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Long-lived Subsets and Heterogeneous Plasma Cells in Response to Microbiota, Autoantigen and Vaccination

Chiranjeev Bisht [1*], Ankit Pandey[2] and Tanay Shukla[2]

1Department of Science, MBPG College, Uttarakhand, India

2Department of Biotechnology, IBST, Shri Ramswaroop Memorial University, Uttar Pradesh, India

Corresponding Author*

Chiranjeev Bisht
Department of Science, MBPG College, Uttarakhand, India E-mail: Chiranjeev _b@gmail.com

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Abstract

Long-lived Plasma Cells (LLPCs), which are largely found in the bone marrow, are necessary for the development of durable antibody protection. However, due to the rarity of LLPC, neither their phenotypes nor their heterogeneity have been able to be identified. We demonstrate that IgG and IgM LLPCs exhibit an EpCAMhiCXCR3- phenotype, whereas IgA LLPCs are Ly6AhiTigit-, using single-cell mRNA sequencing, cytometry, and a genetic pulse-chase mice model. IgA and IgM LLPC compartments contain cells with innate characteristics and public antibodies in contrast to IgG and IgA LLPCs, which are mostly contributed by somatically hyper mutated cells after immunisation or infection. In particular, IgM LLPCs differentiate in a T cell-independent way, are substantially enriched with public clones shared among many individual animals, and have affinity for both self-antigens and microbial-derived antigens. Together, our research demonstrates various paths that LLPCs can take and opens the door to a greater comprehension of the cellular and molecular bases of long-lasting antibody protection.

Keywords: Long-lived Plasma Cells • IgA • T cell • Antibody

Introduction

Plasma Cells (PCs) are B cells that have undergone terminal differentiation and have been programmed to produce antibodies. Some of these cells adopt niches in the bone marrow (BM) after first differentiating in secondary lymphoid organs or inflammatory tissues and go on to live as Long-lived PCs (LLPCs), lasting as long as the hosts do without repeated antigen stimulation. LLPCs serve as the foundation for vaccine-induced long-term protection and are significant elements of humoral immunological memory. Understanding LLPC distinction and maintenance is crucial. The scarcity of LLPCs makes research on them difficult. Less than 10 LLPCs produced by a specific vaccine can be identified in 1 ml of Bone Marrow (BM), and in people, LLPCs are only thought to make up about 25% of all Bone Marrow PCs (BMPCs). After lymphocytic choriomeningitis virus infection, the number of virus-specific LLPCs in the BM of mice is thought to be only 20,000–30,000. The fact that PCs in secondary lymphoid organs and BM seem to be a varied population made up of cells produced from numerous B cell progenitors through various activation routes and at various stages of differentiation adds to the problems. All of these PCs in mice express a common set of intracellular and surface markers, such as CD138, XBP1, BLIMP1 (encoded by prdm1), and IRF4.

As a result, it is still difficult to distinguish genuine LLPCs from all other PCs, which is necessary to gain a deeper understanding of the cell biology that underlies their differentiation and maintenance. Long-lasting LLPCs (LLPCs) often have B Cell Receptors (BCRs) that are highly altered and have greater affinities, indicating that they originated from

Germinal Centres (GCs). It has been widely accepted that T cell assistance and affinity maturation during the GC reaction are essential for LLPC formation and survival. In the BM compartment, where comparable enrichment of LLPCs is anticipated, transcriptomic investigations of bulk splenic PCs and BMPCs at the population level have shown overexpression of genes involved in metabolism, chemotaxis, and cell-cell interactions. It is yet unclear whether and how GC experience might encourage those improvements, and it is also unclear whether of those changes specifically apply to LLPCs. The observations suggesting GC-independent LLPC production might potentially occur compound this ambiguity even more. B1 cells and traditional B2 cells are the two main lineages of mature B cells. B1 cells are innate-like B cells that form in the peritoneal and pleural cavities as well as solid organs during the foetal and neonatal stages of development. When compared to B2 cells, B1 cells have a different antigen receptor repertoire, which includes BCRs that preferentially rearrange themselves throughout early development and identify common self-antigens and microbial products. PCs can develop from both B1 and B2 lineages of B cells, although LLPCs are believed to be mostly produced from B2 cells, supporting the idea of GC dependency. Murine BM has PCs with B1-lineage signatures, although it is unclear if these PCs are LLPCs.

We have combined Single-cell RNA Sequencing (scRNA-seq) to analyse the transcriptomes and BCR repertoires of Splenic PCs (SPPCs) and BMPCs in naive and immunised mice, immune profiling to identify subset-defining surface markers, and a genetic pulse-chase approach to estimate the half-lives of PC subsets in order to better characterise LLPCs and probe their heterogeneity and function. Our findings show that Ly6AhiTigit- and EpCAMhiCXCR3- surface phenotypes can be used to specifically identify mouse antigen-specific IgA and IgG LLPCs. We also present a subgroup of unmutated IgM LLPCs that, despite transcriptional similarities to IgG LLPCs generated by T cell-dependent antigens, develops in mice at rest in a T cell-independent manner. These cells are concentrated in public antibody sequences, such as those found in B1a cells that detect self-antigen and commensal microorganisms, and they are somewhat dependent on the microbiota.

Results

Differential SPPC and BMPC phenotypes

IgG LLPCs were largely produced as a result of this vaccination. The detection of PCs was aided by the bacterial artificial chromosome transgenic Blimp1-enhanced yellow fluorescent protein reporter strain. BCRs with a VH1-72 heavy chain and a -light chain were reactive to NP hapten1 in B6 mice, allowing us to sequence-track antigen-specific PCs. We examined two separate time series, sampling SPPCs and BMPCs from six mice in each condition, to determine the temporal sequence of PC production. The surface expression of CD138 on Spleen (SP) and BM cells was used to enrich PCs, which were subsequently sorted and purified as CD138+eYFP+ cells. To process all samples, 10x Genomics performed scRNA-seq runs and four different library preparations. Across all time points and tissue types, 44,189 PCs with constructed BCRs were recovered in total. Automatic clustering divided PCs into 15 distinct clusters based on their transcriptomes after excluding transcripts for IgG after accounting for batch effects. By examining the uniform distribution of genes and Unique Molecular Identifiers (UMIs) found per cell, we evaluated the quality of our datasets.

