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Posted Date: 30 January 2024

doi: 10.20944/preprints202401.1989.v1

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Review

Cancer Treatments: Past, Present, and Future

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Abstract: There is a rich history of cancer treatments which provides a number of important lessons for present and future cancer therapies. We outline this history by looking in the past, reviewing the current landscape of cancer treatments, and by glancing at the potential future cancer therapies.

Keywords: cancer; cancer treatment; cancer treatments history; cancer therapy; oncology; immunology; chemotherapy; radiation therapy; ADC; CART; BiTE; targeted therapy; cancer genetics

Introduction

There are a number of rationally devised cancer treatments which were introduced over the last few centuries. Many cancer therapies introduced a long time ago are still relevant and are still used in oncology practice. We review cancer treatments by looking at therapies introduced before 1970, between 1970 and 2023, and the potential future cancer therapies. 1970 was selected as a demarcation mark because that year tamoxifen, the first important non-cytotoxic small molecule therapeutic, entered clinical trial with the intent to treat breast cancer[1]. Tamoxifen is a selective estrogen receptor modulator known in the 1970s as ICI-46474. The success of tamoxifen initiated the era of molecularly targeted cancer treatments.

Cancer treatments introduced prior to 1970

Surgery was the first rational cancer treatment. Surgery started to evolve into a modern form after anesthesia and antisepsis became available in 19th century[2]. Surgical techniques improved over time with better understanding of cancer biology, improvements of imaging capabilities, and surgical instruments. Improvements in early cancer detection contributed to the increase in the effectiveness of surgical procedures[3]. Surgical procedures in oncology have a variety of goals: preventive as for example removal of potentially pre-cancerous colorectal polyps, potently curative in cases of localized tumors, debulking larger tumors, and palliative. Surgeries have risks of mortality and morbidity; such risks vary by surgery type and extent. Minimally invasive surgeries, laser ablation, cryoablation, can help to minimize such risks. Some surgical procedures which were commonly used in the past, for example radical mastectomy, are now used only in a small subset of cases, after clinical trials proved that in the majority of cases less extensive surgery is equally effective and results in fewer side effects.

Interest in radiation as a treatment modality for cancer was initiated shortly after X-ray discovery in 1895 by Wilhelm Conrad Röntgen. Marie and Pierre Curie's radioactivity research and isolation of radioactive elements helped to lay the foundation for using radiation as a treatment for cancer in the beginning of 20th century[4]. There are multiple types of cancer radiation treatments including: x-rays, proton beams, fast neutron therapy beams, radionuclide therapy (such as Iodine-131), brachytherapy and systemically delivered radionuclides conjugated to antibodies. Brachytherapy involves implanting sealed radioactive seeds and is usually done as an outpatient minimally invasive surgical procedure; however, brachytherapy can be employed as part of an extensive surgical procedure[5]. Radiation therapy is often administered as adjuvant therapy after

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initial surgical treatment, however radiation therapy can also be used with curative or palliative intent, and as neoadjuvant therapy prior to surgical treatment.

Radiation therapy is cytotoxic to cancer cells because it leads to DNA strand breaks leading to cell death. For therapeutic treatment radiation is delivered to the tumor mass and treatments are planned carefully to minimize normal tissue radiation exposure; however, such exposure is usually unavoidable and results in a number of side effects. Normal tissue fibrosis and potentially secondary malignancies as a late sequalae of radiation treatment are known. Radiation therapy to the head may cause cognitive decline, especially in young pediatric patients.

Anticancer chemotherapy development started in the first half of 20th century; based in part on observations of bone marrow and lymph nodes depletion in people exposed to mustard gas during World War I (WWI) chemical warfare and exposure to mustard gas after bombing of US naval ship loaded with mustard gas munition at Bari Harbor, Italy, in 1943 during WWII[6]. Initial articles on nitrogen mustard chemotherapy in patients for treatment of cancer were published in 1946[7]. Nitrogen mustard (mechlorethamine) is a bi-functional alkylating agent, and its mechanism of action is based on producing DNA double strand crossing-links. Folate antagonists such as methotrexate were tested in children with acute leukemia a few years later[8].

