NEU PRESS

JGEHES Journal of General Health Sciences
GENEL SAĞLIK BİLİMLERİ DERGİSİ

Cilt/Volume:7 Sayı/Issue:3 Yıl:2025 Derleme/Review e-ISSN: 2687-5403

https://doi.org/10.51123/jgehes.2025.200

# Treatment Methods in Cancer

**Melisa BEYHAN YILMAZ[1] Turgut ANUK[2]**

[1] Tekirdağ Namık Kemal University, Institute of Health Sciences, Tekirdağ, Turkey
[2] Health Sciences University Erzurum Regional Health Application And Research Center, Department Of Surgical Medical Sciences, Erzurum, Turkey

**Article Info**

**Article History**
**Received:** 13.07.2024
**Accepted:** 17.03.2025
**Published:**26.12.2025

**Keywords**
Chemotherapy,
Radiotherapy,
Gene Therapy,
Cancer Vaccines,
İmmunotherapy.

**ABSTRACT**

The biggest challenges in cancer include mutations in hundreds of different genes that contribute to tumor development and metastasis, as well as effects on epithelial cells, stromal cells, and blood cells. Additionally, cancer continuously accumulates new mutations, enabling it to evolve without remaining stable. Cancer treatment is selected based on the origin, localized area, and progression of the cancer, and varies accordingly. There are many treatment methods for cancer, including traditional approaches such as surgery, chemotherapy, and radiotherapy. These methods involve removing the cancerous region from the body or causing cancer cells to undergo cell death using various agents. However, these approaches can lead to cancer recurrence and damage both cancerous and healthy cells. Therefore, a wide variety of new treatment methods are being explored today. These therapies go beyond traditional approaches, offering more targeted and personalized options that increase the effectiveness of cancer treatment. Current treatment approaches include gene therapy, CAR T-cell therapy, cancer vaccines, and antibody therapies. The aim of this review is to examine cancer treatment methods and provide a scientific evaluation of current treatments, their progress, and limitations. It discusses different treatment methods—such as surgery, radiotherapy, immunotherapy, targeted therapies, and gene therapy—based on the biological activities of cancerous cells. It also evaluates their effectiveness in disease control and impact on survival, and emphasizes the importance of personalized medicine and the treatment methods developed within this context. This review aims to contribute to advances in cancer treatment both clinically and in research.

## Kanserde Tedavi Yöntemleri

**Makale Bilgisi**

**Makale Geçmişi**
**Geliş:** 13.07.2024
**Kabul:** 17.03.2025
**Yayın:**26.12.2025

**Anahtar Kelimeler**
Kemoterapi,
Radyoterapi,
Gen terapisi,
Kanser aşıları,
İmmünoterapi.

**ÖZET**

Kanserdeki en büyük zorluklar; tümör gelişimi ve metastaza katkıda bulunan yüzlerce farklı gende meydana gelen mutasyonlar ile epitel hücreleri, stromal hücreler ve kan hücreleri üzerindeki etkileri kapsamaktadır. Buna ek olarak kanser, sürekli olarak yeni mutasyonlar biriktirerek stabil kalmayan, evrimsel olarak değişebilen bir yapı sergiler. Kanser tedavisi; tümörün kökenine, lokalize olduğu bölgeye ve hastalığın ilerleme düzeyine bağlı olarak seçilmekte ve buna göre farklılık göstermektedir. Kanser için cerrahi, kemoterapi ve radyoterapi gibi geleneksel yaklaşımlar da dâhil olmak üzere birçok tedavi yöntemi bulunmaktadır. Bu yöntemler, kanserli bölgenin vücuttan çıkarılmasını ya da çeşitli ajanlar aracılığıyla kanser hücrelerinin hücre ölümüne sürüklenmesini amaçlar. Ancak bu yaklaşımlar, kanserin nüks etmesine yol açabilmekte ve hem kanserli hem de sağlıklı hücrelerde hasara neden olabilmektedir. Bu nedenle günümüzde çok sayıda yeni tedavi yöntemi araştırılmaktadır. Bu yeni tedaviler, geleneksel yaklaşımların ötesine geçerek daha hedefe yönelik ve kişiselleştirilmiş seçenekler sunmakta, böylece kanser tedavisinin etkinliğini artırmaktadır. Güncel tedavi yaklaşımları arasında gen tedavisi, CAR T-hücre tedavisi, kanser aşıları ve antikor temelli tedaviler yer almaktadır. Bu derlemenin amacı, kanser tedavi yöntemlerini incelemek ve mevcut tedavileri, bunların ilerleme düzeylerini ve sınırlılıklarını bilimsel bir bakış açısıyla değerlendirmektir. Bu kapsamda cerrahi, radyoterapi, immünoterapi, hedefe yönelik tedaviler ve gen tedavisi gibi farklı tedavi yöntemleri, kanser hücrelerinin biyolojik aktiviteleri temel alınarak ele alınmaktadır. Ayrıca bu yöntemlerin hastalık kontrolündeki etkinliği ve sağkalım üzerindeki etkileri değerlendirilmekte; kişiselleştirilmiş tıbbın önemi ve bu bağlamda geliştirilen tedavi stratejeleri vurgulanmaktadır. Bu derlemenin, hem klinik uygulamalarda hem de araştırma alanında kanser tedavisindeki ilerlemelere katkı sağlaması maçlanmaktadır.

**To cite this article**

Beyhan Yılmaz, M., Anuk T. (2025). Treatment methods in cancer. *Journal of General Health Sciences, 7*(3), 635-651. https://doi.org/10.51123/jgehes.2025.200

***Sorumlu Yazar:** Melisa BEYHAN YILMAZ, mlsa.byhn@gmail.com

## INTRODUCTION

Cancer treatment, addressing one of the leading causes of death globally, involves a complex and demanding process that profoundly impacts patients' quality of life. As a major contemporary health concern, cancer remains at the forefront of medical research due to ongoing advancements in its diagnosis and treatment. One of the biggest challenges in cancer management lies in the presence of hundreds of gene mutations that drive tumor formation and progression. (Duffy, 2013; Zehir et al., 2017). Cancer treatment strategies differ based on the type, location, and stage of the disease. Common approaches include surgery, chemotherapy, radiotherapy, immunotherapy, and gene therapy (Duffy, 2013).

### Surgery

The primary goal of surgery is to excise the tumor while minimizing damage to surrounding healthy tissues and organs. Unlike chemotherapy or radiotherapy, which may affect both cancerous and healthy cells, surgical intervention aims for targeted removal with minimal collateral damage (Kleeff & Ronellenfitsch, 2021). Surgery is often part of a multimodal treatment strategy and may be combined with radiotherapy, immunotherapy, or targeted therapies to enhance effectiveness. While it is frequently used to treat localized tumors, surgical procedures can also serve palliative purposes in metastatic cases. In certain cancers, surgery followed by adjuvant therapy can improve patient outcomes by removing residual tumor cells and lowering the likelihood of recurrence. This combined strategy is known as adjuvant surgery. Conversely, when treatments such as chemotherapy or radiotherapy are administered before surgery to shrink the primary tumor, the approach is referred to as neoadjuvant surgery.

