	Enhanced therapeutic effect was observed, reduced tumor tissue acidity, inhibited tumor recurrence and metastasis, accelerated wound regeneration	Xue et al. (2021)
	✓				✓		✓		Heat-sensitive hydrogel capable of temperature-dependent and extended drug release, showed significant anticancer efficacy with no systemic side effects	Cho and Kwon (2014)

there is an increase in the repair and protect mechanisms as well as the level of molecules associated with them, such as superoxide dismutase and glutathione to name a few (Tarnuzzer et al., 2005). The molecular pathways and mechanisms arising from irradiation therapy-related adverse TME conditions have been described in detail in several reviews (Lara et al., 2015; Morgan and Sowa, 2015; Sprung et al., 2015)

Whilst radiation is effective in initiating damage in cancer cells, it also targets local healthy cells. Not only do some patients get recurrence or metastasis of the cancer from instances where not all cancer cells are depleted following treatment, but the large majority of patients also experience unpleasant side effects. These can vary depending on the region targeted by the radiation beam. For example, a common side effect incurred during radiotherapy for head and neck cancer is xerostomia, more commonly known as dry mouth (Nelson et al., 2013; Holmberg and Hoffman, 2014). This can continue long after the treatment is complete, leaving the patient with life-long conditions. Many of these ailments that arise as a side effect of a particular treatment are only managed using surface-level treatments.

4.2.2 Treatment approaches post-Irradiation therapy

An overview of the methods used to mediate the TME post-irradiation therapy is provided in Table 3. One of the challenges in finding effective methods to overcome damage to normal tissue is the fact that whilst normal tissues will have close to identical cellular processes, there are several independent, localized parameters, such as the loss of stem cells, that can cause different organs to react in a completely different manner. This is covered in detail in a review conducted by Barazzuol et al., which discusses both the short- and long-term effects of radiation on the salivary glands, cardiopulmonary system and brain (Barazzuol et al., 2020).

Recent work has delved into how altering the precision of the radiation dose given can improve treatment by reducing exposure of otherwise healthy tissue. One such method that has been investigated for its beneficial non-invasiveness of non-cancer tissue is intensity-modulated radiotherapy (IMRT), which precisely delivers the target dose of radiation to the tumor or specific areas within the tumor (Taylor and Powell, 2004). A similarly interesting concept, currently in preclinical development, is microbeam radiation therapy (MRT), which delivers one large dose of fractionated radiation across the tumor in a grid pattern, meaning that some areas of the tumor are hit with radiation whilst other areas are spared (Fontanella et al., 2015).

A number of methods focus on reoxygenation of the microenvironment (Siemann and Horsman, 2015; Yang et al., 2021). It is well established that oxygen deficiency, leading to a hypoxic microenvironment, in the TME limits the efficacy of radiotherapy. In an attempt to overcome this, as number of methods have looked at ways in which oxygen levels can be replenished, and what makes the use of biomaterials in such applications particularly exciting is the ability to manipulate the biomaterials to gain different results. For example, Yang et al. developed a hydrogel for the purpose of increasing oxygen delivery to the hypoxic TME. But, what makes this design particularly interesting is its exploitation of the thermosensitive property of polymers. The delivery of a sufficient amount of

oxygen to the hypoxic site without leaking any oxygen into blood circulation had proven difficult, but hydrogels offered one route that the exogenous oxygen could be delivered in a suitable dose, directly to the target site, and activated to trigger the release of oxygen, reducing the aforementioned issues previously encountered. When heated post-injection, the hydrogel released exogenous oxygen to the hypoxic site. When tested on a mouse model, the increase in oxygen was found to not only improve the efficacy of radiotherapy by relieving tumor hypoxia, it also induced downregulation of HIF-α, significantly reducing suppressing tumor growth and subsequently prolonging survival (Yang et al., 2021).

However, not all methods of correction have been successful. In a study performed by Tarnuzzer et al. evaluating the radio-protective effect of cerium oxide nanoparticles in normal and tumor cells, the treatment was almost 99% effective in protecting against radiotherapy in a normal human breast cell line but showed no significant effectiveness against a human breast tumor cell line (Tarnuzzer et al., 2005). Kaigler et al. found that by simply incorporating VEGF into a poly (lactide-co-glycolide) (PLGA) scaffold enabled better angiogenesis/neovascularization/blood vessel formation and function, as well as bone formation/regeneration following radiation (Kaigler et al., 2006).

