# Immunotherapy as a Treatment Modality for Mucosal Melanomas of the Head and Neck: A Systematic Review

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**Abstract**

Abstract Introduction Mucosal melanoma (MM) is a rare disease, accounting for approximately 1.4% of all melanomas and only 0.03% of all new cancer diagnoses [1]. Traditionally, it is associated with a poor prognosis with an overall 5-year survival rate of less than 25%[1]. Progress in treatment has been hindered by rarity and lack of evidence. Studies however of treatment of subcutaneous melanoma with immunotherapy have demonstrated a significant improvement in survival rates and have become a core part of oncological strategy. This paper will discuss revision of the evidence for the use of immunotherapy in the Head and Neck. Design A systematic review was conducted on 19/01/2019. Medline and Embase databases were searched. 509 articles were collated, of which 52 met the inclusion criteria. Results Results were shown as a comparison of yearly survival rates following different treatment modalities (immunotherapy vs non-immunotherapy) at 2 years, 3 years, and 5 years respectively. Conclusions Immunotherapy outcomes in small studies have shown good data for increasing survival rates at all yearly intervals in MM of the head and neck. Larger clinical trials should be done to accurately distinguish efficacy and survival outcomes of immunotherapy when compared to treatment modalities excluding immunotherapy. The ability to perform larger trials are, however, limited by the rarity of MM of the head and neck.

*Abstract*

*Introduction*

Mucosal melanoma (MM) is a rare disease, accounting for approximately 1.4% of all melanomas and only 0.03% of all new cancer diagnoses[1]. Traditionally, it is associated with a poor prognosis with an overall 5-year survival rate of less than 25%[1]. Progress in treatment has been hindered by rarity and lack of evidence. Studies however of treatment of subcutaneous melanoma with immunotherapy have demonstrated a significant improvement in survival rates and have become a core part of oncological strategy. This paper will discuss revision of the evidence for the use of immunotherapy in the Head and Neck.

*Design*

A systematic review was conducted on 19/01/2019. Medline and Embase databases were searched. 509 articles were collated, of which 52 met the inclusion criteria.

*Results*

Results were shown as a comparison of yearly survival rates following different treatment modalities (immunotherapy vs non-immunotherapy) at 2 years, 3 years, and 5 years respectively.

*Conclusions*

Immunotherapy outcomes in small studies have shown good data for increasing survival rates at all yearly intervals in MM of the head and neck. Larger clinical trials should be done to accurately distinguish efficacy and survival outcomes of immunotherapy when compared to treatment modalities excluding immunotherapy. The ability to perform larger trials are, however, limited by the rarity of MM of the head and neck.

*Key Points*

Mucosal Melanoma of the head and neck has a very poor prognosis. Structured treatment directed at these malignancies remains variable due to low incidence of disease. Surgery, radiotherapy, and chemotherapy remain the mainstay of treatment. With limited literature, Immunotherapy demonstrates a promising aspect of treatment in prolonging survival rates in these malignancies. Further trials are necessary to prove efficiency of immunotherapy.

*Introduction:*

Primary mucosal melanomas are rare, biologically aggressive neoplasms, with very poor outcomes. They account for 1.4% of all melanomas and only 0.3% of new cancer diagnoses [1]. The distribution of head and neck, female genital tract, anal/rectal, and urinary tract sites is 55.4%, 18.0%, 23.8%, and 2.8% respectively[2]. The median age of presentation is the seventh decade, with a tendency for women to be affected more than men[2].

In the head and neck region, there seems to be a predominance of the disease in the sinonasal region, accounting for 59-80% of cases[3]. Mutations associated with mucosal melanoma are to this day poorly understood. A paper by Nassar et. al. published in 2020, looking at the mutational landscape of mucosal melanoma, showed, using targeted sequencing, whole-exome sequencing, and whole-genome sequencing, that the mutation is unknown in 44% of cases. However, SF3B1 gene was implicated in 15% of cases, KIT gene in 13%, NF1 in 14%, NRAS in 8%, and BRAF in 6% [4].