Neoadjuvant surgery is employed to reduce tumor size prior to the main surgical procedure, making the operation more effective and less invasive. It is especially beneficial in cases involving large tumors or when preserving clear surgical margins is essential. Beyond treatment, surgery also plays a vital role in confirming a cancer diagnosis, staging the disease, and evaluating the extent of tumor spread. Minimally invasive techniques, such as laparoscopy and endoscopy, are commonly used for both diagnostic purposes and to assess disease progression. Tissue samples obtained during surgery undergo histopathological and molecular analysis, offering critical insights into the tumor’s type, aggressiveness, and potential targets for therapy. In addition, robotic-assisted surgery has emerged as an advanced technique that enhances surgical precision. Systems like the Da Vinci Surgical System provide high-definition, 3D visualizations, enabling surgeons to perform complex procedures with improved accuracy and control.

These systems are particularly useful for prostate cancer, kidney cancer, and some head and neck cancers, enabling surgeons to reach more delicate and hard-to-reach areas. Robotic surgery results in smaller incisions and less bleeding compared to traditional open surgery, which leads to faster recovery and shorter hospital stays for patients. Intraoperative radiotherapy (IORT) is a technique where radiation is directly delivered to the tumor area during surgery. IORT is particularly useful for tumors that cannot be entirely removed through surgery or those with a high risk of recurrence, effectively destroying tumor cells while preserving healthy tissues. This reduces the risk of cancer recurrence and allows patients to achieve better outcomes. For example, IORT applications following surgery for localized cancers such as breast cancer or rectal cancer play a crucial role in eliminating tumor remnants. Sentinel lymph node biopsy is another important innovation in surgery. This method is used to assess the spread of cancer through the lymphatic system. By targeting the lymph node where the tumor first spreads, it allows for a quick assessment of whether the cancer has spread to other regions. This helps avoid unnecessary lymph node removal, leading to a quicker recovery for patients (Baykara, 2016; Tomhe et al., 2017).

### Chemotherapy

Chemotherapy induces cancer cells to undergo apoptosis by causing them to lose their ability to divide using certain agents, thereby halting the progression of cancer. However, its effects extend not only to cancerous cells but also affect healthy cells. Non-targeted chemotherapy can lead to side effects such as hair loss, vomiting, and excessive fatigue due to its impact on healthy cells. Additionally, patients undergoing chemotherapy may experience infections as a result of suppressed immunity. Chemotherapeutic drugs can be classified into two categories: cytostatic agents (biological agents) and cytotoxic agents (Anand et al., 2022). The general mechanism of action of chemotherapeutic agents is to induce cancer cell death pathways by generating reactive oxygen species (ROS) or exerting genotoxic effects (Rodgers et al., 2012).

### Chemotherapeutic Agents

Chemotherapeutic agents are drugs used in cancer treatment to inhibit the growth and proliferation of malignant cells. These agents work through different mechanisms that target the cell cycle, typically by causing DNA damage, inhibiting mitosis, or disrupting metabolic processes to induce cancer cell death. Divided into various classes, such as alkylating agents, antimetabolites, topoisomerase inhibitors, and plant alkaloids, these drugs are selected based on the type and stage of cancer, as well as the individual characteristics of the patient (Table 2). However, the non-selective effects of chemotherapeutic agents can also damage healthy cells, leading to limitations such as toxicity, the development of resistance, and side effects (Table 1). As a result, ongoing research is focused on developing more specific and effective treatment strategies, such as targeted therapies and immunotherapy (Anand et al., 2022).

**Table 1**

*Some Common Chemotherapeutic Agents And Their Side Effects*

| Chemotherapeutic Agent | Common Side Effects | Explanations |
|---|---|---|
| **Doxorubicin** | Cardiotoxicity, nausea, vomiting, hair loss, anemia, immune suppression, mucosal inflammation (stomatitis), cardiovascular toxicity (with long-term use) | **Cardiotoxicity:** May negatively affect heart function. Long-term use can increase the risk of heart failure. |
| **Methotrexate** | Hepatotoxicity, nephrotoxicity, nausea, liver damage, mouth sores, skin rashes, bone marrow suppression (neutropenia, anemia) | **Hepatotoxicity:** Can cause liver damage. **Nephrotoxicity:** May affect kidney function. **Mouth sores:** Stomatitis may develop. |
| **Cisplatin** | Nephrotoxicity (kidney damage), ototoxicity (hearing loss), nausea, vomiting, peripheral neuropathy, bone marrow suppression, loss of appetite | **Nephrotoxicity:** Can lead to kidney damage. **Ototoxicity:** High doses may cause hearing loss. **Peripheral neuropathy:** Nerve damage may lead to numbness and tingling. |
| **Paclitaxel** | Peripheral neuropathy, nausea, vomiting, hair loss, bone marrow suppression (neutropenia, anemia), numbness in hands and feet, skin rashes, fatigue | **Peripheral neuropathy:** Nerve damage may cause numbness and tingling in hands and feet. **Bone marrow suppression:** Can inhibit the production of blood cells. |
| **5-Fluorouracil (5-FU)** | Mucosal inflammation (stomatitis), nausea, vomiting, diarrhea, immune suppression, bone marrow suppression (neutropenia, anemia) | **Stomatitis:** Inflammation and sores in the mouth. **Diarrhea:** May affect the gastrointestinal tract. **Bone marrow suppression:** Can reduce white blood cell counts. |

| | | |
|---|---|---|
| **Cyclophosphamide** | Hair loss, nausea, vomiting, bladder toxicity (hemorrhagic cystitis), bone marrow suppression, immune suppression, infertility risk | **Bladder toxicity (hemorrhagic cystitis):** Inflammation and bleeding in the bladder. **Infertility:** Can affect reproductive capacity in both men and women. |
| **Irinotecan** | Nausea, vomiting, severe diarrhea, bone marrow suppression, liver toxicity, gallbladder inflammation, immune suppression | **Severe diarrhea:** May affect the gastrointestinal system. **Gallbladder inflammation:** May lead to abdominal pain due to inflammation in the gallbladder. |
| **Vincristine** | Peripheral neuropathy, constipation, hair loss, nausea, vomiting, bone marrow suppression (neutropenia, anemia), immune suppression | **Peripheral neuropathy:** Nerve damage can cause numbness and pain. **Constipation:** Reduced bowel movements. **Bone marrow suppression:** Inhibits blood cell production. |
| **Etoposide** | Nausea, vomiting, bone marrow suppression, hair loss, immune suppression, mucosal inflammation | **Bone marrow suppression:** Reduces white blood cell counts, increasing infection risk. **Mucosal inflammation:** May lead to sores and inflammation in the mouth. |

**Alkylating Agents**

These agents directly target DNA, causing DNA damage that prevents cancer cells from proliferating. Generally, lymphoma, multiple myeloma, leukemia, ovarian, breast, lung, and other cancer types can be treated with these agents. The most significant disadvantage of these agents is that, while they cause DNA damage, they can also harm the bone marrow. Prolonged chemotherapy treatment with these agents can lead to acute leukemia (Biersack, 2019).

**Antimetabolite Agents**

These agents function by inhibiting DNA and RNA through interference. They prevent the doubling of DNA during the S phase of cell division. They can be used in the treatment of leukemia, ovarian, intestinal, and breast cancers (Abbas & Rehman, 2018).