4.3 Surgical resection

Surgical resection of solid tumors is another common method of treatment and is the most obvious method of treatment for localized solid tumors. However, when removing the tumor, it is difficult for the surgeon to completely remove the cancerous mass in all of its entirety without touching the surrounding healthy tissue. The aim of surgery is to completely remove the tumor but leave surgical margins of healthy tissue to reduce the chance of the cancer returning. However, depending on the complexity of the tumor this is not always possible and there is no official guideline on what size this margin should be. Studies have shown that the type of cancer affects the conditions within the surrounding TME in different amounts and to different extents; therefore the resection margin differs accordingly and is usually determined on a patient by patient basis (Cha et al., 2020). In such cases, the surgeon will remove as much of the tumor as possible to reduce the tumor mass and then chemotherapy or radiation treatment will be given to clear any remaining cancer cells. This is then routinely confirmed by pathological inspection of the margins, and advice is given on whether further surgery is required. Surgery can also be used as a diagnostic tool in identifying if masses are malignant and to determine if and to what extent the cancer has spread. The surgical methods used in diagnostic cases, namely, biopsies, can induce the same response as tumor removal.

4.3.1 Impact of surgical resection on the TME

Whilst tumor resection does not introduce any drugs to the TME like chemotherapy, or directly induce cell damage and death at the target site in the same manner as radiation therapy, surgical resection of tumors also has a substantial impact on the TME, not just at the primary resection site but also at distant, metastasis sites (Alieva et al., 2018). Evidence that suggests that despite being the current 'gold standard' method of removing solid tumors, even

minor and minimally invasive surgical procedures such as biopsies can cause a response from many different pathological processes, which can not only lead to tumor recurrence but also metastasis (Wang et al., 2017; Alieva et al., 2018; Hu et al., 2021). Even in patients that previously showed no metastatic indicators, there have been numerous instances where the cancer has returned and is metastatic following surgical resection (Chen Z. et al., 2019). Surgical resection can cause direct alterations within the TME that ultimately leads to a number of unfavorable changes including an increase in the number of cancer cells which circulate in the blood and suppression of anti-tumor immunity (Tohme et al., 2017b).

One of the major concerns following surgical resection specifically is local cancer recurrence and is a common problem in several types of cancer often caused by inadequate resection margins, which allows any remnant cancer cells to continue to proliferate. Complete resection with no residual cancer cells is thought to be key in not only preventing metastasis, but also in reducing the likelihood of chemoresistance, which often arises due to chemo-resistant and senescent cells (Bilbao et al., 2021).

The physical act of surgery and cutting through tissue also influences injury-induced inflammation within the TME; this is one of the main causative factors related to surgical resection that contributes to an adverse TME. There is an abundance of evidence regarding inflammation post-surgery and inflammatory cells influencing cancer progression (Forget et al., 2013; Tohme et al., 2017a; Singh et al., 2019; Kinoshita and Goto, 2021; Zhao et al., 2021). An additional aspect that needs to be taken into consideration, specifically when performing surgical resection, is the loss of function within the organ. This is important with organs such as the lung and liver, where organ function reduces quite drastically following resection, particularly in cases where large margins are required (Cha et al., 2020). For example, a lobectomy for lung cancer can reduce the function of the lung by 25%, in addition to its already hindered performance due to the cancer. Whilst a wedge resection is not as drastic, the likelihood of local cancer recurrence increases up to two-fold (Samadzadeh et al., 2021).

4.3.2 Treatment approaches post-surgical resection

As shown in Table 4, the vast majority of interventions used as a reparative approach post-surgery are hydrogel systems placed in the surgical incision site following tumor removal. A recent review by Feng et al. gives a fantastically detailed insight into hydrogel-based biomaterials used postoperatively and is recommended by the authors (Feng et al., 2023). One exciting approach developed by Chen et al. incorporates a bio-responsive immunotherapeutic gel in spray form that can be directly sprayed onto the tumor resection cavity (Chen Q. et al., 2019). The gel contained anti-CD47 antibody, which increases phagocytosis of cancer cells by macrophages. Furthermore, through H^+ scavenging via calcium carbonate nanoparticles, which impairs initial T cell responses that in turn control tumor growth, the gel was also able to facilitate the reversal of the immunosuppressive TME and induce systemic immunological responses to prevent both local recurrence in the tumor cavity and also any potential metastatic spread (Chen Q. et al., 2019).