The overall 5-year survival is poor, with one paper citing a 21.7% rate in 695 patients [5]. Treatment of mucosal melanoma has been subject to multiple different trials, some of which include surgery alone, surgery with chemotherapy, surgery with radiotherapy, surgery with chemo radiotherapy, and finally with or without immunotherapy. Surgery remains the primary therapeutic intervention given that complete resection is feasible in a set anatomical location. Treatment with immunotherapy is novel, and so the literature is lacking in studies proving efficacy of immunotherapy treatment.

*Methods:*

*Literature Search*

Literature review was conducted by searching Medline and Embase, going back as far as the database goes, until 2019. The database was searched using terms outlined in Table 1. A Total of 509 citations were collated.

*Study Selection*

An initial primary screen was conducted by Authors JW and DJ, to include only articles in human subjects, articles in English, and articles with full text availability. Primary screen included carefully reviewing the database for any duplicates. Furthermore, the primary screen included exclusion of articles with non-head and neck mucosal melanomas.

A second screen was done to stratify articles according to anatomical site (Sino nasal or all head and neck), whether they are case reports, whether treatment outcomes were reported, whether one treatment modality was used, and whether or not immunotherapy was used. In total, 52 articles met the inclusion criteria, which consisted of 1) treatment naïve cohorts, 2) those with recurrent disease,3) primary outcomes with overall survival and disease-free survival at 5 years, and at longest follow up 4) studies of adults with mucosal melanoma in whom immunotherapy was reported as a treatment strategy.

The systematic review was conducted and reported in accordance with PRISMA flow chart (Figure1).

*Results:*

Of the 352 titles and abstracts included in the search, 52 were eligible for final synthesis. The PRISMA flowchart (figure 1) details reasons for exclusion at each level of the screening process.

In the included studies, it was found that there wasn't a consistency in survival rates, with some papers citing 1,2,3-year survival rates, others showing 2,3 and 5-year survival rates, and others showing 2,5 and 10-year survival rates. Additionally, not all papers cited survival rates with immunotherapy treatment versus non-immunotherapy treatment.

We sought to standardize survival rates at 2 years, 3 years, and 5 years. Additionally, we stratified survival rates based on treatment with immunotherapy with or without other modalities and non-immunotherapy based treatment, whatever the modality chosen.

The graph (figure 2) demonstrates survival rates with different treatment modalities spread across 2 years, 3 years, and 5 years. The numbers were obtained by gathering data of survival rates in percentages from the different papers at the desired year interval, and calculating the median.

At 2 years, it was found that the overall survival rate was 52.6%, with treatments including immunotherapy showing a 58% survival rate and treatment without immunotherapy showing 50% survival. Similarly, at 3 years, overall survival was 35%, with 70.1% survival rates in immunotherapy treatment and 42.35% in non-immunotherapy treatment. At 5 years, overall survival was 35.7%, with 40.03% survival in immunotherapy treatment and 31.7% in non-immunotherapy treatment.

The results of the literature reviewed clearly showed that in the limited database, involvement of immunotherapy showed overall better survival outcomes.

None of the papers reviewed however, commented on quality of life in those who survived at every interval, treatment related complications, involving significant disabilities, or death in more severe cases.

*Discussion:*

Mucosal Melanoma of the head and neck represent a relatively small pool of malignancies. Not until 2018 was there a work by a team of surgeons, medical oncologists, clinical oncologists, radiologists, pathologists, nurses, as well as patients and carer representatives to form clear guideline on how to manage mucosal melanoma of the head and neck, with a clear pathway diagram outlining steps of referral, assessment and staging, diagnosis, management, and treatment [6].