Identification of immunization-induced LLPCs

We concentrated our investigation on VH1-72++ NP-specific PCs produced in response to NP-KLH vaccination in order to find LLPCs among different PC clusters. In data from immunised mice, a total of 713 such cells were discovered, whereas 4 were discovered in data from naive mice. On the 15-cluster map, the bulk of NP-specific cells were primarily IgG switched and localised in C8 and C9. NP-specific cells showed a spatiotemporal trend of accumulation in C8 and depletion from C9 with time. The BM showed a clear tendency toward C8 accumulation, whereas the SP showed a clear trend toward C9 depletion. We counted the W33L affinity-enhancing mutation and discovered that by day 60, NP-specific BMPCs had the highest affinity for C8, but all SPPCs had the highest affinity for C9 cells. This finding suggests that throughout time, NP-specific cells in splenic C9 may give rise to C8 in the BM. This idea is supported by the fact that the three clusters C3, C7, and C8 had the highest concentrations of immunoglobulin transcripts. Second, genetic data suggests that the antiapoptotic proteins MCL1 and BCL2, the co-stimulatory receptor CD28, and the BCMA receptor are necessary for the long-term survival of LLPCs. All of these genes were found to be substantially expressed in C3, C7, and C8 cells, but Bcl2 was hardly expressed in the shorter-lived C11 IgA and C9 IgG PC subsets.

Surface phenotyping of LLPCs

We carefully examined the expression of genes encoding surface markers that may distinguish the 15 clusters in order to be able to recognise LLPC subsets in the BM or SP by surface phenotyping. Epcam and Cxcr3 were substantially expressed by the long-lived (C7, C8 and C12) and short-lived (C2 and C9) IgG and IgM cells, respectively, in the BM and SP. The relative higher expression of Ly6a and lower expression of Tigit in the long-lived C3 subset of IgA PCs allows for differentiation from the short-lived C11 group. By analysing SPPCs and BMPCs from naive mice using Fluorescence-Activated Cell Sorting (FACS), we discovered that most IgG and IgM PCs in both the BM and SP displayed EpCAM at a variety of levels on the cell surface.

Discussion

Our understanding of long-term antibody-mediated immune protection depends critically on PC lifespan, which appears to be controlled by both extrinsic and internal mechanisms. The long-lived potential of LLPCs is lost when they are removed from their microenvironment, which contains numerous immune and non-immune cell types that produce survival factors like Interleukin-6 (IL-6), CXCL12, APRIL, BAFF, and CD80/CD86. The majority of immunization-induced LLPCs, on the other hand, are hypermutated and require the cytokine IL-21 produced by follicular helper T cells, suggesting that GC PC development may have partially imprinted lifespan. A transcriptomic programme underlying the longevity of LLPCs has been difficult to define, despite the fact that extrinsic factors crucial for LLPC survival are fairly well understood4. This is in part because the BM contains a variety of PCs with various inferred lifespans, but no surface markers have yet been able to separate these subsets. We have described PC subsets in the mouse SP and BM, evaluated their half-lives, and identified the long-lived populations by integrating single-cell sequencing, FACS analysis, and a genetic pulse-chase mouse model.

Our findings support the notion that PC longevity is guided by intrinsic transcription programmes in addition to being influenced by the microenvironment and metabolic changes experienced, and that PC longevity is associated with specific transcriptomic states that take shape relatively early during PC development. BMPCs are movable but also form long-lasting connections with stromal cells, according to intravital imaging. IgG and IgM LLPCs are notable in this context for having high levels of EpCAM expression and low levels of the chemokine receptor CXCR3 expression. EpCAM has a role in the epithelial-to-mesenchymal transition, cancer metastasis, and homophilic adhesion between epithelial cells. EpCAM has also been demonstrated to support memory T cell survival when produced ectopically40. EpCAM may enable IgG and IgM PCs stay anchored to their distinct survival niches and relay signals that control their longevity, while CXCR3 may divert prospective LLPCs away from those niches. It's intriguing that IgA LLPCs are transcriptionally different from IgG and IgM LLPCs, possibly indicating that they have a different history of mucosal development. A recent transcriptome investigation of PCs reported the existence of isotype-specific characteristics in PC transcriptomes. Importantly, IgA LLPCs only express a moderate amount of EpCAM, but their characteristic makes them distinct from other IgA PCs. Both GC-dependent and GC-independent pathways could be used to reach the cell state shared by these two LLPC populations. Most interestingly, C7 IgM LLPC formation does not require T cell assistance, indicating that whatever survival benefit that may be provided by GC exposure may also be imprinted via a fundamentally different mechanism. C7's exclusivity in the public BCR repertoire shows that the precursor state and antigen being identified are crucial.

It is remarkable that different mice have identical clones of the C7 EpCAMhiCXCR3 IgM LLPC in their separate compartments, some of which include antibody sequences specific for phosphatidylcholine that had previously been found in B1a cells that are innately similar. Additionally, while EpCAMhiCXCR3 IgM BMPCs can recover after PC deletion when the microbiota is present as it should be, most of them cannot do so when the microbiota is eliminated by antibiotics, indicating that a sizable portion of these cells are capable of recognising microbiota-associated antigens. At least two C7 public clones that are convincingly able to distinguish between dead cells and intestinal bacteria support this theory. We also found clones in germline configuration with affinity for the microbiota in the IgA LLPC compartment, which lends further credence to this theory. All things considered, our findings show that LLPC development from B cells with innate-like characteristics is possible via a T cell-independent pathway. We discovered that mouse BM contains a lot of IgM PCs, which is in line with earlier research. Contrarily, although IgM BMPCs are also present, human BMPCs are predominately IgA and IgG isotypes. This variation between the two species can be a result of their divergent evolutionary paths. As an alternative, it might originate from SPF mice's comparatively limited antigen exposure history. B1 cells might also be able to change into IgG and IgA isotypes and add to the IgA PC pool.

Future research is necessary to comprehend how innate-like B cells develop into LLPCs and how IgM BMPCs differ between species. As a result, a better mechanistic understanding may hold the key to enhancing our capacity to programme PCs with the desired specificities, isotypes, and longevity for the development of vaccines and the treatment of antibody-mediated diseases.

