

Review

Cutaneous Squamous Cell Carcinoma: An Up-to-Date Comprehensive Review with a Focus on Contemporary Optical Imaging Diagnostic Modalities

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Abstract: Cutaneous squamous cell carcinoma (cSCC) arises from the abnormal proliferation of keratinocytes of the epidermis, most commonly due to UV-light-induced DNA damage. Although histopathological assessment is the gold standard for diagnosing cSCC, nascent optical imaging diagnostic modalities enable clinicians to perform “optical or virtual biopsy” in real-time. We aim to report advances in optical imaging diagnostics for cSCC, along with an updated review of the literature. A comprehensive literature review was performed using PubMed, Embase, and Cochrane databases for manuscripts published from 2008 to 2022. The search yielded a total of 9581 articles, out of which 136 relevant articles were included in the literature review after fulfilling screening and eligibility criteria. This review highlights the current optical imaging devices used for diagnosing cSCC and their diagnostic features. These devices include in vivo and ex vivo reflectance confocal microscopy, optical coherence tomography, line-field confocal optical coherence tomography, multiphoton tomography, and high-frequency ultrasonography. Although surgical excision or Mohs micrographic surgery is considered the gold standard, the latest developments in nonsurgical management of cSCC are discussed. Based on the review of the literature, we conclude that contemporary optical imaging devices such as confocal microscopy, optical coherence tomography, line-field confocal optical coherence tomography and multiphoton tomography have revolutionized real-time diagnostic imaging in dermatology, particularly within the realm of skin cancer. These devices enable rapid diagnoses and allow for a faster initiation of therapy. The application of newer imaging devices to cSCC management may benefit high-risk patients (e.g., chronic UV radiation exposure or organ transplant recipients) or patients with multifocal cSCC, for whom multiple biopsies would be impractical, thus avoiding unnecessary biopsies. Together with dermoscopy, optical imaging technologies can help to improve the efficiency of diagnosis by reducing the turnaround time and the need for extensive laboratory processing resources.

Keywords: squamous cell carcinoma (SCC); cutaneous squamous cell carcinoma (cSCC); reflectance confocal microscopy (RCM); line-field confocal optical coherence tomography (LC-OCT); multiphoton tomography (MPT)



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1. Introduction

The prevalence of cSCC is increasing globally, with lifetime incidences estimated to be 9–14% in males and 4–9% in females [1]. CSCC is a type of non-melanoma skin cancer (NMSC) [2]. Other NMSCs include cutaneous lymphoma, Merkel cell carcinoma, and Kaposi’s sarcoma, which account for less than 1% of all NMSCs [2,3]. The most common cause of cSCC is UV radiation exposure, as it induces mutations in the keratinocyte p53

tumor-suppressor gene [1,4]. Less common causes of cSCC include long-term exposure to cigarette tar, high-degree burn scars, non-healing ulcers or sores for several years, and certain variants of human papillomavirus (HPV) [5]. In recent years, research on chronic immunosuppression and inflammation has elucidated the pathways contributing to tumorigenesis in cSCC [1,6].

Of all NMSCs, cSCC accounts for the majority of morbidity from metastatic burden. Therefore, early identification and management of cSCC is vital to prevent neoplastic advancement [6]. Though histopathology and surgery are the status quo and gold standard for analysis and management of cSCC, newer in vivo optical imaging diagnostic devices can increase the “real time” analytic accuracy of detecting cSCC and other cutaneous pathologies [6]. These devices include reflectance confocal microscopy (RCM), optical coherence tomography (OCT), and line-field confocal optical coherence tomography (LC-OCT) [6]. These devices allow for faster identification and selection of clinically relevant cases for prudent biopsy; they also provide a convenient and precise method of monitoring cSCCs over time [6]. Additionally, newer pharmacological interventions provide convenient ways to treat multiple in situ/low-risk cSCCs (e.g., epidermal growth factor receptor inhibitors and immune checkpoint inhibitors) in cases of locally advanced and metastatic cSCCs [6].

2. Materials and Methods

A literature search was performed using keywords related to cutaneous squamous cell carcinoma in PubMed, Embase, and Cochrane databases. The literature search was designed to extract research articles that discuss cutaneous squamous cell carcinoma: epidemiology, pathogenesis, etiology, clinical presentation, histopathology, non-invasive diagnostic modalities, reflectance confocal microscopy, optical coherence tomography, line-field confocal optical coherence tomography, multiphoton tomography, staging, and treatment. Key terms used in PubMed, Embase, and Cochrane database included “Squamous cell carcinoma” OR “SCC” OR “reflectance confocal microscopy” OR “ex vivo confocal microscopy” OR “fluorescent confocal microscopy” OR “optical coherence tomography” OR “LC-OCT” OR “multiphoton tomography” OR “treatment” OR “confocal features” OR “Line-Field optical coherence tomography” OR “optical imaging diagnostics” OR “non-invasive testing” OR “HD-OCT” and (cutaneous squamous cell carcinoma). Publication dates were searched from January 2008 to August 2022. All articles were included, except for those published in languages other than English. Other exclusion criteria included studies that did not primarily focus on cSCC, those with outdated management protocols, those not related to optical imaging, and duplicates.

Each article was screened initially by title and abstract. Articles were provisionally included if any of the utilized key terms were found in its title or abstract. Following the initial screening, pertinent case reports, case series, systematic reviews, meta-analyses, prospective studies, retrospective studies, clinical trials and topic reviews were included. Full text articles that provided clinically relevant optical imaging diagnostic for cSCC, along with diagnostic features and up-to-date treatment protocols, were selected for full-text review. Advanced imaging modalities, such as nonlinear optical imaging, photoacoustic imaging, fast large area multiphoton exoscope, etc., which are not used in clinical setting yet, were not included in this review.

A total of 25,538 records were found with the initial search of PubMed and Embase. A total of 10 records were found with the initial search of Cochrane database. Out of these, 9581 articles were found from 2008 to 2022. After the removal of duplicates/related publications and screening based on title and abstract assessment, 210 manuscripts were shortlisted for full-text assessment. Among the shortlisted articles, only 136 were considered relevant for our literature review article. Figure 1 summarizes literature search and selection process.