One of the benefits of the various tissue engineering approaches, such as those discussed within this review, is the ability to incorporate components which provide additional benefits. This is highlighted in a method by Wang et al. where they developed an injectable hydrogel containing the chemotherapy drug gemcitabine and anti-PD-L1 blocking antibody (aPDL1) (Wang C. et al., 2018). Whilst the hydrogel locally delivers the chemotherapeutic to promote an immunogenic tumor phenotype within the TME, the release of aPDL1 increases antitumor responses, leading to immune-mediated rejection of the tumor and also preventing tumor recurrence after the tumor has been surgically removed (Wang C. et al., 2018). A similar concept was used by Hu et al. whereby a hydrogel system was used to deliver combination immunotherapy to the surgical resection site following tumor resection to prevent the recurrence of cancer (Hu et al., 2021). Naturally occurring compounds can also be used to exploit their benefits. In a study by Jain et al., (derived from black pepper) was incorporated into an electrospun fibre, and was shown to display anticancer properties (Jain et al., 2016). They found that the inclusion of piperine generated ROS and induced cell cycle arrest, both leading to the death of cancer cells, with no deleterious impact on healthy cells.

5 Emerging technologies for TME remediation

As with any field, there are constantly exciting new and emerging technologies being developed with regards to mediating the damaged microenvironment following cancer. Tissue engineering is one discipline which has been explored to counteract these problems. Such emerging approaches have been summarized in Table 5.

5.1 Biomaterials for targeting the TME

In recent years, there has been an increase in employing the use of biomaterial scaffolds as engineered pre-metastatic niches (Aguado et al., 2018). These sites, conditioned as a subsequent effect of systemic responses to the primary tumor, are found in distant organs and are suited to the growth and survival of tumor cells before the cells are even present in the site (Aguado et al., 2017; 2018; Peinado et al., 2017). It has been found that the introduction of such a scaffold elicits a foreign body response effect when implanted, meaning that immune cells and/or including metastatic cells are drawn to the scaffold (Dondossola et al., 2017). Biodegradable polymers are a good choice of material as once implanted, they safely degrade within the body whilst reinstating the microenvironment, with many polymers, such as polycaprolactone, already having Food and Drug Administration (FDA) approval. It is believed that the main reason for the failure of tissue-engineered constructs *in vivo* is due to incompatibility and the inability to integrate the graft with the patient's own tissues. This is primarily due to poor neovascularization, meaning that the graft is unable to support cell survival and ultimately cannot survive long-term (Gigliobianco et al., 2015; Sun F. et al., 2021). For this reason, there are a number of emerging biomaterials which can incorporate and release growth factors to promote the formation of new blood

TABLE 5 An overview of some of the emerging technologies within the field, including the treatment provided, the reparative approach used and its target.

Cancer (Y/N)	Target			Treatment					Method			Reference
	Environment	Regeneration	Drug delivery	Radiation	Chemotherapy	Surgery	Other	Stem cell therapy	Biomaterial	Drug	Other	
Y	✓					✓			✓	✓	✓	Wang et al. (2018a)
N			✓			✓				✓		Romanò et al. (2016)
Y						✓				✓		Sun et al. (2016)
Y	✓		✓				✓		✓	✓		Mei et al. (2019)
N	✓	✓				✓		✓	✓			Li et al. (2019b)
Y	✓		✓		✓						✓	Yang et al. (2019)
Y	✓						✓				✓	Zhang et al. (2021)
Y			✓				✓		✓	✓		Xie et al. (2021)
Y	✓		✓				✓		✓	✓		Ren et al. (2021)

vessels. Vascular endothelial growth factor (VEGF) is one particularly popular growth factor that is incorporated into scaffolds, as it is believed that even on its own, VEGF is capable of inducing angiogenesis (Gigliobianco et al., 2015; Campbell et al., 2017; Seah et al., 2020; Sun H. et al., 2021; Kim et al., 2021). However, inducing angiogenesis should be undertaken with caution, as inducing the formation of new blood vessels in areas where cancer cells are still present can facilitate tumor growth and could allow the cells to enter the systemic blood flow, with the possibility of inducing metastasis (Muz et al., 2015).

One of the major drawbacks to current chemotherapy treatments is that an ineffective amount of drug reaches the tumor using typical administrative routes. One prime example of this is that when administered intravenously, less than 0.5% of the total dose of paclitaxel given reaches the tumor (Chua et al., 2020). This is difficult to overcome by simply altering the dose as factors such as the drug properties and pharmacokinetics/pharmacodynamics, as well as toxicity, need to be considered. Researchers are currently looking at new drug delivery systems that will enable the drug to be delivered directly to the target site. One popular method is incorporating the drug into biomaterials such as electrospun mats or hydrogel systems. Scaffolds are commonly being used as a local drug delivery method in cancer treatment, as they have the potential to cover multiple avenues, including stimuli-responsive drug release and can be used in combination with other treatment methods such as stem cell treatment and immunotherapy (Zhao and Cui, 2020). One group developed a drug-eluting hydrogel system which, when implanted in a surgical resection site, has the benefits of delivering high doses of the drug directly to the target site, reducing systemic side effects, with continuous and sustained release (unlike intermittent doses with other drug delivery methods) (Brudno et al., 2018). Such qualities are ideal for cancer treatments, as it bypasses systemic administration, meaning less healthy cells are in contact with the chemotherapeutic thus reducing side effects arising from damage to healthy cells, and is overall less invasive and disruptive of the patient's day to day life.