**Anthracycline Agents**

Anthracycline agents are naturally occurring antibiotics that trigger the destruction of DNA replication enzymes, thereby halting the cell cycle. However, their use is limited due to the potential for causing permanent damage to the heart (Abbas & Rehman, 2018).

**Antitumor Antibiotic Agents**

These antibiotics are not included in the anthracycline group (for example, actinomycin D, bleomycin, mitomycin C, mitoxantrone, doxorubicin, etc.). They inhibit topoisomerases, preventing the replication of DNA in cancer cells. However, their use is limited due to the potential for causing permanent damage to the heart during long treatment periods. Another significant side effect is their potential to cause acute leukemia. They can be used in the treatment of cancer types such as prostate, breast, lymphoma, and leukemia (Rawangkan et al., 2022).

**Topoisomerase Inhibitors**

Topoisomerase inhibitors include topotecan (topoisomerase I inhibitor), irinotecan (topoisomerase I inhibitor), etoposide (topoisomerase II inhibitor), and teniposide (topoisomerase II inhibitor). These inhibitors are used in the treatment of leukemia, stomach, intestinal, ovarian, and lung cancers. Their function is to prevent the separation of DNA strands, thereby halting replication (Abbas & Rehman, 2018).

### Mitotic Inhibitors

These inhibitors are naturally occurring substances. Mitotic inhibitors block the function of proteins involved in mitosis, preventing the process of cell division. They can be used to treat lung cancer, myeloma, leukemia, lymphoma, and breast cancer (Yakkala et al., 2023).

**Table 2**

*Classification and Mechanisms of Action of Chemotherapeutic Agents*

| Class | Examples | Mechanism of Action |
|---|---|---|
| **Alkylating Agents** | Cyclophosphamide, Melphalan, Ifosfamide | Bind to DNA, cause cross-linking, leading to DNA strand breakage and inhibition of replication. |
| **Antimetabolites** | Methotrexate, 5-Fluorouracil (5-FU), Cytarabine | Mimic natural metabolites, interfere with DNA/RNA synthesis, and inhibit enzymes like thymidylate synthase. |
| **Antitumor Antibiotics** | Doxorubicin, Bleomycin, Mitomycin C | Intercalate into DNA, inhibit topoisomerase II, and generate free radicals causing DNA damage. |
| **Topoisomerase Inhibitors** | Etoposide (Topo II), Irinotecan (Topo I) | Inhibit topoisomerases, preventing DNA replication and repair. |
| **Mitotic Inhibitors** | Paclitaxel, Vincristine, Vinblastine | Disrupt microtubule dynamics, inhibiting mitotic spindle formation and blocking cell division. |
| **Platinum-Based Agents** | Cisplatin, Carboplatin, Oxaliplatin | Form DNA adducts, causing DNA cross-linking and apoptosis. |
| **Hormonal Agents** | Tamoxifen, Letrozole, Flutamide | Block hormone receptors or inhibit hormone synthesis to reduce growth in hormone-sensitive cancers. |
| **Targeted Therapies** | Imatinib, Trastuzumab, Bevacizumab | Target specific molecular pathways (e.g., tyrosine kinase, HER2, VEGF) involved in cancer growth and survival. |
| **Immunotherapy Agents** | Pembrolizumab, Nivolumab, Ipilimumab | Enhance immune response by targeting immune checkpoints (e.g., PD-1, CTLA-4) or activating T-cells. |
| **Epigenetic Modifiers** | Vorinostat (HDAC inhibitor), Azacitidine (DNMT inhibitor) | Modify epigenetic marks to reactivate tumor suppressor genes or inhibit oncogenes. |
| **Proteasome Inhibitors** | Bortezomib, Carfilzomib | Inhibit proteasome activity, leading to accumulation of misfolded proteins and apoptosis. |
| **PARP Inhibitors** | Olaparib, Rucaparib | Inhibit poly (ADP-ribose) polymerase, preventing repair of single-strand DNA breaks. |

**Radiotherapy**

The type of radiation used in radiotherapy is ionizing radiation. Ionizing radiation causes electric charging of biological molecules, allowing the electrical energy delivered by the radiation to reach cells in the body. The electrical energy reaching cancer cells can directly kill them or induce cell death. In cancer cells exposed to the radiation, DNA replication does not occur, inhibiting cell division and forcing cells into apoptosis. The disadvantage of this treatment method is that, while the radiation is targeted to the tumor area, it also affects surrounding healthy cells (Baskar et al., 2012).

Four main principles based on fundamental biological processes have been established to enhance the effectiveness of radiation therapy and prevent damage to healthy tissues. These principles describe the dynamic biological responses of tumor cells to radiation over time. Reoxygenation occurs as oxygenated cells in the tumor regain their oxygen supply between radiation treatments, which can improve the efficacy of radiation, as oxygen enhances the radiosensitivity of cancer cells. Redistribution involves the movement of tumor cells through different phases of the cell cycle, with cells in the radiosensitive G1 and S phases being more susceptible to radiation. Lastly, Repopulation refers to the regrowth of tumor cells between radiation fractions, a process that can be limited by delivering radiation over shorter intervals or employing therapies that inhibit cell proliferation. Understanding and manipulating these 4 Rs are crucial for improving the therapeutic ratio of radiotherapy, maximizing tumor cell kill while minimizing damage to surrounding healthy tissue (Baskar et al., 2012).

Stereotactic radiotherapy (SRS/SBRT), on the other hand, ensures that high doses of radiation are directed very precisely to the target area, destroying the tumor without damaging the surrounding tissues. More advanced methods such as proton therapy and ion therapy affect cancer cells more deeply and cause less damage to surrounding tissues, so they can be preferred especially for pediatric patients and tumors in sensitive areas. Each type of radiotherapy is individualized depending on factors such as tumor size, location, and the patient's general condition and requires a multidisciplinary approach in treatment planning (Chaput & Regnier, 2021).

**Fractionation**

Fractionation is based on the principle of dividing the dose to be administered to the patient in radiation therapy. This approach increases the likelihood of healthy cells surviving with minimal damage while delivering radiation to cancerous cells. Since the 1920s, different regimens of radiation therapy based on total dose and number of fractions have been applied through fractionation. These applications are based on the refined linear-quadratic formula (a measure of the energy transferred per unit mass of tissue or organ exposed to ionizing radiation), which allows calculation of time-dose factors. Fractionated radiation therapies are typically administered over several weeks with doses ranging from 1.5 to 3 Gy (Gray, a unit measuring the absorbed energy in a substance exposed to radiation) (Table 3) (Chaput & Regnier, 2021).

**3D Conformal Radiotherapy (3DCRT)**

3D conformal radiotherapy is based on computed tomography imaging. The goal of this treatment method is to localize the tumor mass, target the tumor area precisely, and ensure that radiation reaches only the tumor area, thereby maximizing the preservation of healthy tissues (Table 3) (Gupta et al., 2012).

### Intensity-Modulated Radiation Therapy (IMRT)

Intensity-modulated radiation therapy (IMRT) is based on computer-controlled targeting of the tumor using inverse planning software to regulate the intensity of the beam. Generally, IMRT is applied in head and neck cancers, prostate cancers, and gynecological cancers (Table 3) (Cho, 2018).