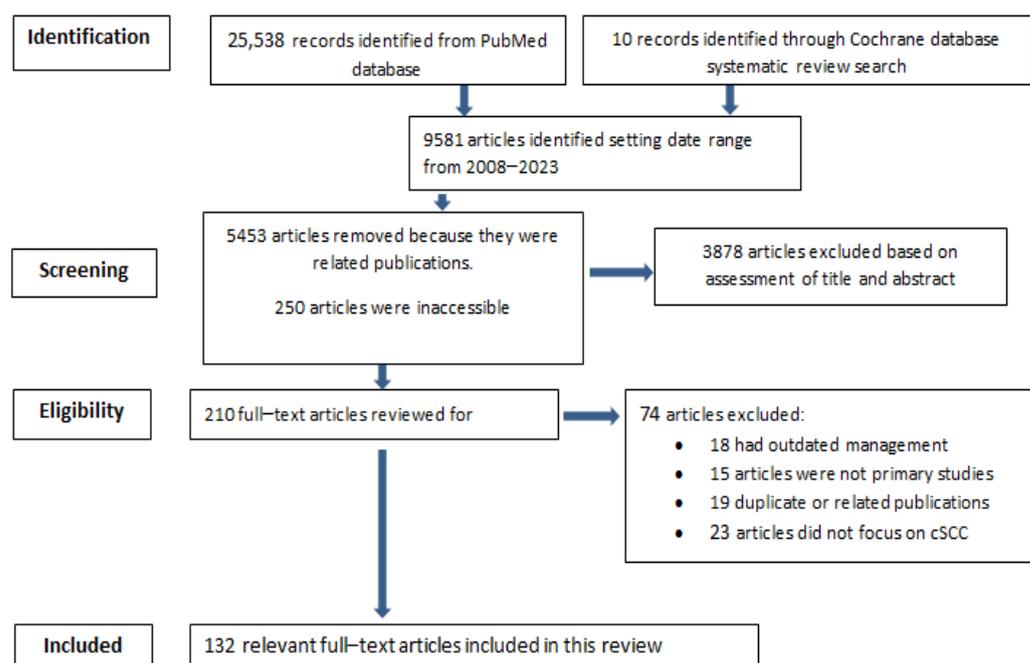


Figure 1. Flow diagram outlining the literature search and selection process.

3. Epidemiology

SCC is the second-most predominant skin malignancy in the USA after BCC [1]. The incidence of cSCC is more than one million per year in the US [7]. Data from the Mayo Clinic’s Rochester Epidemiology Project showed a 263% increase in cSCC incidence between 1976 to 1984 and 2000 to 2010 [8]. Historically, the incidence ratio of SCC to BCC was 3:1 but recent studies suggest that the ratio approaches 1:1 in patients of advanced age [9]. Thus with increasing elderly populace and skin cancer screening, the incidence rates of cSCC are rising progressively [9]. CSCC typically arises in men with light skin (Fitzpatrick-III or lower) with a history of chronic, unprotected UV radiation exposure [6]. On average, cSCC arises in the 5th decade of life typically in areas of sun-exposed skin [6]. CSCC is also prevalent in patients with chronic immunosuppression who are at risk of conversion into more aggressive subtypes [6,10].

4. Pathogenesis

The pathogenesis of cSCC is multifactorial and dependent upon environmental and genetic factors [11]. CSCCs have the presence of keratin pearls, which signify squamous differentiation, and can be classified into histologic subcategories [11]. UV radiation induces mutations in the keratinocyte p53 tumor-suppressor gene commonly seen in progressive keratinocyte dysplasia which begins with actinic keratosis evolving into SCC in situ (SCCIS) and finally invasive SCC [12]. The use of UV radiation from tanning lamps, phototherapy and ionizing radiation are associated with increased rates of cSCC, via dysregulation of the p53 pathway [12,13]. Other major gene mutations associated with tumorigenesis in cSCC include tumor protein 53 (TP53), CDKN2A, Ras, and NOTCH1 [14–18].

The majority of TP53 mutations consist of a single-base transition mutation at dipyrimidine sites in cSCC [17]. The loss of TP53 leads to the loss of apoptosis allowing cancerous cells to grow clonally [18]. Loss of function of the cyclin-dependent kinase inhibitor 2A (CDKN2A), which regulates the cell cycle checkpoint proteins [19], continuous activation of RAS-signal-transducing proteins; or Notch homolog 1 tumor-suppressor gene support cSCC development [20]. In addition, cSCC is a heterogenous disease that may have many undiscovered driver mutations [21]. Premalignant keratinocyte lesions such as actinic keratoses have been reported to have mutations in TP53 and RAS as well [21], but further mutations may be necessary for tumor progression and development [21]. This molecular basis of

pathology can aid in the development of targeted therapies, though the myriad mutations in cSCC poses a challenge against the effectiveness of single-agent targeted therapy [22].

5. Etiology

Risk factors for cSCC are male gender, Fitzpatrick skin types I-III, age over 50, UV radiation exposure, immunosuppression, human papillomavirus (HPV) [23] infection, chronic wounds, environmental exposures, and familial cancer syndromes [14]. Environmental agents causing cSCC include arsenic-contaminated well water [24,25], insecticides with lead arsenate, aromatic polycyclic hydrocarbons (e.g., tar, terrain, and ash), nitrosamines, and alkylating agents [26,27]. Exposure to ionizing radiation, even in limited quantities, has also been linked with more aggressive forms of cSCC (10–30%) [28,29]. Organ transplant recipients (OTRs) have a 20 to 200 times higher risk of cSCC compared to the general population due to lifelong immunosuppression [30]. CSCC formation is proportional to the number of lifetime-use immunosuppressive agents in an OTR [31,32]. Heart and lung transplant recipients are at higher risk of cSCC than renal transplant recipients due to older average age at time of transplant and aggressive immunosuppressive treatment (e.g., azathioprine and cyclosporine) [31,33]. The risk of cSCC development in solid OTRs is also higher than recipients of hematopoietic stem cell transplant [34]. In a cohort of kidney transplant recipients in the U.K., 30% developed cSCC within a decade of the transplant [35]. Patients with chronic lymphocytic leukemia have an 8- to 10-fold higher risk of concomitant cSCC development due to deficiencies in both cell-mediated and humoral immunity [36]. Improving T-cell-mediated antitumor activity can be supportive in regulating advanced cSCC due to the prominent role of antitumor immunological surveillance [37]. Currently, cemiplimab is a programmed death protein 1 (PD1) inhibitor under study, approved in 2018 for locally invasive or metastatic cSCC in patients who are not surgical candidates [37].

Oncogenic subtypes of HPV are preferentially linked to periungual and anogenital cSCC [26]. HPV 16 and 18 subtypes produce E6 and E7 oncoproteins which enable cancerous cells to avert apoptosis and permit the perpetual replication of viral DNA by interfering with the activity of tumor-suppressor genes p53 and retinoblastoma protein (rbp), respectively [26,38]. CSCCs in OTRs may also express HPV subtypes 8, 9, and 15 [39]. HPV is transcriptionally inactive in cSCC as confirmed by examining viral messenger RNA level [40]. This indicates that HPV is potentially engaged in the induction phase of pathogenesis of cSCC but not in the maintenance phase [40].

Defects in the production of antioxidant melanin or increased genetic instability can increase the risk of developing cSCC [41]. For example, albinism, the congenital absence of melanin, is highly associated with a high risk of cSCC development [42]. Uncommon familial cancer syndromes linked with defective DNA repair or photosensitivity can predispose younger individuals to develop multiple cSCC [41]. Xeroderma pigmentosum (XP) is another genetic condition that can predispose young individuals to develop skin cancer [43]. XP is an autosomal recessive pathology that decreases skin's ability to repair DNA damage thus the median age of NMSC development is 18 years [43]. XP arises due to a defect in post-replication repair or DNA nucleotide excision [43,44]. Patients with XP can develop diffuse erythema, bullae, blisters, and ensuing xerosis and scaling with minimal sun exposure [43,44]. In patients with XP, there is 16-fold greater risk for developing cSCC [43,44]. Figure 2 summarizes etiological causes of cSCC.