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Natural Killer Cells in Adoptive Cell Immunotherapy for Cancer

Vikas Yadav* and Deepanshu Kumar

Department of Pharmacy, Noida Institute of Technical Engenieering, Greater Noida, India

Corresponding Author*

Vikas Yadav
Department of Pharmacy, Noida Institute of Technical Engenieering, Greater Noida, India
E-mail: vikasyadav2186@gmail.com

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Abstract

Natural Killer (NK) cells are a distinct subpopulation of innate lymphoid cells with the innate capacity to recognise and destroy cancerous and virally-infected cells. NK cells play a crucial role in anticancer immunity due to their various cytotoxicity mechanisms and capacity to modify the immune response through cytokine production. When NK cells were utilised as immunotherapeutic agents and demonstrated safety and efficacy in the treatment of patients with advanced-stage leukaemia, this role was made clear almost two decades ago. Following the groundbreaking achievements of CAR-engineered adoptive T cell treatment and the development of technologies that can transform cells into potent antitumor weapons, interest in NK cells as a potential immunotherapy option has surged tremendously in recent years. Strategies for the development of NK cell-based therapies emphasise co-stimulatory signalling, checkpoint inhibition, and cytokine armouring to increase NK cell potency and persistence. They also aim to reroute NK cell specificity to the tumour through the expression of CAR or the use of engager molecules. The first generation of NK cell treatments have shown excellent efficacy and amazing safety in the clinic, yielding promising outcomes and igniting strong interest in further research. In this Review, we discuss numerous strategies to increase NK cell cytotoxicity and longevity, assess prospects and obstacles, and consider how the design of future NK cell products will be influenced by the lessons learnt from the clinic and the particular intricacies of each malignancy.

Keywords: Long-lived plasma cells • IgA • T cell •

Antibody

Introduction

Using modified immune effectors in adoptive cell therapy, a promising new treatment option for solid and haematological cancers with few other choices is being explored. Autologous Chimeric Antigen Receptor (CAR) T cell treatment, the first to approach clinical translation and commercialization, has produced long-term sustained remissions in many cases for patients with aggressive B cell malignancies. Nevertheless, difficulties persist despite these gains. The lengthy vein-to-vein time and higher expenses associated with CAR T cell therapy's sophisticated manufacturing process create a challenge for patients who, because of their quickly advancing illness, are in dire need of treatment [1]. Additionally, the need for the patient's own cells as the source material limits eligibility because many patients are frequently extensively pretreated and lymphopenic and might not have enough cells to produce a viable product.

In the clinic, neurotoxicities and CAR T cell-related Cytokine-Release Syndrome (CRS) are additional concerns that necessitate inpatient monitoring. Utilizing CAR T cells in an allogeneic situation necessitates extra genetic editing methods to eliminate the TCR because T cells recognise and mediate a response against non-self via the T cell Receptor (TCR). This reduces the danger of Graft-versus-Host Disease (GvHD) [2]. Natural Killer (NK) cells, on the other hand, are desirable candidates for universal cellular immunotherapy because they are able to recognise their targets without regard to the presence of the Human Leukocyte Antigen (HLA).

An intricate network of activating and inhibiting receptors that can distinguish between healthy and "stressed" cells regulates the action of NK cells' effectors. Whether or not NK cells send out a "kill" or "not kill" signal is determined by the accumulated cues brought on by receptor-ligand interactions. By recognising inhibitory Killer Cell Immunoglobulin-like Receptors (KIRs), which bind self-MHC class I molecules and signal to cease NK cell action, healthy cells are protected. As opposed to this, NK cells attack abnormal self-cells like tumour cells through the mechanism of missing-self recognition [3]. Tumor cells downregulate MHC class I molecule expression in an effort to evade T cell responses and upregulate activating ligands that are induced by stress, such as DNA damage or malignant transformation. These different characteristics give NK cells special advantages for allogeneic medicinal uses. Different NK cell products can be created for cancer treatment thanks to the quick development of novel approaches and the appearance of next-generation technology that enable deeper biological investigations [3]. With the help of next-generation CAR molecules, engineered TCRs, and pre-complexing with cell engagers, we are able to direct NK cells' specificity toward tumours. In this Review, we describe how these special qualities of NK cells are used for adoptive NK cell immunotherapy and give an overview of the evolving engineering strategies to increase NK cell potency and persistence. Finally, we offer a viewpoint on the potential and difficulties that lie ahead as we work to combat solid tumours, protect immune effector cells from the suppressive pressures present in the tumour microenvironment, and develop tools to monitor and address unintended safety concerns.

Biological properties of NK cells

It seems sense to use innate immunity to increase the range of antitumor responses. A role in tumour immunosurveillance is suspected for NK cells, which are specialised immune effector cells within the innate immune system. This hypothesis is supported by preclinical and clinical studies that show a correlation between low NK cell activity and increased cancer susceptibility and higher risk of metastasis. Although it is yet unknown whether NK cells emerge from a distinct set of precursor cells or from multipotent progenitors that also give rise to T lymphocytes, B lymphocytes, and myeloid cells, NK cells are thought to grow from CD34+ progenitor cells in the bone marrow. NK cells lack the expression of the clonotypic TCR and the accompanying CD3 complex, which are necessary for signal transduction, in contrast to T cells and NKT cells. Based on the relative expression of the surface proteins CD56 and CD16, NK cells are often divided into two groups: CD56 bright CD16 low/- (immunomodulatory, cytokine-producing) and CD56 dimCD16+ (cytotoxic) [4].

Strongly cytotoxic, NK cells trigger a powerful immune response by creating immunological synapses with their targets and releasing cytolytic granules and cytotoxic cytokines. Additionally, they can identify antibody-coated cells via their FcRIIIA (CD16) receptor, leading to the generation of cytokines and Antibody-Dependent Cellular Cytotoxicity (ADCC). Due to their capacity to produce a variety of cytokines and chemokines, which influence the activity of dendritic cells, macrophages, and neutrophils, as well as B cell and T cell responses, NK cells have also been referred to as "immune-regulatory" cells.

Memory-like function in NK cells

These cells were interestingly able to reawaken after a dormant period upon cytokine stimulation or activation of activating receptors and displayed an increased IFN response mimicking the memory-like characteristics of adaptive immune cells. Later, Todd Fehniger's team proposed that human NK cells should also possess memory-like characteristics. Their research supported this theory by showing that human NK cells preactivated with IL-12, IL-15, and IL-18 and then rested for 1 weeks-3 weeks were able to produce an increased IFN response in response to cytokines or K562 leukaemia cells [5].