Purine antimetabolites were developed in 1950s[9,10]. In the same decade observation of preferential uptake of uracil by tumors in comparison with normal tissue triggered the development of the fluoropyrimidine 5-fluorouracil (5-FU)[11]. During this time, the search for new cancer therapies became more organized and scientific. In the mid-1960s, Skipper and his group reported on the criteria for ''curability'' and on the kinetics of leukemic cells in mice. The criteria described were derived directly from the behavior of bacterial cell populations exposed to antibacterial agents and were based on findings in mice bearing intraperitoneally implanted murine L1210 or P388 leukemia cells[12]. Rodent solid tumor models, some highly metastatic followed a few years later[13,14]. Tubulin inhibitors were developed in the beginning of the 1960s[15], followed by new alkylating chemotherapies such as procarbazine[16,17], and development of topoisomerase 1 and 2 inhibitors[18]. Exploration of combination chemotherapy regimens in the middle of 1960s propelled major improvement in the efficacy of cancer treatments shifting them from short term transient benefits to sustained remissions[19,20,21]. First combination chemotherapy regimens were primarily used in childhood leukemia and were followed by development of MOMP (mechlorethamine, vincristine (Oncovin), melphalan and prednisone) and MOPP (mechlorethamine, vincristine (Oncovin), procarbazine and prednisone) protocols for treatment of Hodgkin's lymphoma[22]. Also, around the same time, clinical efforts started on integrating radiation therapy and combination chemotherapy regimens[23].

Chemotherapy is most lethal to fast growing cells, which means that many side effects are especially noticeable in normal cells with high proliferation, such as hematopoietic cells, upper and lower gastrointestinal tract cells, and hair follicles[24]. Chemotherapy side effects may include nausea and vomiting, fatigue, oral and gastrointestinal mucositis, anemia, increased risk of infections, increased risk of cardiovascular disease, and central and peripheral neurotoxicity, among others. Many chemotherapies induce DNA damage, and as a result there is a risk of secondary malignancies.

In some tumor types, combination chemotherapy regimens are highly effective, for example in childhood leukemia. However, in many advanced non-pediatric malignancies, duration of remissions is limited. Due to critical normal tissue toxicities, dose reduction, treatment delay or in some cases, treatment cessation are necessary. In some relatively rare instances, local chemotherapy delivery such as intrathecal chemotherapy is a possibility, and it helps to limit systemic side effects.

Allogeneic hematopoietic stem cell transplantation (HSCT) for cancer treatment was first evaluated clinically in the 1950s[25,26]. In the 1960s, methods to identify and type human leukocyte antigens (HLA) were developed which enabled HLA matching between donor and recipient, and initiated major improvements in allogeneic HSCT[27,28]. Prior to allogeneic HSCT, high dose chemotherapy or a combination of chemotherapy and radiotherapy are administered to suppress the recipient immune system, in order to prevent graft rejection via graft versus host disease and treat the malignancy. The intensity of such pre-transplantation treatments is adjusted based on patients

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age, and other factors. Non-relapse related mortality two years after allogeneic HSCT has decreased from about 32% in 1980 to about 15% in 2016; infections, graft vs host disease, and multi-organ failure are main causes of mortality. Two-year overall survival after allogeneic HSCT has increased from about 46% in 1980 to about 62% in 2016, graft vs tumor activity is considered to be an important factor in improving overall survival[29].

After observations of highly effective and durable responses to combination chemotherapy regimens and combined modality regimens with chemotherapy and radiation therapy in pediatric patients, there was some hope of obtaining the same level of clinical benefits for the majority of adult-onset malignancies. However, with time it became clear that while combination chemotherapy regimens and combination of chemotherapy with radiation therapy and surgery might result in highly effective and durable responses for some patients, especially with early-stage cancers, for the majority of patients remissions had limited duration. These observations required some re-thinking of the concept of cancer cell killing called the "log-kill hypothesis". This hypothesis stated that when the growth of a tumor is exponential then when treated with effective anticancer drugs, the tumor shrinks by a constant fraction that is a constant logarithmic amount[30].