As well as incorporating growth factors and drug compounds into biomaterials, more recent studies are beginning to introduce other compounds such as antibiotics and antioxidants (Kim et al., 2004; Romanò et al., 2016; Celebioglu and Uyar, 2020). Such applications have been seen in relation to non-cancerous diseases, but a consideration of the effects of antioxidants in relation to cancer has gained traction in recent years. This approach allows the scaffolds to be produced to target other events and processes/pathways, potentially providing alternative methods of treatment. To date, such compounds are commonly used in wound-healing applications, such as the incorporation of antibiotics in hydrogels to reduce early post-surgical infection (Romanò et al., 2016). This approach is being evaluated in a number of different applications, where bioactive ingredients are being employed to scavenge free radicals, from using vitamin E in intravenous micelle formulations to scaffolds (Banshoya et al., 2021).

5.2 Combined approaches for targeting the TME

As previously mentioned, techniques are more commonly being used in combination to exploit the advantages of each

individual technique and maximise the overall potential, as well as the ability to produce more than one therapeutic response. There are several published examples of such combinations, including incorporating anticancer chemotherapy agents with ROS responsive compounds to mediate the microenvironment, some of which are discussed below. An *in situ*, injectable bio-responsive hydrogel scaffold designed by Wang et al. is one example of this technique (Wang C. et al., 2018). In this study, the scaffold is suitable for localized chemotherapy through the incorporation of gemcitabine and aPDL1 into a ROS-degradable hydrogel which not only promotes tumor regression but also prevents tumor recurrence after primary resection (Wang C. et al., 2018). Another combined approach study delved into intraperitoneal chemotherapy using hydrogel systems to deliver chemotherapeutics directly into the abdomen as opposed to intravenously, in application for ovarian cancer (Sun et al., 2016). Such a targeted-delivery approach would be favourable over typical IV administration, which affects the entire body.

5.3 Nanotechnology for targeting the TME

The field of nanotechnology and the use of nanoparticles (NPs) is a key interest of researchers in both repair and regeneration tissue engineering aspects, as well as in cancer diagnostics and treatments. There are numerous articles detailing the benefits of nanoparticles in cancer treatments, specifically in modulating the TME and drug delivery (Prabaharan et al., 2009; Li et al., 2018; Zhang Y. et al., 2020). They are commonly used in drug delivery systems as they provide numerous benefits including improving drug properties such as biocompatibility and solubility, which typically hinder the effectiveness of a drug (Yang and Gao, 2017). One advantage of NPs is that their surface chemistry can be modified and tailored to suit the desired outcome. This feature has been utilised for numerous applications in cancer therapeutics, including in diagnostics and also as a direct drug delivery system straight to the tumor. However, less than 1% of the NPs actually reach the tumor, with the majority remaining in circulation, again causing an onset of additional side effects alongside those of the drug itself (Chua et al., 2020). Most commonly, various different NPs are incorporated into a scaffold or gel. These are then employed as post-surgical treatments where they are implanted into the tumor resection site (Qiu et al., 2013). A particularly exciting avenue of cancer treatment investigates the practicality of structurally altering a particular drug (to form a pro-drug), in order to render it inactive, whereupon it is activated when in close contact with a catalyst such as gold or palladium. This allows for specific placing of catalyst "beads" in the precise area of treatment, and the systemic administration of the pro-drug, without the commonly associated side-effects (Adam et al., 2018). This approach has been demonstrated as a practical and efficient approach for chemotherapy delivery (Sancho-albero et al., 2019; Pérez-López et al., 2020; Rubio-Ruiz et al., 2021; Adam et al., 2022). More recently, the approach has also been used to deliver a neuroactive agent into the central nervous system, thus demonstrating its potential for wider ranging applications involved in cancer treatment and recovery (Ortega-Liebana et al., 2022).