NK cell source and donor selection The viability of autologous NK cell treatment applications is limited because cancer patients' NK cells frequently have a defective phenotype indicated by altered gene expression profiles and reduced cytotoxic capability. Additionally, autologous manufacturing platforms are laborious and may restrict accessibility if patients are unable to contribute enough cells for engineering and downstream processing. Current NK cell therapy programmes heavily rely on allogeneic sources to avoid the drawbacks of autologous methods because allogeneic NK cells do not result in GvHD. Peripheral blood mononuclear cells, cord blood, immortalised cell lines, Haematopoietic Stem and Progenitor Cells (HSPCs), and induced pluripotent stem cells are some of the sources from which NK cells can be obtained (iPSCs) [6]. All sources have moved into in-human investigations, are capable of producing clinically useful cell dosages, and are amenable to CAR receptor engineering. Despite this, they have special advantages and difficulties, and they could have various underlying transcriptional, phenotypic, and functional characteristics.

Ensuring genomic fidelity in NK cell therapies

Therefore, it is crucial to develop platforms for product screening and characterization in order to spot undesired genomic changes brought on by off-target nuclease activity. As the science develops, worries that some genetic modifications can unintentionally result in malignant mutations continue to echo in the background [7,8]. The US National Institutes of Health (NIH) created the Somatic Cell Genome Engineering (SCGE) programme to address this need. It has two main goals: first, to give researchers financial support to enable the translation of genome editing technologies into the clinic; and second, to encourage the creation of more thorough assays to examine any potential adverse biological effects that may arise from the use of these tools. Additionally, a number of platforms have been created to examine the fidelity of genome editing, including GUIDE-Seq, CIRCLE-Seq, and rhampSeq, which depend on sequencing technologies to objectively detect potential double-stranded break sites in the genome. Furthermore, tests like high-throughput genome-wide translocation sequencing using linear amplification may be used to reveal unexpected genomic rearrangements [9, 10]. Implementing such assays in the development of cell treatments will be crucial as these technologies develop and change, allowing for a better understanding of the efficacy and safety of cellular products such modified NK cell therapies.

Conclusion

Engineered cellular immunotherapies continue to expand dramatically, with a variety of techniques swiftly moving from preclinical research into clinical trials. The most recent development in the field of cell and gene therapy is best exemplified by a recent publication on *the in vivo* editing of hepatocytes in patients with transthyretin amyloidosis. In a related endeavour, a method for enabling T cell-targeted *in vivo* CAR transfection utilising lipid nanoparticles has been devised to target cardiac remodelling in the context of myocardial damage by Fibroblast Activating Protein (FAP)-redirected CAR T cells. Furthermore, recent research has shown that therapeutic genes (such CAR and TCR) can be delivered to T cell populations *in vivo* using Nipah lentivirus vectors that are directed to CD3, CD8, and CD4. By avoiding the need for significant ex vivo manufacture, cutting costs, and speeding up therapy delivery, these technological advancements offer a fresh perspective on off-the-shelf tailored therapeutics. Targeted viral vectors are easily available to be supplied to patients as needed.

Targeted in vivo editing may be used to modify tumour cells in a way that makes them more susceptible to anti-cancer drugs or gets rid of their resistance mechanisms. Although most recent efforts have been on CAR T cell treatment, *in vivo* engineering may also be useful for NK cell-based therapies, such as to increase tumour sensitivity to NK cell-mediated cytotoxicity or to enhance endogenous NK cell function and persistence. As the industry continues to advance quickly, it is crucial to be informed about any potential safety hazards connected to these different gene editing techniques because worries about potential off-target effects are quite pertinent. These worries are justified, and the recent suspension of numerous ongoing cell therapy trials due to chromosomal abnormalities, treatment-associated AML/Myelodysplastic Syndrome (MDS), or malignant transformation of the infused CAR T cell product serve as reminders of the significance of carefully examining the safety of engineered products. Additionally, it is crucial that cell therapy programmes put in place pipelines for comprehensive product screening to evaluate any undesired genetic alterations that can have negative impacts. The initial support required to start these efforts may be provided by utilising resources like the NIH's SCGE programme. Although NK cell-based immunotherapy is positioned as a secure over-the-counter antitumor treatment, significant problems still need to be answered. As the profession develops strategies to deal with issues unique to each disease indication, it will be crucial to clarify the critical factors that govern NK cell potency and persistence.

Finally, in order to maintain excellent product quality, it will be crucial to develop and put into practise the best techniques for NK cell multiplication and cryopreservation. Logistically, it will be crucial to create interdisciplinary team structures including researchers, physicians, and regulatory authorities in order to collectively map out a comprehensive route to clinical translation for developing NK cell treatment programmes.

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The Public Health Approach to Breastfeeding

Al Zahraa Helal*

Claims Section Head at Middle East Healthcare Company, Saudi German Health, Saudi Arabia

Corresponding Author*

Al Zahraa Helal
Claims Section Head at Middle East Healthcare Company, Saudi German Health, Saudi Arabia
E-mail: dr_zahraa.adel@hotmail.com

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Abstract

Breastfeeding is a means of achieving wellness and survival for children globally. In the Middle east region, 66.6% of the population is suffering from the failure of fulfilling breastfeeding although of all sustained efforts by national and international organizations. Marginalization of breastfeeding is like depriving the baby of security and mother's warmth by exposing mothers and babies to infectious and non-infectious diseases.

Keywords: Breastfeeding • Non-infectious diseases

Introduction

Breastfeeding is a means of achieving wellness and survival for children globally. In the Middle east region, 66.6% of the population are suffering from failure of fulfilling breastfeeding although of all sustained efforts by national and international organizations. Marginalization of breastfeeding is like depriving the baby security and the mother's warmth by exposing mothers and babies to infectious and non-infectious diseases. In this study we will evaluate the current situation and progress in the Global approach of located in the Middle East region specifically in Egypt utilizing epidemiological surveys as an adjuvant tool and data of WHO and UNICEF, as a failure of breastfeeding is a major cause of malnutrition so there is a need to apply an effective approach through the best way of communication for promoting breastfeeding and opposing any misinformation about it, carried by the targeted marketing of the companies concerned with profit through products which are sold for babies which sometimes are enriching the idea of that breastfeeding is like something that can be subtracted from women's and babies lives.

Although of the proven impact recently of the public approach of the Baby-friendly Hospital Initiative compared to the past, its effectiveness on the Egypt community's practices has yet to be evaluated. Recent studies have revealed weak rates of exclusive breastfeeding in mothers in urban areas. One study revealed that exclusive breastfeeding was around 12.5% between 400 mothers lactating infants with ages between 2 months-6 months in a Family Medicine center. The information about exclusive breastfeeding was poor and nearly about 4-22 of 27 survey's questions. It was greater in highly educated mothers, working ones, and those who received information from different sources of media [1]. A study done in a clinic located in Alexandria revealed that exclusive breastfeeding was around 4.4% of the cases and 72.4% of them have practiced mixed feeding while the others 23.3% have introduced artificial formula feeding.