At the end of 1960s first successful human tumor xenograft models were developed, taking advantage of immunocompromised strains of mice[31]. There are few advantages of using human tumor xenografts: malignant cells are of human tumors origin, a variety of tumor lines are available, the hosts are readily available, and statistically valid numbers of mice can be used in studies resulting in reasonably reproducible outcomes[14]. In some instances it is important to place tumor cells in the appropriate anatomical location, in such cases instead of subcutaneous tumor implants, human tumor xenografts can be implanted in the relevant orthotopic site[32]. Human tumor xenograft models, and later developed patient-derived xenografts (PDX), in which human cancers are directly engrafted into a immunocompromise mouse without in-vitro cell line creation, became important models for cancer treatments development and efficacy evaluation[33].

Cancer treatments introduced between 1970 and 2023

Pharmacological hormone therapies that remove hormones or block their action have been under development since the 1960s. In 1970, tamoxifen, a selective estrogen receptor modulator, entered the first clinical trial with intent to treat breast cancer. Additional classes of pharmacological hormone treatments for breast cancer have been developed, including estrogen receptor degraders, aromatase inhibitors, and luteinizing hormone-releasing hormone (LHRH) agonists. Hormone therapies for breast cancer played a major role in significant decrease of breast cancer mortality[34]. Multiple classes of pharmacological hormone treatments for prostate cancer have also been developed, including androgen receptor antagonists, LHRH agonists, LHRH antagonists, and CYP17 inhibitors[35]. Side effects of hormone therapies may include the loss of bone density, blood clots, and insulin resistance, among others.

The development of treatments targeting genes with oncogenic alterations and related signaling pathways, based on advances in understanding of molecular cancer biology, was a major step in cancer treatment evolution. The first such treatment was trastuzumab, a monoclonal antibody against the extracellular domain of the transmembrane receptor ERBB2, also known as HER2[36]. Trastuzumab (Herceptin) entered initial clinical trial in 1992 and was approved by FDA in 1998. In 2001 imatinib (Gleevec), an ABL1 kinase inhibitor, became the first FDA approved small molecule growth signal inhibitor for cancer treatment[37]. Many targeted treatments have been developed since then. Most such treatments are based on presence of oncogenic alterations in relevant gene(s). Supplemental Table 1 lists genes with oncogenic alterations for which targeted treatments are available as monotherapy or part of combination therapy in at least one indication. For successful deployment of many targeted therapies, it is essential for patients and oncologists to have timely access to tumor sequencing data and properly performed analysis of such data, and it is also preferable to have access to well-structured molecular tumor board[38,39,40]. Some targeted molecular treatments are used for specific cancer subtypes, for example drugs targeting BCL-2, BTK, CDK4, SMO, HDAC, VEGF, JAK-2; this is

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especially the case for monoclonal antibodies targeting hematopoietic subtypes lineage markers such as CD20, CD52, and CD38.

The efficacy of targeted inhibitors varies significantly across tumor types. CML is one of the few indications in which targeted inhibitors transformed a previously almost uniformly lethal cancer into a manageable disease for the majority of patients with long term survival over 90%[41]. ABL1 inhibitors have been very successful in chronic phase CML, which can be detected early and is driven by a single genetic alteration - BCR-ABL fusion[42]. However, ABL1 inhibitors do not provide meaningful benefit in blast phase CML which is driven, in part, by additional genetic alterations in the tumor suppressors and/or transcription factors *TP53*, *CDKN2A*, *CDKN2B*, *IKZF1* and *RUNX1*. There are essentially no successful therapies to substitute for the loss of function of these genes. Nearly all tumors are driven by multiple genetic alterations, however, currently only a subset of genetic alterations can specifically be targeted by drugs. The inability to target a number of key oncogenic alterations is one of major limitations of targeted inhibitors, in addition to acquired resistance to treatments after initial clinical benefits, as well as treatment-induced on target and off target toxicities.