5.4 Immunotherapy for targeting the TME

In addition to the three aforementioned treatments, immunotherapy is another modality which targets the TME and acts by activating or suppressing the patient's immune responses through modulating their immune system. Whilst it is not as well-established as the other treatments mentioned in this review, primarily due to its inconsistent efficacy, immunotherapy methods have become increasingly popular avenues for exploration and have even had some clinical success (Bates et al., 2018; Bhattacharya et al., 2020). This includes techniques such as reprogramming of immune cells and checkpoint inhibition. Checkpoint inhibition therapy uses immune checkpoint inhibitors to block the pathways which control immune response and block signalling responses, which under normal conditions can help cancer cells avoid cell death (Brahmer et al., 2018). In tissue engineering approaches, immunotherapy methods are often used in combination with other approaches such as scaffolds or hydrogels, and also in combination with other agents such as chemotherapeutics. The challenges and countermeasures of immunotherapy are similar to those for techniques such as chemotherapy, however, these combination approaches are advantageous in that they are able to be specifically designed, enabling them to counteract known side effects associated with treatment types. For example, whilst immune checkpoint blockade has been shown to have a marked effect in treating against some cancers, it is known to cause adverse side effects in healthy organs. However, these effects were seen to a lesser extent in patients who had also received chemotherapy, improving therapeutic responses and reducing side effects such as chemoresistance. Therefore, studies have looked into ways in which chemotherapy and immunotherapy can be combined, for example, in a hydrogel, in order to get the best possible outcome (Wang C. et al., 2018). Importantly, once a course of radiotherapy has been completed, immune cells play an important role in clearing any remaining cancer cells if the irradiated tumor equilibrium is correctly modulated (Koukourakis and Giatromanolaki, 2020). One particular example that utilises this combination approach is discussed in a paper from Mei et al., where they developed a hybrid hydrogel to be used for photothermal therapy (PTT) and immunotherapy (Mei et al., 2019). In this case, the gel encapsulated both a photothermal drug and an immunological agent. Overall, the gel was found to be capable of delivering the therapeutics in a localised and prolonged manner. Excitingly the authors discovered that the initial PTT cleared the primary tumors whilst producing tumor-associated antigens which worked in combination with the immunotherapeutic to protect against recurrence and metastasis (Mei et al., 2019).

5.5 Cell therapy for targeting the TME

Modulating the microenvironment via cell therapy has been successfully performed to treat other non-cancer related injuries, in ways that could be translatable to treating the damaged microenvironment post-cancer treatment and/or to aid with the regeneration process following such damage. One interesting example of this comes from Li et al., using a hydrogel implant following surgery as a means of transplanting mesenchymal stem cells (MSC) (Li L. et al., 2019). Here, MSCs were used to induce regeneration of the central nervous spinal cord tissue in order to restore motor function in a rat following spinal cord injury, alongside magnesium oxide (MnO_2) nanoparticles, which not only act to alleviate the oxidative microenvironment through regulation of ROS but also improve the viability of the implanted MSC (Li L. et al., 2019). This dual approach is an interesting concept with the ability to not only successfully mediate the harsh microenvironment, but also induce regenerative repair to the damaged site.

Another approach worthy of mention is immune cell therapy. Chimeric antigen receptor (CAR) T cells are one example of an immunotherapeutic approach, with increasing popularity. Since the first CAR T cell treatment was approved by the FDA in 2017, there have been five further approved treatments to date (Hamieh et al., 2023). CAR T cells specifically target tumor associated, or tumor-specific antigens to selectively kill the cancer (target) cells (Johnson et al., 2022). This property can allow for TME mediation by, for example, eliminating tumor associated macrophages which in turn delays tumor progression and prolonging survival (Rodriguez-Garcia et al., 2021). For example, in a study by O'Conner et al, it was found that administration of T-cell infusion post-chemotherapy treatment led to improved tumor-free survival (O'Connor et al., 2012). Such results suggest that the combination of chemotherapy with T-cell infusion can modify the TME in such a manner to enhance anti-tumor effects. It is also important to note that administration of CAR T cells pre-treatment can also be used to condition the TME in such a manner to improve the effectiveness of treatment (Rodriguez-Garcia et al., 2021). The ability to engineer CAR T cells, which includes the ability to remove them from the patient and modify them ex-vivo to give personalised treatment, is discussed in detail in numerous reviews (Li D. et al., 2019; Hamieh et al., 2023). Whilst immunotherapy shows great promise, and can result in longer survival post-treatment, the side effects can be extreme–for example, kidney failure. It is also known to be most effective in advanced cancers, particularly where the number of genetic mutations is high. Between this and only limited success on various phase 3 trials, only a minority of patients are currently selected to receive such treatments. This is discussed in more detail by Semstein et al. (Samstein et al., 2019).

5.6 Other strategies

In addition to the aforementioned emerging techniques, there are a number of other interesting techniques that are being introduced to target the TME post-cancer. One particularly exciting avenue is that of exosome-based approaches. Exosomes are secreted by cancer cells and have a profound effect on the TME, impacting both environmental conditions and inflammatory and immune reactions (Jin et al., 2022). Naturally used to encapsulate substances such as proteins and nucleic acids and transport them to target cells, this property of exosomes has been exploited to be used as a drug delivery system, with advantages such as improved biocompatibility and stability, improved targeting, and reduced toxicity. A review by Koh et al. discusses the future direction of exosome-based approaches; their transition into a clinical setting and their advantages and limitations (Koh et al., 2023).