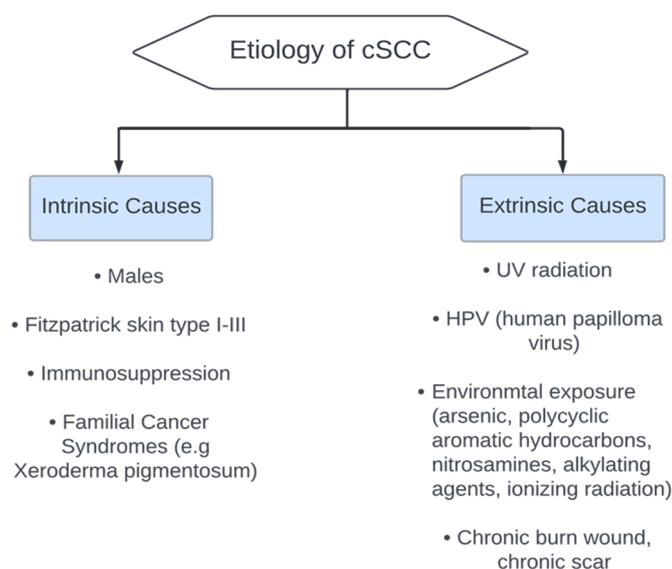


Figure 2. Etiological risk factors of cutaneous squamous cell carcinoma (cSCC).

6. Clinical Presentation

CSCC commonly develops on the face, bald scalp, neck, dorsal hands, and extensor forearms from a precursor lesion, actinic keratosis [45,46]. Body areas with the highest incidence of metastasis include the head and neck, and especially the ear and nonglabrous lip [47,48]. Classically, cSCC appears as erythematous plaques or papules with variable levels of hyperkeratosis, scaling, crusting, and ulceration, with or without telangiectasia or bleeding [12]. CSCC may also appear smooth, nodular or plaque-like with induration and/or subcutaneous spread [12,13]. Seldomly, cSCC can elicit pain and tenderness, signifying perineural invasion [12,13]. Perineural invasion is linked with local neuropathic symptoms, e.g., burning, numbness, paresthesia, or paralysis [49]. Involvement of the non-sun-exposed areas is common in medium brown to dark brown toned skin, though in ivory- to light-brown-toned skin cSCC typically develops on the sun-exposed areas [50,51].

7. Diagnostic Options for Cutaneous Squamous Cell Carcinoma

7.1. Histopathology

Histopathology is the gold standard for diagnosing cSCC [12]. The presence of asymmetrical nests, cords, and sheets of neoplastic keratinocytes within the dermis are histologic characteristics of invasive cSCC [12]. The thickness of the cSCC is important for predicting the risk of metastasis; a thickness > 4 mm is associated with a higher risk of metastasis [12,13]. Immunoperoxidase staining for cytokeratins 5/6/AE1/AE3 can be employed in challenging or poorly differentiated cases [12,13].

The well-differentiated histologic subcategory of SCC has little metastatic probability and encompasses keratoacanthoma and verrucous cancers [52]. Typically keratoacanthomas are crateriform with a large central keratin plug with marked, well-differentiated squamous proliferation [52]. Verrucous cancers can have both endophytic and exophytic growth [52]. The verrucous subtype consists of Buschke–Lowenstein tumors (located in the groin and genitalia) and epithelioma cuniculatum (located on the foot's plantar surface) [52].

Certain histologic variants of cSCC may have a worse prognosis; for example, desmoplastic cSCC is extremely infiltrative, relapses 10 times more often, and metastasizes 6 times more frequently [53]. Desmoplasia is an important prognostic factor for local relapse in SCC (hazard ratio 16.11 (95% confidence interval 6.57–39.49)) in a prospective cohort study [54]. The adenosquamous variant is another subtype which has a secretory tubular arrangement; it has a greater risk of local relapse, metastasis, and mortality [55].

7.2. Dermoscopy

Dermoscopy is helpful in diagnosing and may also be useful in grading cSCC [56]. The two most common vascular patterns for diagnosing cSCC include dotted and glomerular vessels [57]. Looped/hairpin and serpentine vascular patterns can be observed in invasive SCC [57]. Brown globules and gray-brown homogenous vascular patterns can be seen in pigmented SCC in situ [58]. Arborizing vessels are a less common vascular pattern observed in cSCC but may be seen [59]. Other common dermoscopic findings of cSCC include keratin crust/scale, ulceration, and white circle [3]. Figure 3 shows dermoscopic images of cSCC.