Photodynamic therapy, also known as photochemotherapy, is based on a photosensitizer drug which is non-toxic until it is activated locally by light of a specific wavelength. Such an approach allows limited toxic exposure of normal tissues[43]. The first photosensitizer drug approved by FDA in 1994 was porfimer sodium. Currently there are multiple photosensitizer drugs approved for clinical use.

Antibody drug conjugates (ADC) have the potential of decreasing systemic toxicities due to preferential tumor delivery by binding to a protein found only on the cell surface of tumor cells, while delivering highly toxic payload which otherwise would not be possible to administer at sufficiently high concentration. The first ADC was approved in 2000 by FDA, targeting CD33, and at this point more than 10 ADCs have been approved for clinical use[44]. The toxic payload can be attached using cleavable or non-cleavable linkers. Non-cleavable linkers are associated with lower levels of systemic toxicity, while cleavable linkers might allow bystander killing due to toxic payload release into the tumor microenvironment.

An immune checkpoint inhibitor antibody targeting CTLA-4 was approved by FDA in 2011 and initiated renewed interest in immune system stimulation based treatments. In following years additional antibodies targeting immune checkpoint inhibitors such as PD-1, PD-L1, LAG-3 entered clinical practice[45,46]. Immune checkpoint inhibitors have provided significant, and often durable benefits for many cancer patients; however, the response rate is about 15% to 40% in most solid tumors and 40% to 60% in melanoma and tumors with high mutation rates due to impaired DNA repair such as for example mismatch repair (MMR) deficient tumors. Overall, about 10% to 15% of cancer patients benefit from immune checkpoint inhibitors. Acute and chronic immune-related toxicities are some of the potential side effects of immune checkpoint inhibitor treatments[47].

Bispecific T-cell engagers (BiTEs) recruit T cells to tumor cells by simultaneously targeting CD3 molecule and tumor antigen[48]. The first BiTE was approved by FDA in 2014, it was designed to target CD19 which is expressed on B-cells. BiTEs targeting CD20, CD326 (EpCAM), BCMA, PMEL (GP100) have been later approved by FDA. It is interesting to note that PMEL, also known as SILV, has been previously identified by multiple groups as an ADC target in melanoma[49,50]. BiTEs therapy can also cause cytokine storm syndrome, neurotoxicity, and on-target off-tumor toxicity.

The first oncolytic virus therapy was approved by FDA in 2015, this particular therapy talimogene laherparepvec (T-VEC) is a genetically engineered herpes virus type 1 (HSV-1). T-VEC has two viral genes encoding for ICP34.5 and ICP47 removed, and the gene encoding human granulocyte-macrophage colony stimulating factor (GM-CSF) added[51]. ICP47 suppresses the immune response to viral infections, ICP34.5 blocks stress response to viral infections and its deletion prevents T-VEC from replication in normal cells and allows preferential replication in tumor cells which in some cases have disrupted stress response. Oncolytic virus therapy side effects are similar to symptoms due to viral infections.

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In 2017 ^{177}Lu-DOTATATE became the first peptide receptor radionuclide therapy approved for clinical use[52]. In 2022 FDA approved ^{177}Lu-PSMA-617 for the treatment of patients with prostate specific membrane antigen (PSMA) positive metastatic castration-resistant prostate cancer[53].

In 2017 FDA approved chimeric antigen receptor T cell (CAR-T) therapy against B cell malignancies targeting CD19. Also, CAR-T therapy targeting BCMA has been later approved for clinical use. CAR-T is based on extracting patients T-cells, modifying them with chimeric receptor targeting particular tumor antigen, and infusing modified T-cells back into the patient[54]. CAR-T therapy in some instances can provide long term durable benefits, CAR-T therapy can also cause cytokine storm syndrome, neurotoxicity, and on-target off-tumor toxicity[54].

In the last 60 years, cancer models have become better at modeling the biology of tumors, and cancer treatments have become more targeted, as shown in **Figure 1**.