TABLE 6 Clinical Trials using tissue engineering approaches. A combination of data collected from research papers accessed using PubMed and from clinicaltrials.gov (clinical trial ID number (NCT#) provided if known).

Title (NCT#)	Cancer (Y/N)	Method				Clinical study phase					Reference
		Stem cell therapy	Scaffold	Hydrogel	Drug	1	2	3	4	N/A	
Does an antibiotic-loaded hydrogel coating reduce early post-surgical infection after joint arthroplasty? (N/A)	N			✓						✓	Romanò et al. (2016)
First human implantation of a bioresorbable polymer scaffold for acute traumatic spinal cord injury: a clinical pilot study for safety and feasibility NCT02138110	N		✓						✓		Theodore et al. (2016)
NeoVas Bioresorbable Coronary Scaffold	N		✓			✓					ClinicalTrials.gov (2021a)
Neuro-spinal scaffold NCT02195414	N		✓							✓	ClinicalTrials.gov, 2021c
Coronary Microcirculatory and Bioresorbable Vascular Scaffolds (N/A)	N		✓							✓	ClinicalTrials.gov, 2021d
EktoTherix Regenerative Tissue Scaffold for Repair of Surgical Excision Wounds NCT02409628	Y		✓							✓	ClinicalTrials.gov, 2021e
Phase I-II Clinical Trial with Autologous Bone Marrow Derived Mesenchymal Stem Cells for the Therapy of Multiple Sclerosis NCT02035514	N	✓				✓	✓				ClinicalTrials.gov, 2021g
Efficacy of MUCIPLIQ on the incidence of Radio-chemotherapy-induced mucositis in patients suffering from oral cancer NCT01840436	Y		✓							✓	ClinicalTrials.gov, 2021h
Use of Stem Cells Cultured on a Scaffold for the treatment of aneurysmal bond cysts NCT03066245	N	✓	✓			✓	✓				ClinicalTrials.gov, 2021i
Impact of applying a bandage skin hydrogel on the pains of the head and neck in patients with cancer of head and neck treated with radiotherapy NCT01520701	Y			✓				✓			ClinicalTrials.gov, 2021b
The effect of radiaAce gel in the prevention and treatment of radiation dermatitis in breast cancer patients NCT04481802	Y			✓						✓	ClinicalTrials.gov, 2021f
Safety and Efficacy of Doxorubicin-eluting-bead embolization in patients with advanced hepatocellular carcinoma NCT02525380	Y				✓				✓		ClinicalTrials.gov (2021j)
Preclinical animal study and human clinical trial data of co-electrospun poly (l-lactide-co- caprolactone) and fibrinogen mesh for anterior pelvic floor reconstruction (N/A)	N		✓								Wu et al. (2016)
A Multi-institutional Clinical Trial of Rectal Dose Reduction via Injected Polyethylene-Glycol Hydrogel During Intensity Modulated Radiation Therapy for Prostate Cancer: Analysis of Dosimetric Outcomes (N/A)	Y			✓			✓				Song et al. (2013)

(Continued on following page)

TABLE 6 (*Continued*) Clinical Trials using tissue engineering approaches. A combination of data collected from research papers accessed using PubMed and from clinicaltrials.gov (clinical trial ID number (NCT#) provided if known).

Title (NCT#)	Cancer (Y/N)	Method				Clinical study phase					Reference
		Stem cell therapy	Scaffold	Hydrogel	Drug	1	2	3	4	N/A	
Absorbable Hydrogel Spacer Use in Prostate Radiotherapy: A Comprehensive Review of Phase 3 Clinical Trial Published Data (N/A)	Y			✓			✓	✓			Karsh et al. (2018)
A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma (N/A)	Y							✓			Westphal et al. (2004)

6 Clinical trials

Whilst such interventions have proven to be relatively successful *in vitro*, and in some cases *in vivo*, there are still major difficulties in translating these tissue engineering approaches from the laboratory to human clinical trials. Issues arise with biocompatibility and the inability to accurately mimic the complex and patient-distinctive forms of cancer and its microenvironment in one animal model.

In spite of the issues in translating results from lab to clinic, there are some studies which have shown promise (Table 6). One method that successfully completed clinical trials is Lipsod (Delanian et al., 1994). The concept of this study is that liposomal Cu/Zn superoxide dismutase (Lipsod) is an antioxidant and anti-inflammatory agent that has the potential to reduce radiation-induced fibrosis of the skin and underlying tissue. The drug was administered via intermuscular injection twice a week for a total of 3 weeks, and a reduction in fibrotic tissue was seen in all patients. However, despite the initial success of the clinical trial, there are still several unanswered questions regarding the Lipsod treatment with respect to its mechanism of action.