Of the main causes of failure of breastfeeding, around 45.7% were maternal causes including deliveries complications, nipple diseases, and insufficient milk of the breast, while 39.7% of them were infant causes due to prematurity, intended refusal of infant, infant diseases, and continuous crying. The growth of exclusive breastfeeding babies was the best then mixed feeding was better than artificial feeding babies. Gastroenteritis, dermatitis, respiratory tract infections, and otitis media were less common among EBF babies in comparison to MF and AF babies [2]. Fahmi studied regimens of the feeding of infants in Menia including 379 infants, breastfeeding estimated rate was 93.6% and 6.4% of infants were never breastfed. Other types of feeds were given in the first 3 days to 69% of infants and only 31% were exclusive breastfeeding babies [3]. Other types of given feeds were glucose by around (39.2%), herbal fluids by around (35.5%), sweetened water by around (14.3%), milk by around (7.8%), gripe juice by around (1.6%) and water by around (0.8%). Formula milk feeding was estimated by 10.6%. Mothers' information about the benefits of breastfeeding was gained mostly from their own mothers. It was noticed that 40% of mothers did not have any idea about the benefits of breastfeeding for them or their baby and only 0.5% had listed around 4 benefits of breastfeeding and about 12.3% were able to define what is meant by exclusive breastfeeding.

A study was established in hospitals of Cairo university to identify barriers toward breastfeeding in 3500 as a sample of selected women randomly between 2007 and 2011 [4]. At the postpartum period, only 78% of women who had started breastfeeding were still going for babies' breastfeeding and only 45% of who were still going to breastfeed were exclusively breastfeeding. According to the study there were given reasons for early termination of breastfeeding like: fears about weight of the baby, baby is preferring bottle, painful breastfeeding, preparing to go back to work for working mothers, concern from obesity and concern from breast disfigurement [5]. The regression analysis has identified 3 risk factors causing failed breastfeeding which were young maternal age, high rate of employment and the baby with low birth weight. Other factors included mode of delivery, socioeconomic status, parity, educational level, sex of the baby, and separation from the baby at the time of delivery. Religion influence also is a factor as Muslim mothers stated that Islam encouraged them to breastfeed and 36.8% explained that Islam clarified the duration of breastfeeding [6]. Social support also is a factor as some mothers stated that their husbands and mothers supported them to breastfeed while others reported a lack of support. Participants answered questions on their comfort toward breastfeeding in public and over 50% of women agreed that they were comfortable with breastfeeding in the presence of female friends or family members or their children but there was consistency in responses among mothers by around 37 % with discomfort issues to breastfeed in front of others in public [7,8].

Egypt is one of those countries which were nominated to start the BFHI in the World. By the mid-1990 there were 126 certified hospitals as Baby-friendly by the National Breastfeeding promoting committee. Recently, the ministry of health has designated 75 primary health care centers and 14 hospitals to share in the BFHI. The current laws in Egypt allow mothers to have full paid maternity leave for 3 months. Mothers are entitled to a one-hour break for breastfeeding and to have unpaid leave for 2 years up to 6 years for a maximum of 3 children without losing their position. Another facility is workplaces that have women employees over no. 99 ones should have a nursery that is established within or near to the workplace (ILO, 2012) [9-12].

In sum, improving exclusive breastfeeding requires a collaborative approach through different healthcare system plans, family involvement, and public health awareness campaigns to achieve optimal breastfeeding

practice, especially for those who are in need like in distant rural areas and less educated women. However, identifying the current breastfeeding practices related to national and international guidelines plus identifying associated facilitators, barriers and factors should be considered at all to achieve the goals.

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Hypertrophic Cardiomyopathy Risk Factors for Sudden Cardiac Arrest

Aditya Mishra* **and Divya Sharma**

Department of Biotechnology, Anand Engineering College, Agra, India

*Corresponding Author**

Aditya Mishra
Department of Biotechnology, Anand Engineering College, Agra, India
E-mail: adi7905428546@gmail.com

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Abstract

One of the most common causes of Sudden Cardiac Death (SCD) in young people and athletes is Hypertrophic Cardiomyopathy (HCM). Finding the SCD risk factors in people with HCM is essential. The risk factors for SCD in patients with HCM will be the main topic of this review, which is based on recent systematic literature investigations. New risk markers have appeared as a result of more studies exploring the factors that may increase the risk of SCD in individuals with HCM. Additionally, more precise approaches for categorization and estimate of SCD risk have been suggested and are being developed. The discovery of independent risk factors for SCD caused by HCM would probably aid in risk categorization. SCD occurs annually in about 1% of adult patients with HCM, therefore it is challenging to forecast with full confidence. A family history of SCD, unexplained syncope, and other new risk factors are discussed in the review along with the existing risk factors. The results of this analysis show that SCD risk classification in HCM patients is still a clinical problem and that more research is required on specific risk variables.

Keywords: Sudden cardiac death • Hypertrophic cardiomyopathy • Tumor • Transferrin receptor 1

Introduction

A hereditary cardiomyopathy with asymmetric aberrant enlargement of the left ventricular muscle and a nondilated left ventricle is known as Hypertrophic Cardiomyopathy (HCM) (LV). The estimated frequency of HCM in the general population is at least 1 in 500, and SCD might be the condition's initial symptom in asymptomatic or younger patients. HCM is also one of the primary causes of SCD in young people and sports. The annual incidence of SCD in adults with HCM is about 1%, but it is much greater in children with HCM. In order to inform prevention initiatives, it is crucial to identify the risk factors for SCD and rule out possible HCM patients who are at a high risk of developing the disease. Age, left atrial diameter, and Left Ventricular Outflow Track Obstruction (LVOTO) were added as new risk factors. As new clinical risk factors for SCD in HCM patients, the 2020 AHA/ACCF guidelines have added HCM with left ventricular systolic dysfunction, Left Ventricular Apical Aneurysm (LVAA), and substantial Late Gadolinium Enhancement (LGE). The B-type natriuretic peptide level, atrial fibrillation, and New York Heart Association functional class are a few other risk factors that have been documented in pertinent research as being linked to SCD risk.