### Image-Guided Radiation Therapy (IGRT)

Image-guided radiation therapy ensures accurate positioning of the beam and targets only the tumor region by using imaging before radiation therapy. This helps prevent errors such as positional mistakes in the tumor area and inadvertent radiation to healthy tissues. IGRT involves computerized tomography scans, similar to 3D conformal radiotherapy. The dosage to be administered to the patient is determined using this imaging. IGRT is commonly used in head and neck cancers and prostate cancers (Table 3) (Sterzing et al., 2011).

### Stereotactic Body Radiation Therapy (SBRT)

Stereotactic body radiation therapy is used when the tumor site cannot be cleared using surgical methods. This treatment method delivers high-dose radiation precisely to the tumor area. It is commonly effective in cancers such as non-small cell lung cancer, prostate cancer, head and neck cancer, kidney cancer, liver cancer, and pancreatic cancer (Table 2) (Freeman & King, 2011).

**Table 3**

*Radiotherapy Methods, Cancer Types And Treatment Goals*

| Radiotherapy Method | Cancer Type | Purpose | Explanation |
|---|---|---|---|
| **Fractionation** | **Various Cancer Types** (Breast, Prostate, Lung, Head/Neck) | Delivery of radiation in multiple smaller doses to protect healthy tissues while effectively treating the tumor. Goals include tumor growth inhibition, post-surgical eradication of residual cells, pain relief, and symptom management. | This technique involves delivering radiation in multiple smaller doses over a period of time. It aims to protect surrounding healthy tissues while effectively targeting the tumor. |
| **3D Conformal Radiotherapy (3DCRT)** | **Breast Cancer** | Post-surgical eradication of residual cells, reduction of tumor size, and protection of surrounding healthy tissues by precisely targeting the tumor. | 3DCRT uses advanced imaging to shape the radiation beams to match the tumor's three-dimensional shape. This technique is particularly useful in targeting tumors while minimizing damage to nearby healthy tissues. |
| | **Lung Cancer** | Tumor shrinkage, protection of surrounding healthy tissues, and palliative care. | This method uses conformal radiation to target tumors while reducing damage to surrounding tissues. It is effective for various types of localized cancers, including lung cancer. |
| | **Prostate Cancer** | Local treatment of the tumor and targeting of remaining cells post-surgery. | 3DCRT delivers high-precision radiation to prostate tumors while limiting exposure to nearby tissues such as the bladder and rectum. |

| | | | |
|---|---|---|---|
| | **Head and Neck Cancers** | Local treatment of tumors, eradication of residual tumor cells post-surgery. | This technique allows for precise targeting of head and neck tumors while sparing critical structures like the spinal cord and salivary glands. |
| | **Rectal Cancer** | Tumor shrinkage, alternative to surgery. | 3DCRT is particularly effective in treating rectal tumors, delivering radiation directly to the tumor while minimizing damage to surrounding structures like the bladder and small intestine. |
| **Intensity-Modulated Radiation Therapy (IMRT)** | **Breast Cancer** | Delivery of high-dose radiation to the tumor while minimizing damage to surrounding tissues. | IMRT allows for the modulation of the intensity of the radiation beams to precisely target the tumor, while reducing radiation exposure to surrounding healthy tissues. It is commonly used in cancers where high precision is required. |
| | **Prostate Cancer** | High-precision targeting of the tumor while protecting nearby healthy tissues. | IMRT is particularly effective in treating prostate cancer, where it targets the tumor with precision while sparing critical structures like the rectum and bladder. |
| | **Head/Neck Cancers** | Increased targeting accuracy, protecting surrounding tissues while delivering radiation precisely to the tumor site. | This technique is beneficial for head and neck cancers due to its ability to shape radiation beams to conform to complex tumor shapes while protecting sensitive surrounding structures. |
| | **Lung Cancer** | Treatment of localized tumors, precise radiation delivery with minimal healthy tissue damage. | IMRT can be used in lung cancer to deliver high doses of radiation precisely to the tumor while minimizing radiation exposure to nearby healthy tissues. |
| | **Pediatric Cancers** | Ensuring minimal radiation to surrounding healthy tissues while effectively targeting the tumor in children. | IMRT is highly valuable for pediatric cancers, as it offers precision in delivering radiation with minimal damage to growing, healthy tissues. |
| **Image-Guided Radiation Therapy (IGRT)** | **Breast Cancer** | Real-time tracking of tumor motion to ensure precise radiation delivery. | IGRT uses imaging techniques during treatment to monitor the tumor's position, allowing for real-time adjustments to the radiation delivery. It improves accuracy, especially when the tumor moves during treatment. |
| | **Prostate Cancer** | Monitoring tumor position during treatment for accurate radiation targeting. | IGRT allows for precise targeting of prostate tumors by tracking their position during each radiation session, ensuring accuracy despite patient movement. |

| | | | |
|---|---|---|---|
| | **Lung Cancer** | Monitoring tumor movement due to breathing or other factors, ensuring precise treatment delivery. | For lung cancer, IGRT is essential to track tumor motion caused by respiratory movement, allowing radiation to be delivered accurately even if the tumor shifts. |
| | **Head/Neck Cancers** | Real-time tracking of tumor position to enhance treatment accuracy. | IGRT is used in head/neck cancers to continuously track tumor position during treatment, improving accuracy and effectiveness. |
| | **Liver Cancer** | Tracking tumor position to ensure radiation is delivered accurately during treatment. | IGRT ensures that liver tumors are precisely targeted during each session, accounting for potential movement due to respiratory cycles. |
| **Stereotactic Body Radiation Therapy (SBRT)** | **Brain Cancer** | Treatment of small, localized tumors with a single, high-dose radiation delivery. | SBRT delivers high doses of radiation to small, well-defined tumors in a single or few sessions. It is highly precise and effective for small brain tumors. |
| | **Lung Cancer** | Alternative to surgery for small, localized tumors, with minimal damage to surrounding tissues. | SBRT is an effective treatment for small, localized lung tumors, delivering high doses of radiation in a short period, often serving as an alternative to surgery. |
| | **Liver Cancer** | Palliative treatment to control tumor growth, sparing surrounding healthy tissues. | SBRT is used to treat liver cancer by delivering focused radiation to the tumor, aiming to shrink or control tumor growth while preserving healthy tissue. |
| | **Prostate Cancer** | Treatment of localized tumors, minimizing damage to surrounding healthy tissues. | SBRT is increasingly used for prostate cancer, offering precise treatment of localized tumors with minimal damage to surrounding tissues. |
| | **Metastatic Cancers** | Treatment of tumors that have spread to other areas of the body, aiming to shrink or control tumor growth. | SBRT is also used in cases of metastatic cancer, where it can target tumors that have spread to distant organs, such as the lungs, liver, and spine, effectively shrinking or controlling growth. |

### Gene Therapy

It is typically used as a potential solution for diseases based on genetic disorders such as cystic fibrosis, hemophilia, muscular dystrophy, and sickle cell anemia, as well as in the treatment of cancer, AIDS, and other viral diseases. To date, several gene therapy applications have been used clinically.

Gene therapy involves using vectors such as plasmids, nanojels, or viral vectors to deliver genes that need to be expressed in target cells using recombinant DNA technology. It is also used to introduce genetic material into invasive cells that are unrecognized by immune cells. Vectors must be purified at high concentrations to avoid causing inflammation or allergic reactions in cells after administration to the organism. These vectors aim to enhance the expression of missing genes, increase the functions of non-functional genes, and halt harmful activities in cells (Dunbar et al., 2018).