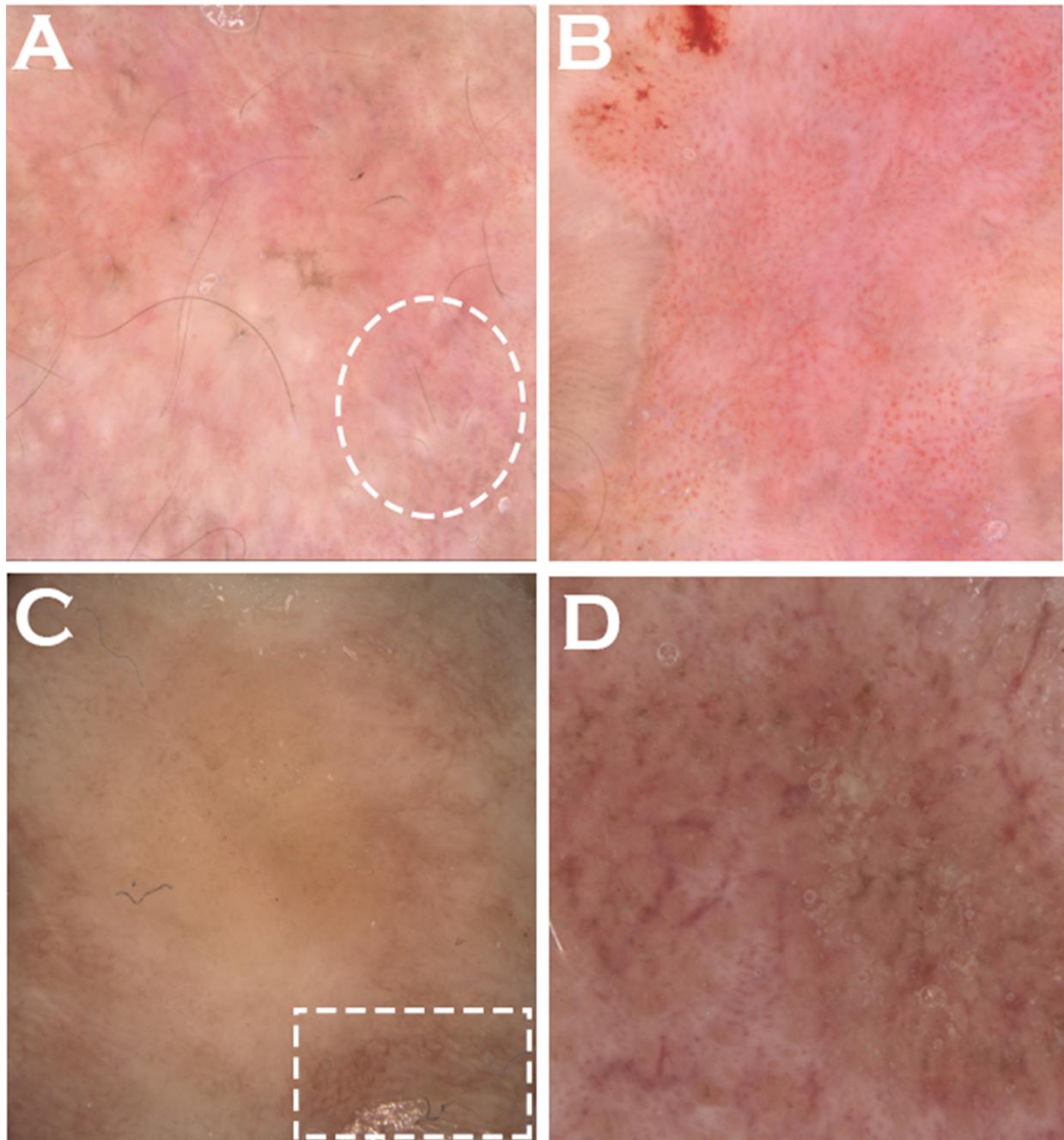


Figure 3. Dermoscopic view of in vivo reflectance confocal microscopy (Vivascope 1500[®] (Caliber Imaging and Diagnostics, Rochester, NY, USA)). Dermoscopic features of cutaneous squamous cell carcinoma (cSCC). (A) Dotted and hair-pin-like vessels. (B) Hair-pin like vessels. (C) Glomerular vessels. (D) Arborizing vessels (atypical presentation of cSCC).

7.3. High Frequency Ultrasonography

High-frequency ultrasonography (HFUS) is capable of visualizing the size and depth of tumors in real-time [60]. HFUS has been shown to increase the accuracy of clinical diagnosis from 73% to 97% in a large retrospective study [60]. It may be used as a complementary tool to aid in the preoperative planning of tumor resection but is not suitable for use by itself as all non-melanoma skin cancers appear hypoechoic [61–63]. HFUS can visualize depths of up to 1.5–8 mm while attaining a resolution of 80–200 μm when used with a transducer with a frequency of 20–100 MH [64]. The features of AK, SCC in situ, and invasive SCC can be analyzed by HFUS with a specificity of 73.6–88% and a sensitivity of 85.3–92.3% [65]. HFUS has the greatest utility in its potential to differentiate between SCC in situ and invasive SCC [66]. In addition, ultrasound is particularly useful in detecting nodal cSCC in the head and neck with 91% sensitivity [67].

7.4. Optical Imaging Diagnostic Modalities

Over the past decade, dermatology has been revolutionized by the emergence of optical imaging diagnostic technologies. Confocal microscopy, optical coherence tomography, and multiphoton tomography serve as promising potential alternatives to traditional biopsy and excision [68]. Figure 4 summarizes the current diagnostic options for cSCC.

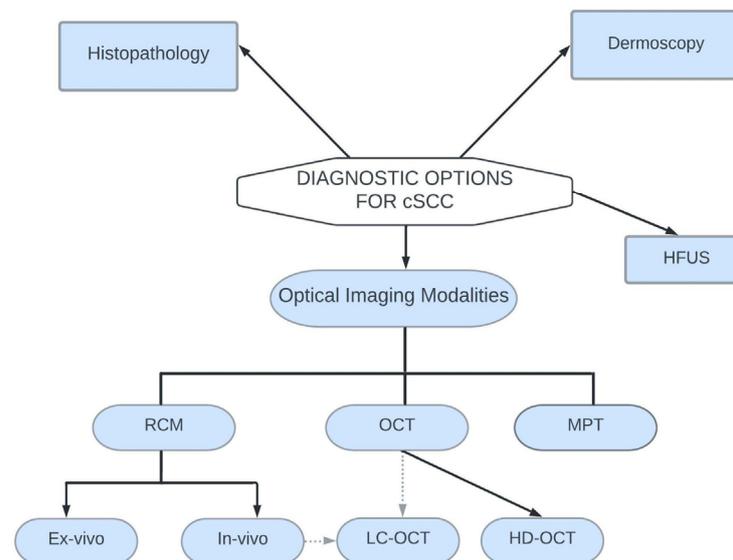


Figure 4. Diagnostic options for cutaneous squamous cell carcinoma (cSCC) (RCM = Reflectance confocal microscopy; OCT = optical coherence tomography; MPT = multiphoton tomography; HFUS = high-frequency ultrasonography; LC-OCT = line-field confocal optical coherence tomography; HD-OCT = high-definition optical coherence tomography).

7.4.1. Reflectance Confocal Microscopy

A. In Vivo Reflectance Confocal Microscopy

In vivo reflectance confocal microscopy (IVRCM) is a means of non-invasive “optical biopsy” and quasi-histologic imaging [69]. IVRCM allows optimum visualization up to 200 μm corresponding to the superficial dermis. The optical resolution of IVRCM is 3–4 μm in the axial direction and 0.5–1 μm in lateral direction [69]. Commercial IVRCM is available as Vivascope 1500 and 3000 in the USA. Vivascope 1500 allows images to be captured as “mosaics” and “stacks” [69]. Mosaic-type images consist of the en-face view of multiple image tiles stitched together at a single depth for a large field of visualization [69]. Stack-type images consist of multiple en-face layers, allowing for comparative analysis. RCM utilizes reflectance to visually differentiate structures based on differences in refractive indices [69].

On RCM, cSCCs and AK both display a mildly atypical or disarranged honeycomb pattern [69]. However, cSCCs exhibit increased keratinocyte atypia and architectural

disorder [69]. Invasive cSCCs exhibit further architectural disarrangement with atypical cells such as polygonal or round cells with a speckled appearance, prominent dark nucleus in the epidermis, sharply demarcated contours filled with amorphous material, ulceration/erosion, and an absence of hyperkeratosis [70]. Irregularly dilated vessels are associated with invasive cSCC [70]. In contrast, well differentiated or moderately well differentiated cSCCs have some preservation of normal architecture with the presence of speckled nucleated cells within the epidermis [70]. Figure 5 highlights various features of cSCC observed under IVRCM.