In order to provide a reference for clinical therapeutic decision-making, the aim of this study was to conduct a comprehensive literature review of publications on clinical risk factors for SCD in patients with HCM in recent years. One or more first-degree relatives under the age of 40 or 50 who incidentally passed away within one hour (if witnessed) or twenty-four hours (if seen in an asymptomatic state) of the symptom's onset are considered to have a family history of SCD. There is agreement that SCD episodes in first-degree relatives raise a person's risk of developing SCD, notwithstanding definitional differences. Patients with a family history of SCD had a 20% higher risk of developing the condition compared to HCM patients without a clear family history. A family history of SCD is a Class IIa recommendation for ICD inclusion in the ACCF/AHA recommendations and is included in the HCM Risk-SCD Calculator due to the familial clustering of risk.

Unexplained syncope

A single incident of an unexplained loss of consciousness within the last six months is considered one episode of unexplained syncope. In one of every four HCM patients, syncope is common, but it can have a variety of reasons, including supraventricular arrhythmia, sinus node dysfunction, and full heart block. Unaccounted for syncope has been linked to a higher risk of SCD, according to a number of studies. Unexplained syncope is taken into consideration when making ICD decisions by both the ACCF/AHA recommendations (Class IIa) and the ESC guidelines. Spirito showed that the relative risk of SCD was five times higher in patients with recent, unexplained syncope (within six months) compared in patients without syncope. The risk of SCD was not higher in older patients who had isolated syncopal episodes.

NSVT

Three or more consecutive ventricular beats that occur at a rate of at least 120 beats per minute and last for less than 30 s are referred to be NSVT. With a high incidence rate of 20%-30% in HCM patients over the age of 40, NSVT is quite prevalent in this condition. According to a study, NSVT is only indicative of SCD when it happens frequently or is accompanied by symptoms. A further study found that HCM patients with NSVT had a higher risk of developing SCD, but only if they were under 30 years old, and that the frequency, duration, and rate of the NSVT had no prognostic significance.

Maximum left ventricular wall thickness

The largest end-diastolic dimension inside the chamber is the thickness of the left ventricular wall. The maximum wall thickness is thought to be the thickest measurement made at any point along the LV. Studies have demonstrated that having a left ventricular wall thickness of at least 30 mm is independently related with SCD, and the ACCF/AHA guidelines classify this as a Class IIa recommendation for ICD implantation. A binary cutoff for decision-making, however, ignores the gradationally increased risk of left ventricular hypertrophy. The HCM Risk-SCD calculator's use of left ventricular thickness as a continuous variable probably results in a more thorough evaluation of risk in this area.

Abnormal exercise blood pressure response

Failure of an SBP increase of more than 20 mmHg or an SBP decrease of 10 mmHg during exercise is considered an abnormal blood pressure response. More than one in three HCM patients experience an irregular blood pressure response to physical activity. The majority of research demonstrate that abnormal blood pressure response increases the risk of SCD in HCM patients who are younger (under 40 years old), and it is unknown what significance abnormal blood pressure response has for patients who are older (over 40 years).

Hypertrophic cardiomyopathy risk-sudden cardiac death tool

The ESC model contains age, outflow tract gradient, and LAD in addition to those characteristics that are shared with the ACCF/AHA approach. Patients are assigned to one of three 5-year SCD risk groups based on the results of the HCM Risk-SCD tool: less than 4%, 4%-6%, or more than 6%. ICDs should not be considered for the lower-risk group, but they may be for the intermediate-risk group and higher-risk group. The ESC model exhibited a superior discriminative C-statistic than the current "risk factor" method, according to statistical validation in two retrospective cohorts. However, only 20% of the 1629 AHA risk-stratified patients in a real-world cohort who used the HCM risk-SCD algorithm had experienced SCD.

Late gadolinium enhancement on cardiac magnetic resonance imaging

A sign of myocardial fibrosis in HCM is LGE-CMR. Numerous investigations have demonstrated that a high risk of SCD is independently linked to widespread LGE. In a cohort of 1293 HCM patients, data from Chan et al. showed that LGE was more effective than individual risk factors in predicting SCD. A quantitation of at least 15% LGE showed a two-fold increase in SCD, and a meta-analysis showed that the risk of SCD was significantly correlated with the degree of LGE, increasing by 36% for every 10% increase in LGE. Regarding whether LGE offers additional information to conventional risk variables in HCM, there is still considerable debate. While past studies reported that the degree of LGE was not a reliable predictor of SCD in HCM, recent research demonstrated a substantial relationship between the risk of SCD in patients with HCM and the extent of LGE. Three groundbreaking studies found a connection between the location of LGE and severe arrhythmia and SCD in HCM patients. There was a significantly higher incidence of SCD in patients with LGE outside the interventricular septum than there was in patients with LGE only in the interventricular septum in our cohort study of 557 HCM patients with a mean follow-up time of 83.0 months, showing that the location of LGE plays as important a predictive role as the presence of LGE.

Left atrial diameter or left atrial volume

The most precise approach for determining left atrial size, according to recent echocardiographic standards, is the Left Atrial Volume (LAV). A persistent increase in left atrial pressure, which is the result of impaired diastolic function, mitral regurgitation, and atrial arrhythmias, is measured by left atrial enlargement. A substantial difference in SCD risk between patients with and without an expanded LAD was not observed among those with confirmed atrial fibrillation, despite the fact that enlarged LAD was an independent predictor of SCD risk among patients without atrial fibrillation. These findings imply that the presence or absence of atrial fibrillation in HCM patients affects the connection between LAD and SCD.

Other risk factors have been described in addition to the above stated risk factors for SCD in HCM patients. According to studies, a rise in BNP levels is associated with the development of SCD and/or malignant ventricular arrhythmia. Atrial fibrillation has been linked in several studies to a significant risk of cardiovascular death. Additionally, Sorajja et al. discovered that among individuals with HCM, the sole risk factor for SCD was persistent atrial fibrillation. A few researchers have also suggested that the NYHA functional class may be a risk factor for the development of SCD.

Conclusion

In patients with HCM, there are numerous risk factors for SCD. Finding SCD individuals at high risk, however, is still difficult. To identify and confirm the various risk factors for SCD in individuals with HCM in larger HCM patient cohorts, more research is needed. By combining genetic information and machine learning analytics with LGE in CMR, more accurate risk predictions may be possible. However, there will always be tradeoffs in determining how to strike a balance between the number of lives saved and the chances of consequences from ICD implantation, regardless of how accurate the risk estimations become.