It should also provide safety not only for the treated organism but also for its surroundings. Vector applications may include DNA microinjection, cationic liposomes, cationic polymers, polymer networks that release bound molecules upon contact with cells, particle bombardment, and so on. Gene therapy in cancer patients aims to address defects in anti-apoptotic and pro-apoptotic genes, correct anomalies in cell death processes, and prevent immune evasion by cancer cells (Dunbar et al., 2018). Genes related to apoptosis (e.g., caspases and the Bcl-2 family) can impact cancer cells beyond apoptotic cell death (Jia et al., 2012; Lebedeva et al., 2003;). Significant gene therapy initiatives include restoring tumor suppressor proteins like p53, Rb (retinoblastoma), p16INK/CDKN2, and PTEN, which regulate the cell cycle and revert cancer cells to their normal state when these proteins are disrupted (Shanker et al., 2011; Vogelstein et al., 2000;).

Gene therapy has long been studied for its potential in treating cancer cells. Indeed, these are significant historical studies in gene therapy. Additionally, the use of antisense oligonucleotides targeting the c-myc gene to slow down melanoma cell growth in another study demonstrated promising results (Fleming et al., 2005). These studies highlight early attempts and successes in applying gene therapy to combat cancer. In addition to the studies mentioned, antisense RNAs targeting mutations in the RAS gene family have been used to suppress tumor growth in colon cancers (Krens et al., 2010; Fleming et al., 2005). Another key aspect of gene therapy involves oncogenic miRNAs, which have specific effects on post-transcriptional genes and are utilized in cancer gene therapy (Broderick & Zamore, 2011; squela-Kerscher & Slack, 2006).

Genes encoding converting enzymes have been translated into multiple clinical studies today (e.g., in prostate cancer and malignant glioma treatment) (Colombo et al., 2005; Nasu et al., 2007; Natsume & Yoshida, 2008). Gene therapies are increasingly being explored for various types of cancer, offering promising alternatives or complementary strategies to conventional treatments. Prostate cancer and malignant gliomas (including glioblastomas) are among the cancers most frequently treated using gene therapy. In these cancers, gene therapy is often applied as part of suicide gene therapy strategies, where therapeutic genes are introduced to convert harmless prodrugs into toxic compounds within the tumor.

Other cancers, such as lung cancer, melanoma, and breast cancer, are also subjects of gene therapy research, aiming to modify tumor cells' genetic makeup to either increase the immune response or restore the function of tumor suppressor genes like p53. Additionally, hematological cancers, such as leukemia and lymphoma, benefit from gene therapies targeting immune cells, enhancing their ability to recognize and kill cancer cells. Overall, gene therapy in cancer is aimed at improving tumor targeting, reducing systemic toxicity, and enhancing the body's own ability to fight cancer, offering the potential for more personalized and effective treatment regimens (Colombo et al., 2005; Nasu et al., 2007; Natsume & Yoshida, 2008).

**Immunotherapy**

Immunotherapy is a treatment method that enhances anti-tumor effects by mobilizing the immune system to eliminate cancer cells through vaccines, monoclonal antibodies, cytokines, and lymphocytes (Syn et al., 2017).

**Cell-Based Cancer Vaccines**

Cell-based cancer vaccines are divided into two types: whole tumor vaccines containing all tumor antigens, including CD4+ and CD8+ epitopes, and dendritic cell vaccines that play a significant role in immunity. Whole tumor vaccines are a simpler type of vaccine compared to dendritic cell vaccines. Dendritic cells are the most potent antigen-presenting cells in the immune system and are considered the most effective pathway for activating T cells. Dendritic cell vaccines work by introducing tumor antigens to dendritic cells, which then present these antigens to CD4+ and CD8+ T cells when administered to the organism. DCexos are membrane vesicles that can express MHC-I (major histocompatibility complex class I) and MHC-II (major histocompatibility complex class II). MHC-I and MHC-II are involved in presenting protein peptide fragments to CD8+ T cells and stimulating the immune system against these fragments (Fu et al., 2020; Yao et al., 2021).

**Viral-Based Cancer Vaccines**

Viral vaccines are preferred for their ability to effectively stimulate the immune system for extended periods. These vaccines are categorized into four types: live attenuated vaccines, inactivated vaccines, viral vector vaccines, and oncolytic virus vaccines (Tashiro & Brenner, 2017). Among these, oncolytic virus vaccines are used in targeted tumor therapy by modifying the virus structure through genetic engineering methods. Oncolytic viruses are selectively capable of killing tumor cells. As a result, tumor antigens are released, and T cells recognize tumor cells. Studies have identified herpes simplex virus, adenovirus, reovirus, vesicular stomatitis virus, and others as oncolytic viruses (Kaufman et al., 2015; Raja et al., 2018).

**Peptide-Based Cancer Vaccines**

Peptide-based vaccines have lower immunogenicity compared to other immunotherapeutic vaccines. These vaccines consist of epitopes from tumor antigens and are often combined with adjuvants to enhance immune system stimulation. Peptide-based vaccines use both CD8+ T cell epitopes and CD4+ T cell epitopes. CD8+ T cell epitopes stimulate immunity through cross-presentation of antigens, while CD4+ T cell epitopes are essential for sustaining immune activation (Tay et al., 2021).

Peptide-based cancer vaccines consist of short peptide chains and long peptide chains. The half-life of short peptide chains is brief, and they transiently activate cytotoxic T cells. Short-chain peptides are limited by MHC-I and MHC-II. Long peptides increase immunogenicity. Additionally, long peptides are processed by antigen-presenting cells, unlike short peptides that directly interact with MHC molecules. These peptides lose some of their chains due to endosomal destruction after cell entry. A portion of the chain loads onto MHC-II and is recognized by CD4+ T cells. Long peptide vaccines are more effective in stimulating immunity for longer periods than short peptide vaccines, showing more effective antitumor effects (Bijker et al., 2007; Bijker et al., 2008; Jhunjhunwala et al., 2021).

**Nucleic Acid-Based Cancer Vaccines**

These vaccines rely on vectors such as plasmids, viruses, etc., to deliver genetic information that codes for tumor antigens into the organism, aiming to increase the expression of these antigens. Nucleic acid vaccines are divided into DNA vaccines and mRNA vaccines (Lıu, 2011; Pollard et al., 2013).

**DNA Vaccines**

These vaccines target the cell nucleus and induce the production of antigens encoded by cytosolic protein synthesis. The produced antigen is processed by MHC-I and MHC-II, allowing presentation to both CD4+ and CD8+ T cells. DNA vaccines are cost-effective, reliable, and specific to their targets. The tumor antigens produced by these vaccines have similar modifications to naturally expressed tumor antigens. Despite their advantages over other cancer vaccines, DNA vaccines are limited by their weak immunogenicity (Suschak et al., 2017; Wang et al., 2004).