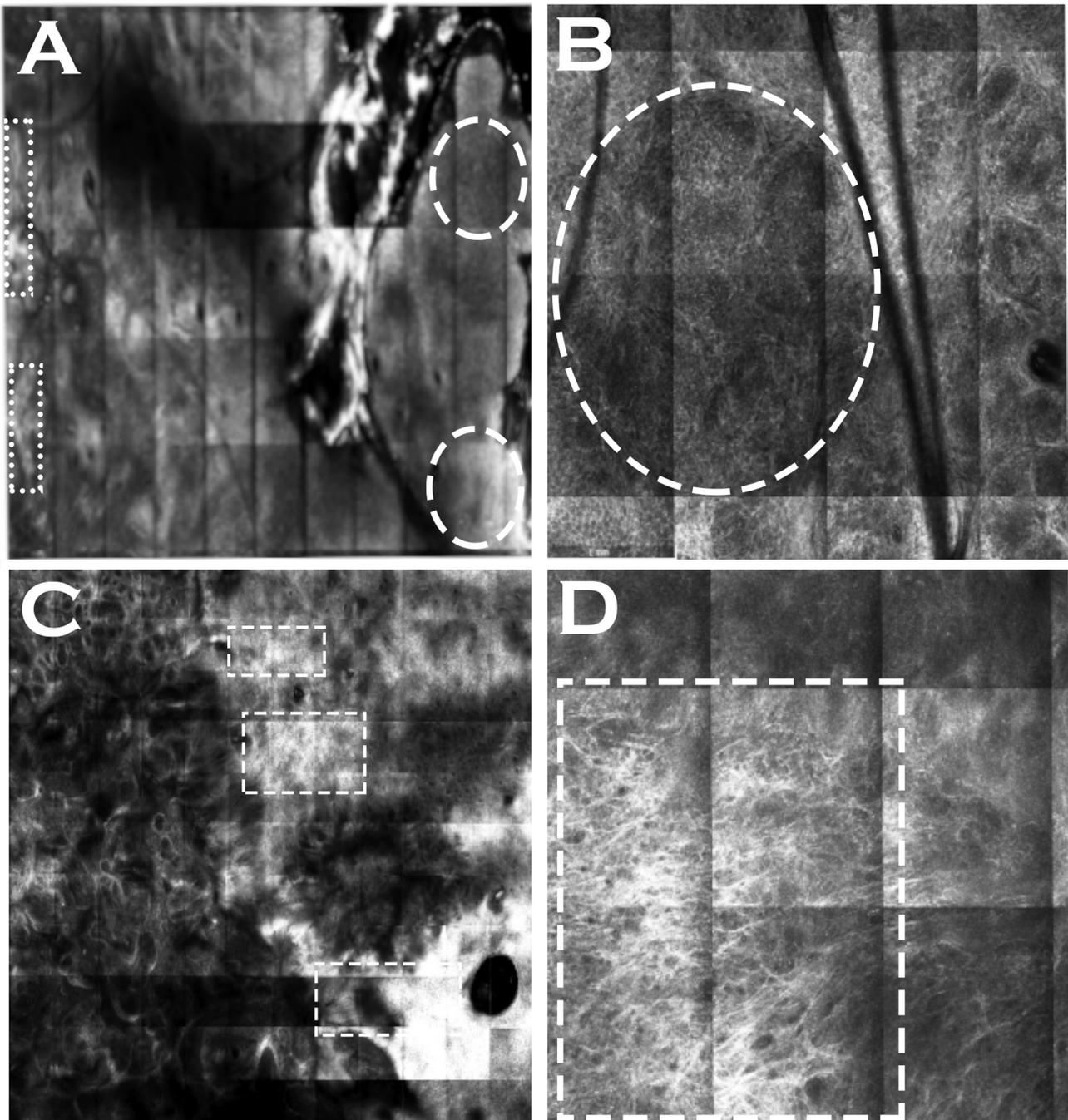


Figure 5. In vivo reflectance confocal microscopic (Vivascope 1500[®]) features of cutaneous squamous cell carcinoma at various levels of depth in the epidermis (cSCC). (A) Atypical honeycomb pattern (represented within oval) with keratinocytic pleomorphism (represented within rectangle). (B) Keratinocytes pleomorphism and epidermal disarray. (C) Keratinocytic atypia/disarray. (D) Atypical keratinocytes.

B. Ex Vivo Confocal Microscopy

Ex vivo confocal microscopy (EVCN) is commercially available as Vivascope 2500, Generation 4 in the USA [71]. EVCN is a burgeoning imaging technique that enables real-time, quasi-histologic imaging of excised tissues without traditional tissue processing, embedding, or sectioning [71]. Vivascope 2500 utilizes two lasers for the visualization of excised tissues/biopsies in four different imaging modes (reflectance, fluorescence, pseudo color, and fusion mode (combined fluorescence and reflectance mode)) [71]. EVCN uses two simultaneous wavelengths of 488 nm and 785 nm for fluorescence mode and reflectance mode, respectively. EVCN allows optimum visualization to a depth up to 250 μm [71]. The Vivascope 2500 also provides image acquisition in fusion mode which combines both confocal and fluorescence modes [71].

The fluorescence mode of EVCN is useful for grading and studying the features of cSCC. The assessment of margins between fluorescent EVCN and frozen histopathologic sections were concordant in 41 of 43 mosaics in a study of 13 SCCs [72]. However, there was a case of SCC in situ where the histologic margin was positive, but the fluorescent mode of EVCN was negative [72]. This study highlights the fact that, although it may be challenging to detect cSCC in situ, detecting cSCCs is possible with fluorescence EVCN [72]. cSCC can be identified by its irregular nuclei that are densely packed [73,74]. The degree of differentiation and invasion can be accessed via fluorescence mode [74].

7.4.2. Optical Coherence Tomography

A. High-Definition Optical Coherence Tomography

Nascent high-definition optical coherence tomography (HD-OCT) is a combination of cross sectional and *en face* imaging, which makes three-dimensional (3-D) imaging possible [75,76]. HD-OCT visualizes cytological architecture up to 570 μm with an axial and lateral resolution of 3 μm [75,77]. The most useful criteria to distinguish cSCC from normal skin and AK is the presence or absence of an outlined dermal–epidermal junction (DEJ) [78]. The absence of a clear outline of a DEJ helps to rule out cSCC [78]. In cSCC, the absence of a DEJ outline may be related to the budding of the epidermis into the upper dermis [78]. Histologically, all cSCCs display alternating parakeratosis/hyperkeratosis and rarely show alternating atrophy or hypertrophy with acanthosis [78]. The ability to view the entire DEJ lends HD-OCT an advantage in recognizing early invasive cSCC, compared to dermoscopy and RCM [78]. In addition, HD-OCT may also serve as a useful tool for monitoring treatment efficacy [78].

7.4.3. Line-Field Confocal Optical Coherence Tomography

Line-field confocal optical coherence tomography (LC-OCT) is the latest non-invasive diagnostic modality that combines the high penetration depth of optical coherence tomography with the high resolution of confocal microscopy to create 3D images [79]. LC-OCT rapidly performs a quasi-histologic examination to visualize cellular-level changes [79]. Due to its infancy in production and distribution in the United States, the potential of LC-OCT in diagnosing and treating squamous cell carcinoma (SCC) remains largely unexplored [79].

A study analyzed 108 cSCCs (62 in situ and 46 invasive) based on previously described histological criteria for SCC in reference to reflectance confocal microscopy, conventional OCT, and HD-OCT [80]. Under LC-OCT, the three key features of cSCCs were disarranged epithelial architecture, dyskeratotic keratinocytes, and atypical nuclei (Table 1) [80]. Identifying the DEJ was noted to be difficult in some lesions due to hyperkeratosis and acanthosis [80]. However, this study noted that an outlined DEJ without broad strands was visible in all in situ cSCCs, but in only three invasive cSCCs ($p < 0.001$) when a DEJ was detected [80]. Non-outlined DEJ and broad strands were noted in invasive tumors [80]. Several other features were identified that discriminated cSCCs from normal skin, including hyperkeratosis, acanthosis, parakeratosis, erosion/ulceration, crowded nuclei, tumor-budding, and dilated vessels [80]. LC-OCT images of cSCC showed adnexal involvement by demonstrating an enlarged hair-follicle epithelium with nuclei of irregular

shape and size [80]. Signs of solar elastosis were also present in the lesions [80]. Figure 6 highlights modes of LC-OCT and visible features of a biopsy-proven cSCC.