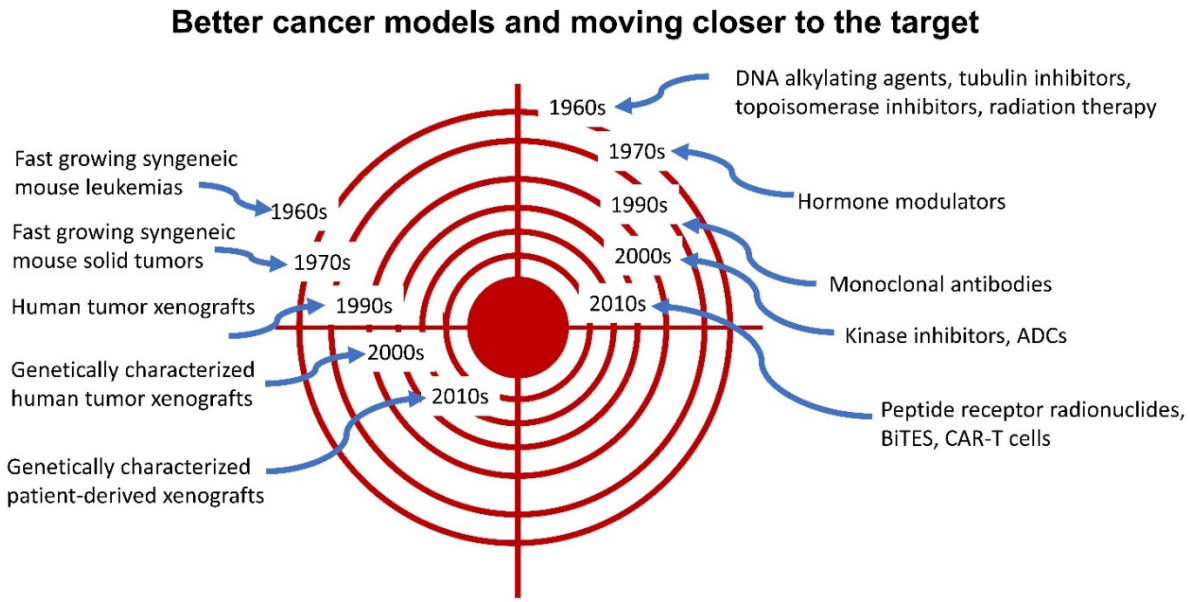

Figure 1. Trends in better cancer models and more targeted cancer treatments.

The advent of targeted therapies resulted in significant improvement in cancer treatment efficacy, increases in remissions duration, decreases in treatments toxicities, and marked by decreases in cancer mortality. For a few malignancies, like CML, where early detection is currently possible, targeted therapies provided the most transformational outcomes. However, due in part to multiple mechanisms of resistance, efficacy of targeted therapies is often limited.

Future of Cancer treatments

Surgery is likely going to continue to be an important cancer treatment modality for the foreseeable future, especially keeping in mind the likely increase in fraction of cancers detected early due in part to advances in circulating tumor-derived DNA (ctDNA) analysis[55] and imaging technologies. The ctDNA analysis will likely need to include examination of ctDNA for oncogenic alterations, in addition to methylation and fragmentation analysis, to achieve clinically relevant levels of specificity. Approaches currently under development to better determine tumor margins should help to increase the efficacy of surgical procedures. Further improvements in minimally invasive procedures and other surgical techniques should help to decrease the morbidity and mortality of surgical procedures.

Radiation therapy is likely going to continue to be an important cancer treatment modality for the foreseeable future. New techniques such as flash radiotherapy[56], the probable increase in use of unsealed radionuclide therapies, and improvements in minimizing radiation exposure to normal tissues are likely going to help to increase the efficacy and decrease the toxicities associated with radiation therapy.

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Chemotherapy is likely going to continue to be an important cancer treatment modality for the foreseeable future, as demonstrate, in part, by unfortunate recent instances of shortages of a number of chemotherapeutic drugs. New formulations, better release control, local administration may help to increase efficacy and decrease toxicities of existing chemotherapeutic agents.

Allogeneic hematopoietic stem cell transplantation is likely going to continue to be an important cancer treatment modality for the foreseeable future. Improvements in HLA matching, managing infections, and managing graft vs host disease will likely help to continue the trend of decreases of non-relapsed related mortality.