**mRNA Vaccines**

mRNA vaccines are divided into non-replicating mRNA and self-amplifying mRNA. Non-replicating mRNA includes a 5' 7-methylguanosine (m7G) cap, 5'-untranslated region (5'-UTR), open reading frame (ORF), 3'-untranslated region (3'-UTR), and 3' poly-A tail regions. These regions are regulatory factors that ensure mRNA stability and transcription formation. After in vitro transcription, an enzyme can add a 5' cap and 3' poly-A tail to the mRNA. Self-amplifying mRNAs contain two ORF regions. One ORF region codes for antigens, while the second ORF region ensures long-term RNA synthesis in cells. Due to their alphavirus-derived nature, self-amplifying mRNAs generate a strong immune response. Self-amplifying mRNAs are often used in cancer vaccine production but are still in the preclinical stage (Bloom et al., 2021; Faghfuri et al., 2021; Pardi et al., 2018).

**Antibodies**

In immunotherapy, antibodies are the most commonly used ligands. These ligands can be used either naked or attached to a nanoparticle. They function by binding to specific and overexpressed antigens on cancer cell surfaces. The most commonly used antibodies for therapeutic purposes bind to HER2 (human epidermal growth factor receptor 2), EGFR (epidermal growth factor receptor), TfR (transferrin receptor), and PSMA (prostate-specific membrane antigen) (Sharkey & Goldenberg, 2009).

In immunotherapy, these antibodies act as inhibitors that enable T cells to recognize checkpoint proteins on the surface of cancer cells, thereby stimulating non-specific immunity against cancer (McCune, 2018).

**CAR-T Cell Therapy**

CAR-T cell (Chimeric Antigen Receptor T-cell) studies are being attempted in various types of cancers, primarily hematologic cancers (Hiramaya et al., 2019; June et al., 2018).

In cancer therapy, CAR-T trials have shown promising results. For instance, CAR-T cell therapy targeting the CD19 antigen has demonstrated significant efficacy in eliminating tumors in B-cell lymphomas. This success is attributed to the sufficient expression of CD19 on the surface of B-cell lymphomas, making it a favorable target for CAR-T cells (Guedan et al., 2018; Hay & Turtle, 2017; Schuster et al., 2019; Sterner and Sterner, 2021;). Other studies have applied CAR-T therapy in cancer types such as non-Hodgkin's B-cell lymphoma (B-NHL) and chronic lymphocytic leukemia (CLL), showing regression of tumor growth and anti-tumor activity in patients. Additionally, in recent years, CAR-T therapy has been explored in solid cancers (e.g., breast, liver, pancreas) beyond hematologic cancers (Hartmann et al., 2017; Park et al., 2018).

The first CAR-T design received FDA approval and was launched in 2017, specifically for B-cell acute lymphoblastic leukemia (B-ALL). Subsequently, in 2010, a second CAR-T therapy received FDA approval (Lim & June, 2017; Neelapu et al., 2017).

## CONCLUSION

Traditional methods used in cancer treatment, such as surgical intervention, chemotherapy, and radiotherapy, have managed to extend patients' lifespans. However, these treatment approaches also target healthy cells, causing the death of both cancerous and healthy cells. Therefore, there is an increasing need for new methods to make cancer treatment more effective and less prone to side effects. In addition, advanced technologies such as minimally invasive surgical techniques, robotic surgery, and intraoperative radiotherapy have made significant contributions to cancer treatment. Furthermore, with the advancement of technology and a better understanding of the cells, targeted therapies and personalized treatment strategies have emerged as revolutionary approaches in cancer treatment. These innovative treatments, including gene therapy, immunotherapy, cancer vaccines, and CAR-T cell therapy, aim to define specific targets for cancer cells while maintaining the normal function of healthy cells and improving treatment efficacy.

These treatment methods, through genetic profiling of patients, enable more accurate predictions of treatment responses and minimize side effects. Thus, personalized and targeted treatment approaches provide a more effective, safer, and less invasive strategy in cancer treatment, improving patients' quality of life.

This article thoroughly examines various methods used in cancer treatment, evaluating the effectiveness, advantages, and limitations of these approaches. It explores how strategies such as surgery, chemotherapy, radiotherapy, immunotherapy, targeted therapies, and gene therapy are applied depending on the stage and biological characteristics of the disease. The critical role of combined treatment approaches in enhancing cancer control and the importance of personalized medicine in improving treatment responses and minimizing side effects are emphasized.

Innovative treatment methods developed in recent years have shown promising results in the fight against cancer, and future research should focus on developing more effective and individualized treatment strategies.

## LIMITATIONS

The lack of sufficient studies and the inability to fully demonstrate the effectiveness of new treatment methods have caused limitations in this review.

### Ethical Approval

At all stages of the study, including preparation, information presentation, literature review, and writing, the study was conducted in accordance with scientific and ethical rules. Care was taken to cite all data and information used within the scope of the study. The study complies with all the terms of the Committee on Publication Ethics (COPE) and was conducted in accordance with the World Medical Association (WMA) Declaration of Helsinki.

### Conflict of Interest

There is no conflict of interest.

### Financial support

There is no financial support.

### Author Contributions

Design: M.B.Y., T. A., Data Collection or Processing: M.B.Y., T. A., Analysis or Interpretation: M.B.Y., T. A., Literature Search: M.B.Y., T. A., Writing: M.B.Y., T. A.

## REFERENCE


Abbas, Z., & Rehman, S. (2018). An overview of cancer treatment modalities. In *Neoplasm*. IntechOpen. https://doi.org/10.5772/intechopen.76558

Anand, U., Dey, A., Chandel, A. K. S., Sanyal, R., Mishra, A., Pandey, D. K., De Falco, V., Upadhyay, A., Kandimalla, R., Chaudhary, A., Dhanjal, J. K., Dewanjee, S., Vallamkondu, J., & Pérez de la Lastra, J. M. (2022). Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes & Diseases, 10*(4), 1367–1401. https://doi.org/10.1016/j.gendis.2022.02.007

Baskar, R., Lee, K. A., Yeo, R., & Yeoh, K. W. (2012). Cancer and radiation therapy: Current advances and future directions. *International Journal of Medical Sciences, 9*(3), 193–199. https://doi.org/10.7150/ijms.3635

Baykara, O. (2016). Kanser tedavisinde güncel yaklaşımlar. *Balıkesir Sağlık Bilimleri Dergisi, 5*(3), 154–165. https://doi.org/10.5505/bsbd.2016.93823

Biersack, B. (2019). Alkylating anticancer agents and their relations to microRNAs. *Cancer Drug Resistance, 2*(1), 1–17. https://doi.org/10.20517/cdr.2019.09

Bijker, M. S., van den Eeden, S. J. F., Franken, K. L. E., Melief, C. J. M., van der Burg, S. H., & Offringa, R. (2008). Superior induction of anti-tumor CTL immunity by extended peptide vaccines involves prolonged, DC-focused antigen presentation. *European Journal of Immunology, 38*(4), 1033–1042. https://doi.org/10.1002/eji.200737995

Bijker, M. S., van den Eeden, S. J. F., Franken, K. L. E., Melief, C. J. M., Offringa, R., & van der Burg, S. H. (2007). CD8+ CTL priming by exact peptide epitopes in incomplete Freund's adjuvant induces a vanishing CTL response, whereas long peptides induce sustained CTL reactivity. *The Journal of Immunology, 179*(8), 5033–5040. https://doi.org/10.4049/jimmunol.179.8.5033

Bloom, K., van den Berg, F., & Arbuthnot, P. (2021). Self-amplifying RNA vaccines for infectious diseases. *Gene Therapy, 28*(3–4), 117–129. https://doi.org/10.1038/s41434-020-00204-y