Table 1. Optical Imaging Diagnostic Features of Cutaneous Squamous Cell Carcinoma. Modified from [70,72,80]. IVRCM—in vivo reflectance confocal microscopy; EVCM—ex vivo confocal microscopy; HD-OCT—high-definition optical coherence tomography; OCT—optical coherence tomography; LC-OCT—line-field confocal optical coherence tomography; MPT—multiphoton tomography.

Features of Squamous Cell Carcinoma	Definition	IVRCM	EVCM	OCT, HD-OCT	LC-OCT Prevalence in Studied Lesions (%) [80]	MPT
Disorganized/absent dermal–epidermal junction	Linear or jagged homogeneous hyporeflexive bands separating the epidermis from the dermis.	X	X	X	Visible DEJ: 44% Outlined DEJ, if visible: 22%	
Hyperkeratosis, parakeratosis Hyperkeratosis of horned layer in MPT	Stratum corneum exceeding greater than 20 µm in thickness along with presence of retained nuclei in the stratum corneum			X	77%, 52%	X
Absence of hyperkeratosis		X	X	X		
Disorganized epidermal structure	Variation in reflectivity along with shape and size of epidermal nuclei of keratinocytes; the normal architecture of the epidermis is disrupted disarranged honeycomb pattern on RCM	X	X		99%	
“Cocarde image” around the hair follicle	Enlarged hair follicle epithelium with nuclei of irregular shape and size			X	31%	
Erosion, ulceration	Irregularly contoured dark areas with sharp borders with cellular debris and amorphous material	X	X		66%	
Acanthosis	Epidermal thickness greater than 60 µm			X	77%	
Dendritic cells in epidermis	Large elongated cells with clearly visible dendrites connected to the cell	X				
Keratinocytic atypia (Plump, bright, or speckled cells in the epidermis)	Hyper-reflective large, round cells within the epidermis Roundish to polygonal, slightly larger, bright cells with speckled appearance or indistinct borders in the epidermis	X	X		73%	
Atypical nuclei	Irregular nuclei in shape and size	X	X		94%	X
Tumor budding	Atypical keratinocytes with blurred outline forming a rounded projection				31%	
Dilated linear vessels	Elongated areas in the dermis, well-defined, with blood cells.	X	X		53%	
Plump or bright speckled cells in the dermis	Roundish to polygonal, slightly larger, bright cells with speckled appearance or indistinct borders in the dermis	X	X			
Keratin pearls	Whorl-shaped accumulation of keratin appearing as bright, lamellar, sometimes speckled aggregations in the dermis. Often appearance of black hole in the center of the structure is present		X			

Table 1. Cont.

Features of Squamous Cell Carcinoma	Definition	IVRCM	EVCN	OCT, HD-OCT	LC-OCT Prevalence in Studied Lesions (%) [80]	MPT
Inflammatory infiltration	Tiny, regular, roundish to oval, bright dots in the dermis	X	X			
Nest-like structures in the dermis	Dermal, irregular aggregates of cells that are larger than inflammatory cells	X	X			
Dilated blood vessels	Dilated horizontal blood vessels in the dermis, with visible blood flow in their inside.	X				
Button-hole vessels	Dilated blood vessels within the dermal papillae that run perpendicular to the horizontal RCM plane of imaging	X				

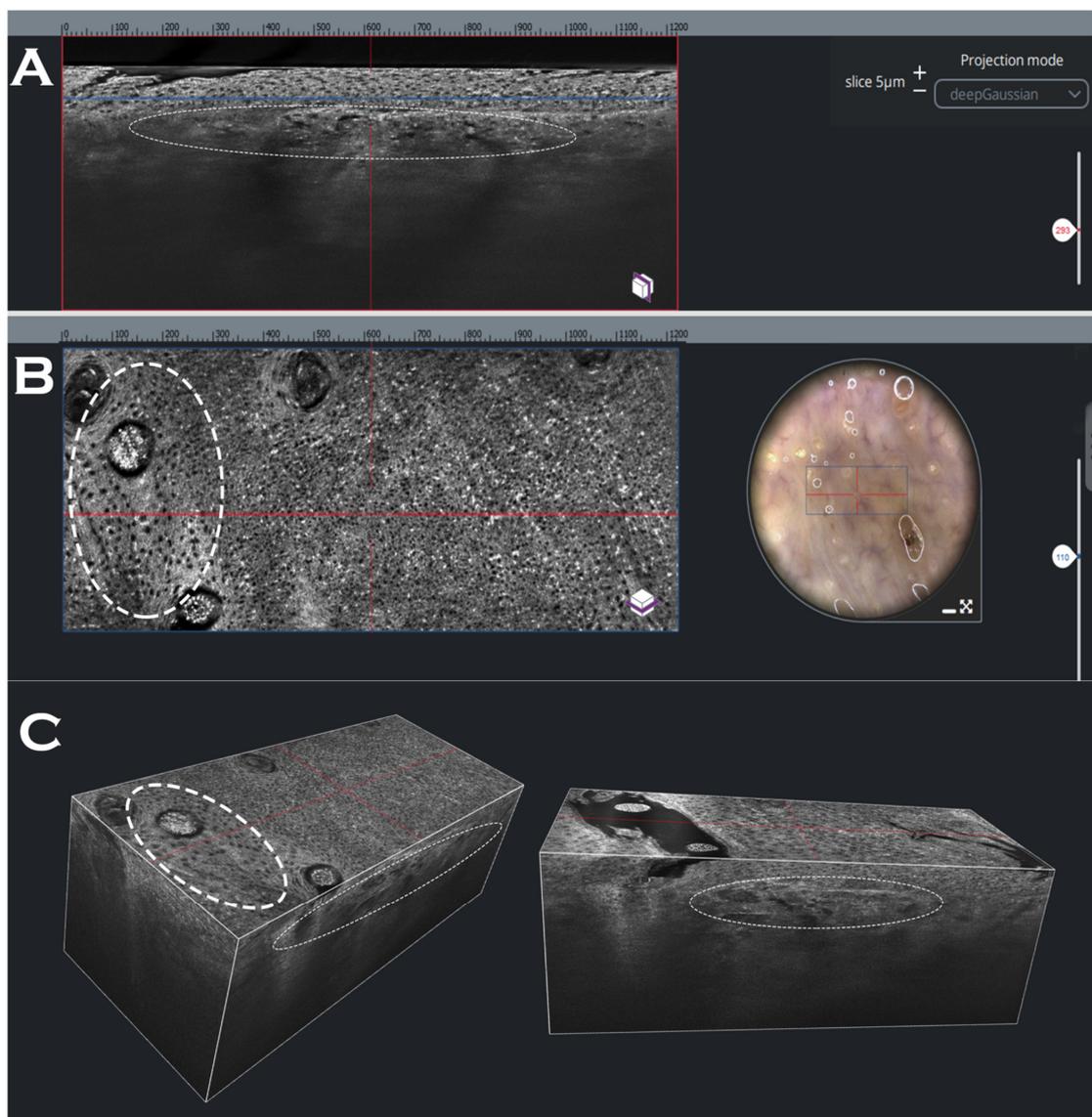


Figure 6. Line-field confocal optical coherence tomography (LC-OCT) features of squamous cell carcinoma. (A) Optical coherence tomography or en-coupe view showing ill-defined DEJ. (B) Confocal or en-face view highlighting atypical nuclei on left side and dermoscopic view on right side. (C) Three-dimensional view.