As previously mentioned, hypoxia is heavily involved in the reduced efficacy of both chemotherapy and radiotherapy. Hypoxic cells have a limited lifespan but exist in equilibrium with their proliferation and migration in the TME matching the rate of cell death in hypoxic regions. Radiotherapy creates free ROS radicals, a mechanism reliant on the presence of oxygen, to exert its toxic effect, meaning that hypoxic cells are resistant to it; and chemotherapy drugs fail to reach tumor cells that are in these hypoxic areas due to poor blood perfusion (Saggar and Tannock, 2015; Graham and Unger, 2018). Both treatments are delivered as multiple individual doses to provide as much protection for healthy cells as possible and to allow for components such as bone marrow to repopulate and repair. However, this simultaneously allows time for hypoxic cells to reoxygenate and any remaining tumor cells to proliferate, reducing the clinical outcome of both treatments (Saggar and Tannock, 2015). Hypoxia-activated pro-drugs (HAPs) have been a research focus for several decades. More recently, TH-302 was used to deliver a cytotoxic warhead to the hypoxic region of the tumor without inducing significant systemic toxicity (Liu et al., 2012). TH-302 research had been both extensive and promising, with the treatment reaching clinic but failing in the stage three trials (Li et al., 2021).

Despite this, researchers are still studying the effects of TH-302 as a promising therapeutic option.

Whilst there are a limited number of treatments/therapeutics in clinical trial stages specifically for post-cancer treatments, the techniques discussed in this review have been successful in other applications. There is potential crossover and application in the repair and/or regeneration of the damaged microenvironment post cancer treatment, where the approach contains certain components that is capable of triggering certain responses which can create a microenvironment favorable for regeneration. One application in which extensive research has looked at using both electrospun fiber mat and hydrogel scaffolds is wound repair and skin regeneration (Zahid et al., 2019). Such scaffolds are used in multiple applications from surgical wounds to major burn victims (Dimatteo et al., 2018; Asiri et al., 2021). Another common application is following surgery for spinal cord injury, where there have been a range of techniques applied in this field to aid repair. The first use of a bioresorbable polymer scaffold for human spinal cord injury was administered to a patient following a spinal fracture and was directly implanted into the spinal cord (Theodore et al., 2016). During the period of study, improvement to the injury was observed, along with no complications or issues arising from the implanted scaffold.

Some of the most common tissue engineering approaches that reach clinical trial stages cannot be easily applied to cancer settings. For example, decellularized ECM (dECM) is commonly incorporated into biomaterials and used for tissue regeneration, however challenges arise when using dECM for cancer research as the ECM can differ significantly in terms of composition and microstructure between individual patients (Hoshiba, 2019).

Based on the focus of the current emerging technologies and those currently in clinical trial, it is clear that the concept of using biomaterials, predominantly hydrogels, to deliver local chemotherapy directly to the target site following surgical resection is where the majority of research is currently focused. This is most likely due to ease of administration via the surgical site without inducing any further stress on the body. Future work into how such therapeutics can be translated for alternative approaches to the delivery of treatments such as chemotherapy and irradiation therapy will further improve the efficacy of cancer treatments whilst reducing systemic side effects.

TABLE 7 A summary of the most common biomaterials used post-radiotherapy and –surgical resection (≥3) and their form, taken from the data collected and provided in the Supplementary Material S1 and organized from most common to least.

Biomaterial	Form		Treatment method	
	Electrospun fibres	Hydrogel	Radiotherapy	Surgical resection
PLGA	✓	✓	✓	✓
Gelatin	✓	✓		✓
Fibrin	✓	✓		✓
PCL	✓			✓
PEG		✓	✓	✓

7 Summary

The cancer death rate has fallen consistently since its peak in 1991, reaching a total decline of 31% in 2018; and this is partially due to improvements in terms of treatment, as well as other factors including better awareness and improved health and lifestyle choices (Siegel et al., 2021). Whilst this reflects the significant improvement in treating cancer, this subsequently means that there are more patients suffering from the, in some cases debilitating, long-term effects caused by damage to the microenvironment during treatment. This highlights the need for mediation treatments capable of restoring the microenvironment with subsequent potential regeneration and restoration of tissue function, improving the patient's quality of life post-cancer remission.

Whilst there are limited options available to patients to alleviate some of the long-term side effects caused by cancer therapeutics, these are often medication-dependent approaches that, with long term use, will eventually lead to damage of other organs, such as the kidneys and liver (Ricart, 2017; Perazella and Shirali, 2018). Tissue engineering approaches offer a fresh alternative to the current route of heavy medication and lifelong dependence.