Broderick, J. A., & Zamore, P. D. (2011). MicroRNA therapeutics. *Gene Therapy, 18*(12), 1104–1110. https://doi.org/10.1038/gt.2011.50

Chaput, G., & Régnier, L. (2021). Radiotherapy: Clinical pearls for primary care. *Canadian Family Physician, 67*(10), 753–757. https://doi.org/10.46747/cfp.6710753

Cho, B. (2018). Intensity-modulated radiation therapy: A review with a physics perspective. *Radiation Oncology Journal, 36*(1), 1–10. https://doi.org/10.3857/roj.2018.00322

Colombo, F., Barzon, L., Franchin, E., Pacenti, M., Pinna, V., Danieli, D., Zanusso, M., & Palù, G. (2005). Combined HSV-TK/IL-2 gene therapy in patients with recurrent glioblastoma multiforme: Biological and clinical results. *Cancer Gene Therapy, 12*, 835–848. https://doi.org/10.1038/sj.cgt.7700857

Duffy, M. J. (2013). The war on cancer: Are we winning? *Tumor Biology, 34*(3), 1275–1284. https://doi.org/10.1007/s13277-012-0567-6

Dunbar, C. E., High, K. A., Joung, J. K., Kohn, D. B., Ozawa, K., & Sadelain, M. (2018). Gene therapy comes of age. *Science, 359*(6382), eaan3672. https://doi.org/10.1126/science.aan3672

Esquela-Kerscher, A., & Slack, F. J. (2006). Oncomirs – microRNAs with a role in cancer. *Nature Reviews Cancer, 6*, 259–269. https://doi.org/10.1038/nrc1840

Faghfouri, E., Pourfarzi, F., Faghfouri, A. H., Abdoli, S. M., Hajiasgharzadeh, K., & Baradaran, B. (2021). Recent developments of RNA-based vaccines in cancer immunotherapy. *Expert Opinion on Biological Therapy, 21*(2), 201–218. https://doi.org/10.1080/14712598.2021.1863644

Fleming, J. B., Shen, G., Holloway, S. E., Davis, M., & Brekken, R. A. (2005). Molecular consequences of silencing mutant K-ras in pancreatic cancer cells: Justification for K-ras-directed therapy. *Molecular Cancer Research, 3*, 413–423. https://doi.org/10.1158/1541-7786.MCR-04-0320

Freeman, D. E., & King, C. R. (2011). Stereotactic body radiotherapy for low-risk prostate cancer: Five-year results. *Radiation Oncology, 6*, 3. https://doi.org/10.1186/1748-717X-6-3

Fu, C., Zhou, L., Mi, Q. S., & Jiang, A. (2020). DC-based vaccines for cancer immunotherapy. *Vaccines (Basel), 8*(4), 706. https://doi.org/10.3390/vaccines8040706

Guedan, S., Calderon, H., Posey, A. D., & Maus, M. V. Jr. (2018). Engineering and design of chimeric antigen receptors. *Molecular Therapy – Methods & Clinical Development, 12*, 145–156. https://doi.org/10.1016/j.omtm.2018.06.002

Gupta, T., Agarwal, J., Jain, S., Phurailatpam, R., Kannan, S., Ghost-Laskar, S., … D'Cruz, A. (2012). Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: A randomized controlled trial. *Radiotherapy and Oncology, 104*(3), 343–348. https://doi.org/10.1016/j.radonc.2012.03.020

Hartmann, J., Schüssler-Lenz, M., Bondanza, A., & Buchholz, C. J. (2017). Clinical development of CAR T cells—Challenges and opportunities in translating innovative treatment concepts. *EMBO Molecular Medicine, 9*(9), 1183–1197. https://doi.org/10.15252/emmm.201707481

Hay, K. A., & Turtle, C. J. (2017). Chimeric antigen receptor (CAR) T cells: Lessons learned from targeting of CD19 in B-cell malignancies. *Drugs, 77*(3), 237–245. https://doi.org/10.1007/s40265-017-0701-3

Hirayama, A. V., Gauthier, J., Hay, K. A., Voutsinas, J. M., Wu, Q., Pender, B. S., … Turtle, C. J. (2019). High rate of durable complete remission in follicular lymphoma after CD19 CAR-T cell immunotherapy. *Blood, 134*(7), 636–640. https://doi.org/10.1182/blood.201888219

Jhunjhunwala, S., Hammer, C., & Delamarre, L. (2021). Antigen presentation in cancer: Insights into tumour immunogenicity and immune evasion. *Nature Reviews Cancer, 21*(5), 298–312. https://doi.org/10.1038/s41568-021-00339-z

Jia, L. T., Chen, S. Y., & Yang, A. G. (2012). Cancer gene therapy targeting cellular apoptosis machinery. *Cancer Treatment Reviews, 38*, 868–876. https://doi.org/10.1016/j.ctrv.2012.01.004

June, C. H., O'Connor, R. S., Kawalekar, O. U., Ghassemi, S., & Milone, M. C. (2018). CAR T cell immunotherapy for human cancer. *Science, 359*(6382), 1361–1365. https://doi.org/10.1126/science.aar6711

Kaufman, H. L., Kohlhapp, F. J., & Zloza, A. (2015). Oncolytic viruses: A new class of immunotherapy drugs. *Nature Reviews Drug Discovery, 14*(9), 642–662. https://doi.org/10.1038/nrd4591

Kleeff, J., & Ronellenfitsch, U. (2021). Surgical oncology: Multidisciplinarity to improve cancer treatment and outcomes. *Current Oncology, 28*(6), 4471–4473. https://doi.org/10.3390/curroncol28060338

Krens, L. L., Baas, J. M., Gelderblom, H., & Guchelaar, H. J. (2010). Therapeutic modulation of k-ras signaling in colorectal cancer. *Drug Discovery Today, 15*, 502–516. https://doi.org/10.1016/j.drudis.2010.02.004

Lebedeva, I. V., Su, Z. Z., Sarkar, D., & Fisher, P. B. (2003). Restoring apoptosis as a strategy for cancer gene therapy: Focus on p53 and mda-7. *Seminars in Cancer Biology, 13*(2), 169–178. https://doi.org/10.1016/S1044-579X(03)00020-8

Lim, W. A., & June, C. H. (2017). The principles of engineering immune cells to treat cancer. *Cell, 168*(4), 724–740. https://doi.org/10.1016/j.cell.2017.01.016

Liu, M. A. (2011). DNA vaccines: An historical perspective and view to the future. *Immunological Reviews, 239*(1), 62–84. https://doi.org/10.1111/j.1600-065X.2010.00978.x

McCune, J. S. (2018). Rapid advances in immunotherapy to treat cancer. *Clinical Pharmacology & Therapeutics, 103*(4), 540–544. https://doi.org/10.1002/cpt.989

Naldini, L. (2015). Gene therapy returns to centre stage. *Nature, 526*(7573), 274–283. https://doi.org/10.1038/nature15818

Nasu, Y., Saika, T., Ebara, S., Kusaka, N., Kaku, H., Abarzua, F., Manabe, D., Thompson, T. C., & Kumon, H. (2007). Suicide gene therapy with adenoviral delivery of HSV-tk gene for patients with local recurrence of prostate cancer after hormonal therapy. *Molecular Therapy, 15*(4), 834–840. https://doi.org/10.1038/sj.mt.6300122