Pharmacological hormone therapy is likely going to continue to be an important cancer treatment modality for the foreseeable future. Hormone therapies are an important part of treatment protocols for breast, endometrial, and prostate cancers.

Treatments targeting genes with oncogenic alterations and related signaling pathways are going to continue to be an important cancer treatment modality for the foreseeable future since cancer is a genetic disease driven by oncogenic alterations. There are number of new classes of targeted cancer treatments under development, for example: MAPK1 (ERK) inhibitors, PTPN11 (SHP2) inhibitors, KRAS G12D inhibitors and degraders, RAS(ON) inhibitors, ATR inhibitors, ATM inhibitors, PCNA inhibitors, MYC interaction inhibitors, MDM2/TP53 interaction inhibitors in TP53 WT tumors, spliceosome inhibitors, CLDN 18.2 targeting monoclonal antibodies. Recent efforts transitioning drug development thinking from the maximal tolerated drug dose (MTD) to the lower more precise biologically sufficient dose may help to decrease on-target and off-target normal tissue toxicities. Proteolysis-targeting chimeras (PROTACs) and molecular glue degraders might add additional approach for development of targeted cancer treatments[57,58]. MRT-2359 is an example of a molecular glue degrader targeting the translation termination factor GSPT1 which is under development. Using measurable/minimal residual disease (MRD) to personalize treatment duration might also help to improve effectiveness of treatments[59].

Antibody drug conjugates are likely going to continue to be an important cancer treatment modality for the foreseeable future. There are more than 100 new ADCs under development, some of the targets are: CD20, CD22, CD123, CEACAM5, EphA3. The application of radioligands as the toxic payload is under development, and a possibility of simultaneously attaching different toxic payloads to antibody is being considered. Bispecific antibodies may also provide additional improvements. One of the inherent difficulties in ADC development is identifying cell surface targets with sufficiently high expression on tumor cells and sufficiently low expression on normal cells.

Immune checkpoint inhibitors are likely going to continue to be an important cancer treatment modality for the foreseeable future. TIGIT is one of the newer targets for immune checkpoint inhibitors[60]. Combinations of different immune checkpoint inhibitors, and combinations of immune checkpoint inhibitors with cancer vaccines may help to increase efficacy and the percentage of patients who might benefit from immune checkpoint inhibitors.

Bispecific T-cell engagers are likely going to continue to be an important cancer treatment modality for the foreseeable future. There are a number of new BiTEs under development, these are some of the targets: PSMA, EGFRvIII, CLDN18.2, GD2, DLL3[61,62]. As with ADCs one of the inherent difficulties with BiTEs development is finding the targets with sufficiently high expression on tumor cells and sufficiently low expression on normal tissues cells.

Oncolytic virus therapy is likely going to continue to be available as a cancer treatment modality for the foreseeable future. There are multiple oncolytic virus therapies under development, for example BT-001, RP1, and Teserpaturev/G47Δ (conditionally approved for clinical use in Japan)[63]. Combining oncolytic virus therapies with immune checkpoint inhibitors is one of the potentially most promising strategies[64, 65].

Chimeric antigen receptor T cell therapy is likely going to continue to be an important cancer treatment modality for the foreseeable future. There are several new CAR-Ts under development, these are some of the targets: CD20, CD22, DLL3, CLDN6, CLDN18.2. Currently a large infrastructure is necessary for CAR-Ts production, which makes CAR-T cells rather expensive, there are few efforts under development which might help to decrease cost of CAR-T cell treatments. Armored CAR-T

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cells can secrete cytokines or express cytokine receptors and may potentially increase efficacy, especially against solid tumors[66]. As with ADCs and BiTEs, one of the inherent difficulties in CAR-T cell development is on-target, off-tumor toxicity. Development of Boolean logic antigen engagement control for CAR-T cells might enable decrease in on-target off-tumor toxicity[67]. A recently developed 2-part approach might enable CAR-T cells to target all blood cancer malignancies. CAR-T cells are developed against an antigen present on all blood cancers, for example CD45, CAR-Ts CD45 is modified so CAR-Ts would not target each other; also, CD45 in hematopoietic stem cells is modified so CAR-Ts would not target them, and modified hematopoietic stem cells are used to repopulate patient bone marrow[68].