Each of the current treatment approaches have their positive and negative attributes in terms of the impact that they have on the microenvironment, but on top of this, there are considerations including the location and accessibility of the TME which all play a role in how the damaged microenvironment can be reversed. As discussed, ways to alleviate this include biomaterials and tissue engineering, in addition to new therapies. Based on the location and accessibility of the tumor, and the initial treatment given, this leads on to possible post-cancer treatments in the microenvironment, with the ultimate goal for post-cancer treatment being the development of a method in which the damaged microenvironment can be mediated following initial treatment, with the conclusive aim of initiating the regeneration process.

In terms of biomaterials used, some trends can be seen. Stem cell therapy has been typically used alone in post-chemotherapy methods of remediation, whereas when used following radiotherapy and surgery, stem cell therapy has been combined with a polymer material in either an electrospun scaffold or within a hydrogel system. Hydrogels are more commonly used for surgery, but within this, different administration routes were used, ranging from implants to injections to sprays. The uses and forms of the most common biomaterials encountered during this review have been summarised in Table 7. The most popular biomaterial used in the selection of studies discussed within this review is PLGA, whether that be alone or in combination with other polymers and biomaterials. Approved for clinical use by the US FDA, PLGA is a popular choice for biomaterials for many reasons, including its biocompatibility and degradation properties, which can be tailored based on its molecular weight and, if used in combination with another polymer, its copolymer ratio (Gentile et al., 2014; Patel et al., 2021). It also has the added beneficial properties of favourable drug encapsulation and sustained drug release (Patel et al., 2021). This follows true for the other popular polymers used, such as polycaprolactone (PCL) and polyethylene glycol (PEG). PLGA has great potential as a biomaterial in particular as research has found that PLGA coatings have shown the capability to tune properties such as biocompatibility and degradability, but also mechanical characteristics such as tensile and compressive properties (Maadani et al., 2023). This is key in providing an environment that can mimic that of the natural tissue, including the ability to support the survival and proliferation of cells. For post-surgical repair methods, inclusion of a drug compound, particularly anticancer drugs such as paclitaxel, is also common. There are several additional reasons that polymer-based drug delivery systems are increasing in popularity, some of which include non-immunogenicity, long blood circulation time and high drug loading capacity (Fazal et al., 2023). Such properties are highly beneficial when it comes to designing a drug delivery system, as this would overcome several of the commonly known issues that hinder the efficacy of drug treatments. For further detail, the review by Khan et al. provides an extensive and detailed exploration of the current realm of polymer based biomaterials in tissue engineering (Khan et al., 2023). Furthermore, these polymers can be utilised in different forms and tailored for specific uses. For example, as seen in the studies explored within this review, electrospun scaffolds can be adhered to the tissue itself through a simple stitching; whereas hydrogels can be designed to be injected, implanted, or sprayed topically.

The vast majority of emerging technology is still focused on the idea of containing any further development or recurrence of cancer rather than microenvironmental reversal and what can be done to improve quality of life post-cancer. Whilst this current area of research is of high importance, the significant increase in the number of cancer survivors means that the need for more than palliative-level treatment for the long-term damaged caused by

cancer treatment is now greater than ever. There is still a major lack of investigation into whether the microenvironment can be mediated and returned to its normal state of homeostasis, with the potential of promoting regeneration and return of function to damaged tissue. Additionally, in order to understand the complex relationship between cancer cells and the TME, more research needs to focus on the cancer cells themselves, including looking at patient-derived multi-cell populations which, due to the heterogeneity of cancers, would be necessary to obtain more clinically relevant data. Additionally, as this area is still in its infancy in terms of developing post-cancer treatments, future reviews providing insight into mechanistic action associated with the biomaterials will be important to consider once these technologies have matured further.

Whilst there is still considerable research required with regards to the effects that current cancer treatments have on the TME, it is clear that they do impact said microenvironment in a negative manner and finding a way to combat this issue has the potential to not only improve the efficacy of treatment, but also reduce associated side effects. Tissue engineering approaches have shown promise in the laboratory setting, however translating these results into human clinical studies will be the next major breakthrough. Whilst all have been considered individually, the findings within this review indicate that a treatment option that can not only suppress the cancer but also, whether it be simultaneously or subsequently, neutralize the microenvironment and promote regeneration of healthy tissue is highly desirable and could benefit the lives of patients post-cancer remission.

Author contributions

LW: Writing–review and editing, Writing–original draft, Investigation, Conceptualization. IN: Writing–review and editing. EE: Writing–review and editing, Investigation. AC: Writing–review and editing, Conceptualization.

Funding

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fbiom.2024.1347324/full#supplementary-material

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