Natsume, A., & Yoshida, J. (2008). Gene therapy for high-grade glioma: Current approaches and future directions. *Cell Adhesion & Migration, 2*(4), 186–191. https://doi.org/10.4161/cam.2.4.7068

Neelapu, S. S., Locke, F. L., Bartlett, N. L., Lekakis, L. J., Miklos, D. B., Jacobson, C. A., Braunschweig, I., Oluwole, O. O., Siddiqi, T., Lin, Y., Timmerman, J. M., Stiff, P. J., Friedberg, J. W., Flinn, I. W., Goy, A., Hill, B. T., Smith, M. R., Deol, A., … Go, W. Y. (2017). Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *New England Journal of Medicine, 377*(26), 2531–2544. https://doi.org/10.1056/NEJMoa1707447

Pardi, N., Hogan, M. J., Porter, F. W., & Weissman, D. (2018). mRNA vaccines — a new era in vaccinology. *Nature Reviews Drug Discovery*, *17*(4), 261–279. https://doi.org/10.1038/nrd.2017.243

Park, J. H., Rivière, I., Gonen, M., Wang, X., Sénéchal, B., Curran, K. J., Sauter, C., Wang, Y., Santomasso, B., Mead, E., Roshal, M., Maslak, P., Davila, M., Brentjens, R. J., & Sadelain, M. (2018). Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *New England Journal of Medicine*, *378*(5), 449–459. https://doi.org/10.1056/NEJMoa1709919

Pollard, C., De Koker, S., Saelens, X., Vanham, G., & Grooten, J. (2013). Challenges and advances towards the rational design of mRNA vaccines. *Trends in Molecular Medicine*, *19*(12), 705–713. https://doi.org/10.1016/j.molmed.2013.09.006

Raja, J., Ludwig, J. M., Geter, S. N., Schalper, K. A., & Kim, H. S. (2018). Oncolytic virus immunotherapy: Future prospects for oncology. *Journal for ImmunoTherapy of Cancer*, *6*(1), 140. https://doi.org/10.1186/s40425-018-0440-2

Rawangkan, A., Wongsirisin, P., Pook-In, G., Siriphap, A., Yosboonruang, A., Kiddee, A., Chuerduangphui, J., Reukngam, N., Duangjai, A., Saokaew, S., & Praphasawat, R. (2022). Dinactin: A new antitumor antibiotic with cell cycle progression and cancer stemness inhibiting activities in lung cancer. *Antibiotics*, *11*(12), 1845. https://doi.org/10.3390/antibiotics11121845

Rodgers, G. M., Becker, P. S., Blinder, M., Cella, D., Chanan-Khan, A., Cleeland, C., Coccia, P. F., Djulbegovic, B., Gilreath, J. A., Kraut, E. H., Matulonis, U. A., Millenson, M. M., Reinke, D., Rosenthal, J., Schwartz, R. N., Soff, G., Stein, R. S., Vlahovic, G., & Weir, A. B. (2012). Cancer- and chemotherapy-induced anemia. *Journal of the National Comprehensive Cancer Network*, *10*(5), 628–653. https://doi.org/10.6004/jnccn.2012.0147

Schuster, S. J., Bishop, M. R., Tam, C. S., Waller, E. K., Borchmann, P., McGuirk, J. P., Jäger, U., Jaglowski, S., Andreadis, C., Westin, J. R., Fleury, I., Bachanova, V., Foley, S. R., Ho, P. J., Mielke, S., Magenau, J. M., Holte, H., Pantano, S., Pacaud, L. B., Awasthi, R., Chu, J., Anak, Ö., Salles, G., Maziarz, R. T., & JULIET Investigators. (2019). Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *New England Journal of Medicine*, *380*(1), 45–56. https://doi.org/10.1056/NEJMoa1809860

Shanker, M., Jin, J., Branch, C. D., Miyamoto, S., Grimm, E. A., Roth, J. A., & Ramesh, R. (2011). Tumor suppressor gene-based nanotherapy: From test tube to the clinic. *Journal of Drug Delivery*, *2011*, 465845. https://doi.org/10.1155/2011/465845

Sharkey, R. M., & Goldenberg, D. M. (2009). Targeted therapy of cancer: New prospects for antibodies and immunoconjugates. *CA: A Cancer Journal for Clinicians*, *59*(4), 226–243. https://doi.org/10.3322/caac.20021

Sterner, R. C., & Sterner, R. M. (2021). CAR-T cell therapy: Current limitations and potential strategies. *Blood Cancer Journal*, *11*(4), 69. https://doi.org/10.1038/s41408-021-00459-7

Sterzing, F., Engenhart-Cabillic, R., Flentje, M., & Debus, J. (2011). Image-guided radiotherapy: A new dimension in radiation oncology. *Deutsches Ärzteblatt International*, *108*(16), 274–280. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097488/

Suschak, J. J., Williams, J. A., & Schmaljohn, C. S. (2017). Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity. *Human Vaccines & Immunotherapeutics*, *13*(12), 2837–2848. https://doi.org/10.1080/21645515.2017.1343776

Syn, N. L., Teng, M. W. L., Mok, P. T. S., & R.A.S., M. (2017). De-novo and acquired resistance to immune checkpoint targeting. *The Lancet Oncology*, *18*(12), e731–e741. https://doi.org/10.1016/S1470-2045(17)30606-5

Tashiro, H., & Brenner, M. K. (2017). Immunotherapy against cancer-associated viruses. *Cell Research*, *27*(1), 59–73. https://doi.org/10.1038/cr.2016.140

Tay, R. E., Richardson, E. K., & Toh, H. C. (2021). Revisiting the role of CD4(+) T cells in cancer immunotherapy — New insights into old paradigms. *Cancer Gene Therapy*, *28*(1–2), 5–17. https://doi.org/10.1038/s41417-020-0183-x

Tohme, S., Simmons, R. L., & Tsung, A. (2017). Surgery for cancer: A trigger for metastases. *Cancer Research*, *77*(7), 1548–1552. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5380551/

Vogelstein, B., Lane, D., & Levine, A. J. (2000). Surfing the p53 network. *Nature*, *408*(6810), 307–310. https://doi.org/10.1038/35042675

Wang, F., Ma, Y., Barrett, J. W., Gao, X., Loh, J., Barton, E., Virgin, H. W., & McFadden, G. (2004). Disruption of Erk-dependent type I interferon induction breaks the myxoma virus species barrier. *Nature Immunology, 5*(12), 1266–1274. https://doi.org/10.1038/ni1125

Yakkala, P. A., Penumallu, N. R., Shafi, S., & Kamal, A. (2023). Prospects of topoisomerase inhibitors as promising anti-cancer agents. *Pharmaceuticals, 16*(10), 1456. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10609717/

Yao, Y., Fu, C., Zhou, L., Mi, Q. S., & Jiang, A. (2021). DC-derived exosomes for cancer immunotherapy. *Cancers, 13*(15), 3667. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8345209/

Zehir, A., Benayed, R., Shah, R. H., Syed, A., Middha, S., Kim, H. R., … Berger, M. F. (2017). Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nature Medicine, 23*(6), 703–713. https://doi.org/10.1038/nm.4333