Cancer vaccines have been in development for a few decades, recent technological developments allow reasonably efficient production of personalized cancer vaccines which might have clinical efficacy[69], mRNA-4157 is an example of such a vaccine under development. There are a number of different cancer vaccines strategies under development, EO2401 vaccine is an example of an approach attempting to activate memory commensal specific T-cells that are cross-reactive against validated tumor associated antigens[70].

The development of microRNA (miRNA), short hairpin RNA (shRNA), and short interfering RNA (siRNA) based cancer therapeutics development began in the beginning of 21th century[71,72]. The following are examples of such therapeutics under development: modified version of miR-34a, nano-formulated miR-122[73]. So far, the biggest challenge for small RNA therapeutics have been inability to provide clinically significant anti-tumor activity in clinical trials.

Pulsed electromagnetic field (PEMF) therapy research started after WWII. PEMF therapy has been approved by the FDA for bone growth simulation[74]. Over the last few decades PEMF therapy use has been investigated as potential cancer treatment, and translational efforts have reached the stage of clinical trials[75].

Observations of preferential homing of some stem/progenitor cells and some bacteria to tumors have opened the possibility of new cancer treatment approaches, which for example may deliver a toxic payload or trigger/guide immune response[76,77,78].

Initial observations of tumor Innervation have been documented at the end of 19th century and over the last few decades an increasing amount of evidence points to potential biological and clinical significance of tumor Innervation[79]. Targeting electrochemical communication between neurons and tumor cells might represent potential cancer treatment modality[80].

There are a number of different gene therapy approaches under development. RZ-001 is an approach based on ribozyme-based RNA reprogramming. Targeting tumor-specific repeat sequences and tumor-specific junctions created by somatic structural alterations using CRISPR has been recently proposed[81,82]. Cancer treatment based on using somatic mutations as targets for insertion of sequences coding for peptides known to trigger immune response due to previous routine vaccination such as measles, mumps, rubella, etc., or coding for peptides triggering cell death is another potential gene therapy approach. Continuing improvements of efficiency of delivery of nanoparticles to different organs and continuing improvements in efficiency of gene editing are expected to make such approaches more likely to succeed as time goes by.

Multiple approaches are likely going to be needed for cancer treatment for the foreseeable future. As summarized in Table 1 all rational cancer treatment modalities introduced prior to 1970 are still in use today and likely will be in use for the foreseeable future, along with all other cancer treatment modalities in use today.

Table 1. Cancer treatment modalities.

Cancer treatment modality	Prior to 1970	1970 to 2023	Future
Surgery	✓	✓	✓
Radiation therapy	✓	✓	✓
Chemotherapy	✓	✓	✓
Allogeneic hematopoietic stem cell transplantation	✓	✓	✓
Pharmacological hormone therapy		✓	✓

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Treatments targeting genes with oncogenic alterations and related signaling pathways	✓	✓
Photodynamic therapy	✓	✓
Antibody drug conjugates	✓	✓
Immune check point inhibitors	✓	✓
Bispecific T-cell engagers	✓	✓
Oncolytic virus therapy	✓	✓
Chimeric antigen receptor T cell therapy	✓	✓

There is unfortunately still a large number of patients, especially those with metastasis, such as brain and liver metastasis who have exhausted all available treatments and have no viable clinical treatment option. Advances in early cancer detection may allow the treatment of more patients before the onset of metastatic disease and, hopefully, with a decreased number and decreased heterogeneity of oncogenic alterations. Additional cancer treatment modalities under development and improvements in existing cancer treatment modalities will be critical in improving clinical care of cancer patients.

The opinions expressed in this manuscript are the authors' own and do not necessarily reflect the view of the National Cancer Institute, the National Institutes of Health, the Department of Health and Human Services, or the United States government.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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