7.4.4. Multiphoton Tomography

Multiphoton tomography (MPT) provides visualization up to 200 μm with a field of view (FOV) of 350 × 350 μm [81]. The optical resolution of MPT is 1–2 μm in the axial direction and 0.5 μm in lateral direction [82]. MPT can aid in the visualization of hornification and hyperkeratosis in the epidermis. The cells showed greater space between each other, presented with enlarged nuclei, and loss of normal structure [83]. The nucleus to cytoplasm ratio was significantly higher in the spinous and granular layer compared to the healthy skin [83]. Based on these in vivo findings, MPT has great potential to be used clinically to diagnose cSCC.

8. Staging and Gene Expression Profiling

Cancer staging allows for risk stratification based on the likelihood of metastasis, and aids in the selection of patients for clinical trials [84]. The American Joint Committee on Cancer (AJCC)’s AJCC-8 guideline introduced in 2016 characterizes high-risk features as tumor diameter ≥ 4 cm, minor bone erosion, perineural invasion 0.1 mm or in subcutis, or deep invasion (≥6 mm or beyond the subcutaneous fat). High-risk features result in upstaging to T3; cortical bone involvement or marrow invasion increases to stage T4 [84].

The Brigham and Women’s Hospital (BWH) staging method is an alternative staging system proposed in 2013 [85]. It defines the high-risk group, T2b, as having the presence of ≥2 risk factors [85]. Group T2b accounts for 72% of nodal metastases and 83% of mortalities from cSCC [85]. High-risk factors include tumor invasion beyond subcutaneous fat, perineural incursion ≥ 0.1 mm, and poor differentiation. Ruiz et al. (2019) compared the AJCC8 system with the BWH system at a single-center institutional study with a large cohort; they concluded that the BWH system had a higher positive predictive value and higher specificity than the AJCC8 [86]. Another study by Venables et al. (2022) had similar findings to the aforementioned study; additionally, they found that the AJCC8 system had a slightly higher negative predictive value [87]. Based on these studies, it can be concluded that the BWH system is better at identifying low-risk cSCC than the AJCC8 [88]. The AJCC8 and BWH tumor-staging methods are summarized in Table 2. Various studies have described the size of primary lesions in cSCC as a significant predictor of lymph node metastasis [89–93]. In addition, according to the N1S1 revised nodal staging method, the number of involved nodes and diameter of metastatic foci in lymph nodes has a substantial influence on clinical outcomes [94]. Primary invasive cSCC should be differentiated from metastatic cSCC and a staging system is recommended to identify high-risk patients [95]. Nascent gene expression profiling performed on biopsied cSCC tissue determines the prognosis and stratifies patients into three groups (class 1 (low risk), class 2A (high risk), and class 2B (highest risk)) [96]. Individualized treatment recommendations can be proposed with the use of gene profiling in conjunction with staging systems [97]. Although this gene expression profiling is commercially available in the United States, it is yet to be incorporated into AAD cSCC management guidelines [1,97].

Table 2. Summary of BWH and AJCC8 staging systems for cSCC. (PNI—perineural invasion).

BWH Staging System		AJCC8 Staging System	
Stage	Features	Stage	Features
T1	No high-risk characteristics	T1	Tumor diameter < 2 cm
T2a	One high-risk characteristic	T2	Tumor diameter > 2 cm and <4 cm
T2b	2–3 high-risk characteristics	T3	Tumor diameter > 4 cm, or PNI, or minor bone erosion, or deep invasion.
T3	All four high-risk characteristics or bone invasion	T4	Tumor with gross cortical bone/marrow invasion
High-risk Factors	Tumor diameter ≥ 2 cm, poorly differentiated, invasion beyond fat, PNI ≥ 0.1 mm		

9. Management

Standardized guidelines from the National Comprehensive Cancer Network (NCCN) [98] and the American Academy of Dermatology (AAD) are available for cSCC treatment [1]. Stratification of cSCC into low- and high-risk subtypes aids in management decisions [99]. The primary aim of cSCC treatment is the complete elimination of a tumor via surgery, with preservation of normal tissue to attain a satisfactory cosmetic outcome [100]. Surgery with margin analysis is the main treatment modality for cSCC. Two forms of margin analysis are sectional evaluation for standard excision and complete circumferential, peripheral, and deep margin analysis (CCPDMA) for Mohs surgery and its variants (e.g., the Tubingen torte technique or the muffin technique) [100]. Sectional evaluation utilizes bread-loafing and permits visual evaluation of about 1% of the marginal surface area of the tissue sample [1,98]. CCPDMA allows histologic assessment of the entire margin by *en face* segmenting. For localized, low-risk cSCC, first-line therapy consists of standard excision with 4–6 mm margins and postoperative margin evaluation [1,98]. Mohs surgery is the treatment of choice when the head or neck, immunosuppressed patients, recurrent disease, aggressive histologic subtypes, or lesions with ≥ 2 mm depth are involved [101,102].

The destruction of cSCC with curettage and electrodesiccation (C&E) or liquid nitrogen can be employed in low-risk cSCC or cSCCIS [103]. A cSCC greater than 2 cm, can be treated with C&E but there is a 11.8% rate of recurrence [104]. Radiation therapy can be employed in cases of relapse, perineural invasion, or positive margins after excision [105]. Radiation therapy (RT) is useful in areas that are close to cosmetically sensitive areas such as the lower eyelid, inner canthus, lip, nose tip, or ear [106]. RT commonly causes treatment-related adverse effects such as skin pallor and telangiectasia; thus, for some patients, the scar formed from standard excision/surgery may be a more acceptable cosmetic outcome [107]. The cure rate for RT is also lower compared to standard surgical excision [104]. In high-risk cSCC, RT can be used as an adjunct following surgery [28,108]. Ablative laser therapy (carbon dioxide laser) has been used to treat 48 cases of cSCCIS, with one or more passes, with a recurrence rate of 6.8% after follow-up at 18 months [109].

Commonly used topical treatment for low-risk cSCCIS consists of 5-fluorouracil (5FU), trichloroacetic acid, or imiquimod [110,111]. These treatments can also be used for human papillomavirus (HPV)-associated, multifocal cSCCIS [112,113]. Topical therapy can also be used as an adjunct when surgical margins are positive for cSCC associated with HPV [112,113]. Topical 5-FU cleared 70% of facial SCC in 10 individuals with XP when applied for 6 months, twice daily [114]. Photodynamic therapy (PDT) has also been recognized as an effective therapy for AK, cSCCIS, and NMSCs. PDT incorporates a topical photosensitizer, e.g., methyl aminolevulinate or aminolevulinic acid with phototherapy [112]. Methyl aminolevulinate PDT (MAL-PDT) delivers a cure rate of 86–93% for cSCCIS and a 70–90% lifetime cure rate for NMSC, but is not recommended for invasive cSCC due to a high recurrence rate [115,116].