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Swallowing Dysfunction and its Impact on Patients Undergoing Oncological Treatment

Sharjeel Chaudhry[1*] and Zarmina Ehtesham[2]

[1] *House officer, Dow University of Health Sciences, Pakistan*
[2] *Final year dental student, Hamdard University, Pakistan*

Corresponding Author*
Sharjeel Chaudhry
House officer, Dow University of Health Sciences, Pakistan
E-mail: sharjeelchaudhry1999@gmail.com

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Abstract

Loco-regional control rates and tumour response have increased as a result of advancements in Head and Neck Cancer (HNC) therapy. Moreover, mortality is still high despite advancements in treatment and diagnostic methods. Altered fractionation Radiotherapy (RT) or Chemoradiotherapy (CRT) treatment escalation leads to significant late and early pharyngeal and mucosal toxicities but is related to better outcomes. A sign of HNC that is underdiagnosed in patients is oropharyngeal dysphagia. Dysphagia frequently results from structural, iatrogenic, neuromuscular, and neurological dysfunction. Dysphagia must not be disregarded because it can significantly lower the Quality of Life (QoL).

Keywords: Covid-19 pandemic • Nigeria situation

• Global perspective

Introduction

Loco-regional control rates and tumour response have increased as a result of advancements in Head and Neck Cancer (HNC) therapy. Moreover, mortality is still high despite advancements in treatment and diagnostic methods. Altered fractionation Radiotherapy (RT) or Chemoradiotherapy (CRT) treatment escalation leads to significant late and early pharyngeal and mucosal toxicities but is related to better outcomes. A sign of HNC that is underdiagnosed in patients is oropharyngeal dysphagia. Dysphagia frequently results from structural, iatrogenic, neuromuscular, and neurological dysfunction. Dysphagia must not be disregarded because it can significantly lower the Quality of Life (QoL) [1]. As a result of poor swallowing, dehydration, malnutrition, and also aspiration pneumonia may ensue. Depending on the structures connected with the tumour and the types of treatments used, swallowing difficulties are frequently predictable [2]. A proper pre-treatment preference. for individuals who are most at risk for dysphagia might enhance therapeutic and functional outcomes. The cure is typically the priority for the individual suffering from head and neck cancer.

Due to its temporary nature, acute dysphagia is frequently thought to be less concerning. However, it is a well-known cause of malnutrition, which results in substantially a worse quality of life, morbidity, and higher mortality. Additionally, higher acute toxicity may intensify late consequences like lymphedema and fibrosis, which would worsen dysphagia. To limit late dysphagia, avoid malnutrition, and offer aspiration, it is critical for doctors to be aware of the relationships between the middle of late and acute toxicities and to be able to identify patients who are at risk for severe acute dysphagia.

A comprehensive dosage administration of Radiation Therapy (RT) and Chemotherapy (CT) may promote compliance with the therapeutic regimen with adequate care and diagnosis throughout the treatment [3]. We have now evaluated the pertinent literature in terms of definition, physiology and aetiology, predictive factors, and supporting measures for palliative therapy to achieve the goal and also provide a conclusion.

Definition, physiology, and causes

The inability or discomfort of swallowing medications, food, or liquids is referred to as dysphagia. The oesophageal or oropharyngeal phases of swallowing can both experience dysphagia. "The pharyngeal receptors, the swallowing centre in the brainstem and the cranial nerves (V, VII, IX sensory, IX motor, X, and XII) for chemical stimuli, pressure, water, and touch all work together to maintain a normal pattern of normal swallowing, which is a coordinated and complicated process requiring neurological regulation. The four stages of a typical swallow are the oral preparation, the oral stage, the pharyngeal stage, and the oesophageal stage" [4].

The food is mashed and combined with saliva to produce a bolus during the swallowing phase of the oral preparation. The bolus travels to the throat during the oral phase. The pharyngeal phase is when the swallowing reflex is activated. This causes the larynx to close to prevent aspiration, the pharyngeal constrictors to contract from superior to inferior, the epiglottis to invert and the laryngeal opening and the cricopharyngeal to relax to allow the bolus of food to travel into the oesophagus [5]. The bolus is moved into the stomach at the last stage by the oesophageal muscles' movement known as peristalsis. Dysphagia can be caused by a malfunction in any of these processes. Furthermore, the carotid sheath and the pharyngeal structures must be flexible in the prevertebral space and spine region for neck movement and swallowing to occur. In essence, the pharynx is a muscular tube that is hanging from the base of the skull. This pharyngeal expansion and movement that is necessary are made possible by the fat in the para-pharyngeal regions and retropharyngeal. The entrance of substance into the larynx that does not go behind the vocal folds is referred to as penetration. Although they are not included in the definition, the quantity of substance, the depth of penetration, and whether all or a portion is afterwards evacuated are all potentially important factors that should be studied. Material moving below the vocal folds is referred to as aspiration (Table 1).

Table 1. Correlations with head and neck cancer treatment or neurologic damage.

Parameter of Interest	Head and Neck Cancer	Neurological Damage
Saliva	Xerostomia or Dry Mouth	Drooling, Excess
Mastication	Edentulous	Week or Awkward
Aspiration	Often after swallowing	Before or during swallowing
Taste	Altered or Reduced Taste	Intact Structures
Oral containments	Intact	Problematic
Swallowing movements	Reduced	Reduced and delayed
Anatomic structures	Altered by Fibrosis	Normal unless paresis

Dysphagia can be brought on by a variety of swallowing-related changes that can impair the physiological processes at each of the previously mentioned steps. Normal physiology may be hampered by an injury to neurological impairment or anatomical structures. Improper movement of the vestibule, supraglottic larynx and epiglottis, prevertebral space changes, structural dissoluteness of the oral cavity, decreased pharyngeal peristalsis, and other impairments of neurological and muscular are among the most frequent abnormalities [6]. After head and neck cancer therapy, each of these damage types contributes contrastingly and to variable degrees to dysphagia.

Aspiration, which generally has an unimpaired reflex of cough, can be caused by abnormalities of the swallow. The causes of aspiration can be categorised as those that happen before, in the middle, and after the process of swallowing [7]. In individuals with head and neck cancer, aspiration after swallowing occurs as a result of intemperate remnants entering the larynx through damaged areas, as opposed to the neurological aspiration that normally happens before or during swallowing. Certain swallowing issues can result from structural and neurological dysfunction.

Although all of these issues may occur simultaneously in head and neck cancer patients, structural impairment typically predominates as a result of structural damage involving the muscles or nerves or connected to the use of specific drugs. Xerostomia can be brought on by asthma medications, anticholinergic drugs, vasoconstrictors or steroids. "The central nervous system can be depressed by hypnotic agents, antipsychotics, sedatives, antidepressants, and anti-anxiety agents. Additionally, extra-pyramidal symptoms like mouth and facial dyskinesias are possible with several antipsychotics. The neuromuscular junction may be blocked by antibiotics or penicillamine like erythromycin and aminoglycosides" [8]. Drug-induced myopathy can be brought on by lipid-lowering or corticosteroid medications.