Chemopreventive agents include topical and oral retinoids, 5-FU, nicotinamide, capecitabine, imiquimod, and intralesional interferon- α (IFN- α) [117]. There is contradictory evidence regarding the chemopreventive effects of retinoids. Therefore, the AAD recommends against the use of retinoids, except acitren, which may be used in patients with a history of cSCC or solid organ transplant [1,117,118]. Prophylactic use of 5-FU cream is associated with a 75% reduction in the development of cSCC in patients with a history of NMSC [119]. Nicotinamide, a modified form of vitamin B3, showed a 30% reduction in cSCC after 12 months of therapy in a phase 3, double-blinded RCT but the benefit was short-lived and decreased significantly after the discontinuation of nicotinamide [120]. Capecitabine, an oral precursor of 5-FU, has shown a 50% reduction in cSCC in 13 of 18 OTR patients, but 56% of patients ended up discontinuing capecitabine for various reasons [120]. In a study of 20 patients, topical imiquimod led to decreased squamous skin tumor development [121]. In a case study, two patients with aggressive and recurrent SCC treated with intralesional interferon- α (IFN- α) reported no recurrence of cSCC [122].

Standard systemic treatment of cSCCs includes chemotherapy, immunotherapy, and epidermal growth factor receptor inhibitors (EGFRi) [123]. Chemotherapy is only warranted for localized lesions not responsive to surgery. In the case of metastatic cSCC, chemotherapy such as cisplatin, 5-FU, doxorubicin, bleomycin monotherapy, or their combinations has been effective in only limited case series and single-arm studies [123]. The off-label use of cisplatin or carboplatin, 5-fluorouracil, methotrexate, adriamycin, bleomycin, taxanes, and gemcitabine has been reported in advanced cSCC patients [95]. The response to chemotherapy is often short-lived and associated with significant toxicity [95]. Immunotherapy with immune checkpoint inhibitors (ICI) consists of program death 1 inhibitors (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 inhibitor (CTLA-4) [124]. Cemiplimab, a humanized IgG4 PD-1 blocker, has been approved by the FDA (September 2018) to treat adult non-surgical or non-radiotherapy candidates who have locally advanced or metastatic SCC [124]. Cemiplimab has a satisfactory safety profile and a sturdy response, providing higher rates of progression-free survival and overall survival [124,125]. Pembrolizumab was also approved by the FDA in June 2020 for patients with recurrent or metastatic cSCC not treatable with surgery or radiation [126,127]. Ipilimumab is another FDA-approved antibody against CTLA-4 that, compared to other ICIs, has a worse safety profile and a smaller role in cSCC treatment [128]. Systemic targeted therapy with epidermal growth factor receptor (EGFR) inhibitors includes gefitinib, erlotinib, cetuximab, panitumumab, and IV monoclonal antibodies. EGFR inhibitors are used in patients who are ineligible for clinical trials or ICI therapy [97].

Patients with cSCC should be counseled about skin protection from UV radiation by using protective clothing, sunscreen, and sun protective behaviors [129,130]. Patients with a history of cSCC and AKs require regular skin exams every 6–12 months, while those with several cSCCs or aggressive tumors should be examined more frequently [1,131]. Self-surveillance plays an important role for the early detection of new primary cSCC and other skin cancers [132]. Family members can also be helpful for the patients in detection of skin cancers, especially in areas that are not easily evaluated by the patient such as the back [132]. Figure 7 highlights management options for cSCC.

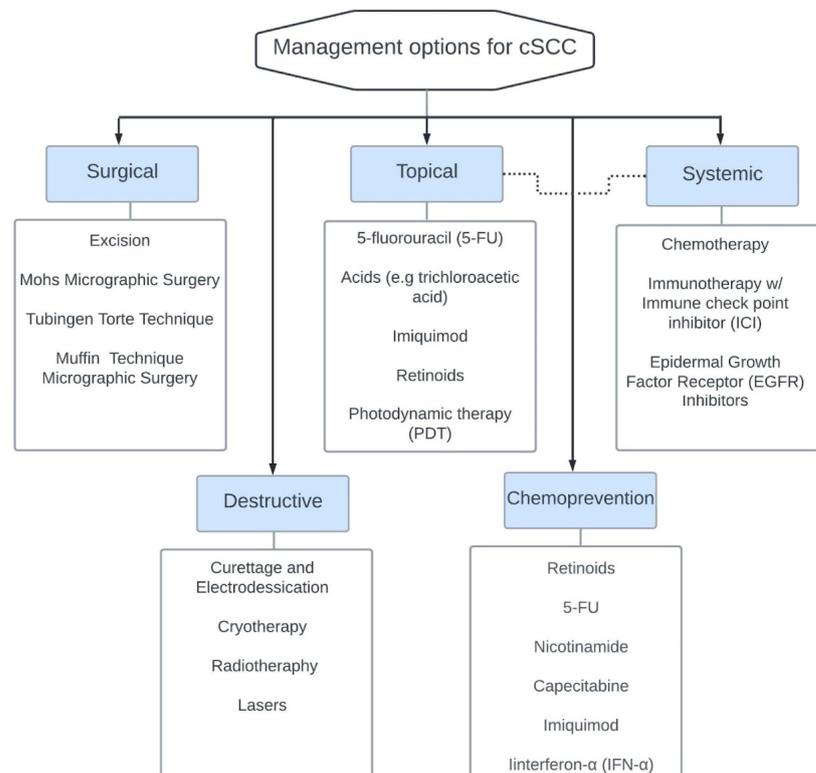


Figure 7. Management options for cutaneous squamous cell carcinoma (cSCC).

10. Conclusions

The emergence of new optical imaging modalities such as confocal microscopy, OCT, LC-OCT, and MPT has revolutionized diagnostic imaging in dermatology, particularly within the realm of skin cancer. Applications of newer imaging devices to cSCC management may benefit high-risk patients (e.g., chronic UV radiation exposure or OTR) or patients with multifocal cSCC that make multiple biopsies impractical, thus avoiding unnecessary biopsies. Together with dermoscopy, optical imaging technologies can help to improve the efficiency of diagnosis by decreasing the turnaround time and reducing laboratory processing resources. Confocal microscopy provides non-invasive imaging up to 200 μm , corresponding to the superficial dermis. It enables visualization in en-face view. OCT enables visualization in en-coupe view. HD-OCT visualizes up to 570 μm . LC-OCT enables visualization in horizontal, vertical, and 3D modes up to 500 μm . MPT provides visualization up to 200 μm . All these devices help diagnose cSCC in vivo (except ex vivo devices) and provide real-time diagnosis. All these devices are commercially available in the United States and are being used to study cutaneous tumors, including cSCCs.

While surgical intervention remains the definitive treatment for cSCC, optical imaging technology can be utilized to plan preoperative and postoperative treatment. With non-surgical cSCC interventions such as oral or topical retinoids, photodynamic therapy, topical 5-FU, electrodesiccation, cemiplimab, or pembrolizumab, non-invasive imaging may have a role in quantitating treatment monitoring and effectiveness.

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