Factors predictive of dysphagia

The probability of late and acute dysphagia is predicted by the T and N stage, the main location, the kind of treatment, "the extent of the treated region, and patient characteristics (baseline swallowing function, Performance Status (PS), smoking and alcohol misuse, age, lean mass, and gender). All forms of therapy, including CRT, surgery and organ-sparing protocols, cause aspiration and swallowing issues" [1]. As a result, we may divide the variables that predict dysphagia into three categories: treatment-related, patient-related, and tumour-related. Dysphagia risk is predicted by patient variables such as lean mass, baseline swallowing performance, PS, alcohol abuse and smoking, gender and age. The severe swallowing difficulty is linked to progressive T and N stages [9]. It is debatable whether the severity and incidence of late and acute dysphagia are better associated with a distinct initial tumour location. Before treatment, aspiration is more common in patients with larynx or hypopharynx cancer; the worse baseline function may explain a greater risk of swallowing impairment in individuals.

Dysphagia after surgery

Patients with head and neck cancer who have surgery run the risk of developing dysphagia if neck fascia is removed or if cartilage, muscles, nerves or bones (neurological structure and swallowing anatomical structures) are removed or damaged. The degree, size and location of surgical resection of the lesion all affect how severe the swallowing deficiency is. In several publications, the significance of the anatomical area of excision has been emphasised. Less prognostic than the excised area is the size of the lesion that was removed [10]. As a result, for specific procedures such as arytenoid cartilage and base of the tongue resections, dysphagia may be precisely anticipated. Even though robotic surgery has improved results, some reconstructions only serve cosmetic rather than functional goals (tissue flaps have no motor function resulting in the loss of propulsive force). Surgery-related issues, such as nerve function disruption, may impair swallowing ability [11]. Furthermore, dependency and aspiration on gastrostomy tubes are also markedly increased by neck dissection. Potential reasons for swallowing difficulties include nerve injury, oedema, pain and scarring as a result of neck dissection.

Dysphagia after surgery

Dysphagia still poses a potentially fatal risk to head and neck cancer patients receiving CRT or RT, even though contemporary RT regimens are meant to protect normal tissue and maintain function and structure.

Dysphagia gets exacerbated as a result of radiation on the swallowing arrangement and different dosage fractionation. Structures that are aspiration or dysphagia related, whose destruction is a result of therapy, have been found by [12]. The glottic larynx and, the supraglottic larynx are examples of dysphagia or aspiration-related structures. According to Taberna, anatomical reasons and the food consistency of dysphagia are related. Dysphagia from solid food is caused by injury to the superior PCM. Pharyngeal clearance requires cricopharyngeal opening and laryngeal elevation, which may cause the patient to self-regulate the viscosity and quantity of consumed food. Aspiration may result if the airway is not sufficiently closed at the supraglottic larynx [13]. This information enables a link between a particular swallowing structure failure and a few inexplicable weight losses in early-stage head and neck cancer.

Palliative treatment

Palliative care seeks to reduce symptoms while enhancing the quality of life. If there are unsettling signs, such as nausea or pain, it can be taken at any stage of the disease. Even if advanced cancer cannot be treated, palliative care can aid a patient to live more comfortably and longer. A vital part of the all-encompassing care provided to cancer patients is palliative care. Its clinical approach is founded on the principle of enhancing the quality of life for individuals suffering from cancer and their families who are dealing with serious diseases. This multidisciplinary speciality seeks to develop goals of treatment by reducing symptom burden, treating spiritual and psychological anguish, and improving knowledge of the condition and prognosis.

Dysphagia can cause weight loss, malnutrition, and reduced eating habits. "In 5 to 71% of head and neck cancer patients, severe weight loss occurs that is unintentional, with an average loss of 6 to 12% of pre-treatment body weight" [14]. Weight loss can be linked to an energy imbalance, which includes increased energy expenditure due to changed metabolism and or lower energy intake via reduced food consumption. Although there is a lot of interest in the treatment and prevention of mucositis and discomfort brought on by swallowing, there is still no gold standard. Most patients might experience considerable pain that needs strong analgesics, both from the tumour and from the therapy. Opioids enhance changes in gastrointestinal motility, and they can also lead to reduced food intake [15]. Managing individuals suffering from terminal cancer includes the palliative therapy of dysphagia. More than half of cancer patients are diagnosed with no curative options due to the typical late onset of symptoms in this disease. Palliative care seeks to lessen symptoms to enhance the quality of life for those who are ill. The major symptoms are dysphagia brought on by concurrent weight loss and oesophageal lumen blockage.

Manage cancer-related symptoms, assist patients with advance care planning, and talk with them about their end-of-life desires [16]. To provide specialised and primary palliative care as effectively as possible, we must create a model that increases the efficiency of healthcare resources and specifies the essential skill sets. The improvement of high-quality patient care and improved triage of the refractory and complex palliative care requirements to palliative care professionals will result from education in fundamental palliative care concepts for all levels of providers and learners in oncology [17]. Oncologists who pursue both pieces of training in palliative care can act as ambassadors since they are adept at bridging the gap and comprehending the subtleties of both fields [18].

Conclusion

In the management of head and neck cancer, dysphagia is an issue that is becoming more widely acknowledged. QoL is impacted, as is survival. An assessment of nutritional status and swallowing function before treatment is required to guarantee that CRT and RT individuals get appropriate therapy. Routine diagnostic treatments and swallowing examinations before, during, and after therapy should be part of a new multidisciplinary standard in the head and neck cancer treatment approach. According to data gathered during the current comprehensive article, surgery CRT or RT may impede swallowing. For the psychological, emotional, and physical well-being of patients with progressive cancer, palliative care is crucial. Its positive synergistic impact on overall survival while enhancing patient quality of life and satisfaction outcomes justifies its inclusion in routine oncologic treatment. To satisfy the needs of a rising cancer disease, ongoing, focused research is required to assess the growth and integration of high-quality services of palliative care.

To aid patients in better understanding and coping with their illnesses, including but not limited to when such illnesses are terminal, medical oncology and other specialities, including interventional radiology, must integrate primary palliative care skills into the practice. They must also collaborate with specialist palliative care physicians.

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