This paper explores the literature for available studies looking mucosal melanoma of the head and neck and the different treatment modalities available. We looked to find treatment modalities consisting of immunotherapy, with or without other treatment modalities. We looked to compare these to treatment options not involving immunotherapy. The results showed a clear improvement in survival outcomes when immunotherapy was used, compared to survival outcomes without immunotherapy, at all yearly intervals studied. It is pertinent to point out, however, that all studies included a small number of patients, and in many cases, did not clearly define their own inclusion criteria. This could be down to the fact that presentation of disease is variable, both in terms of site and duration.

None of the studies reviewed mentioned randomization of patients, which would have eliminated bias and thus decreased likely discrepancies in treatment received, such as addition of immunotherapy/radiotherapy/chemotherapy to those with poorer prognosis as opposed to surgery alone in those with better prognosis.

There was no report of quality of life in different interventions and therefore no subjective feedback on results from intervention.

Adjuvant immunotherapy with anti-PD-1 agents following complete resection of high-risk (Stage III/IV) melanoma, regardless of subtype, is now standard-of-care (NICE Technology Appraisal Guidance TA553 and TA558) [6].

Immune therapy with checkpoint inhibitors has revolutionized management of melanoma. Ipilimumab, nivolumab, and pembrolizumab are all immune checkpoint inhibitors to treat metastatic melanoma. They work by activating the immune system to treat melanoma .

Ipilimumab targets cytotoxic T-lymphocyte antigen 4 (CTLA-4). By doing so, it down regulates receptors on activated T-cells, whose function is to inhibit T-cell activation. By down-regulating CTLA-4, it allows for expansion of naturally developed melanoma-specific cytotoxic T-cells. It resulted in 11% objective response rate and 24% two-year overall survival.7 The 10-year overall survival of ipilimumab is approximately 22% in a pooled analysis of overall survival data from multiple studies[7].

Nivolumab and pembrolizumab, on the other hand, act by inhibiting programmed cell death ligand 1 (PDL-1). PDL-1 acts to inhibit T-cell proliferation allowing cancer cells to evade immune surveillance[7]. However, the expression of PDL-1 in mucosal melanomas is not well understood. One study, by using immunohistochemical staining in 23 tumor samples from patients with primary mucosal melanoma, found an expression in only 13% (3/23) of mucosal melanomas [8]. Treatment outcomes with these modalities showed mixed results. One paper, which studied the outcomes in both mucosal and acral melanoma treatment with PDL-1 inhibitors, showed an 11.5% response rate to treatment[9]. D'angelo et. al. looked at the efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma. Among patients who received nivolumab, median progression-free survival was 3.0 months, with objective response rates of 23.3%. In patients treated with nivolumab in combination with ipilimumab, median progression-free survival was 5.9 months, with objective response rates of 37.1% [10].

Wang Et al reviewed the effect of Interferon-α-2b as an adjuvant therapy and its effect on prolongation of life in patients with previously resected oral mucosal melanoma [11]. Relapse-free survival was significantly prolonged in patients who received postoperative immunotherapy, but there was no significant difference in the overall survival between the those who received immunotherapy versus those who didn't. [11].

Frakes et. al reviewed a single-center case series of 38 patients, of which 6 (16% of patients) received adjuvant immunotherapy. The study concluded that immunotherapy was not associated with improvements in local control, progression-free or overall survival[12].

The above mentioned papers were in contrast to Kanetaka et al, who looked at the effect of using lymphokine-activated killer (LAK) cell transfer therapy in mucosal melanoma of the head and neck. The sample size included 13 patients over 18 years, with 7 receiving immunotherapy. However, there was no clear explanation if these patients also received chemotherapy. The outcome was that in 7 cases receiving adjunctive LAK cell therapy, the 5-year cause-specific survival rate was 66%, while that in 6 cases without adjunctive LAK therapy was 33%. Although a statistical significance was not recognized, LAK therapy is suggested to improve prognosis of mucosal melanoma of the head and neck[13].

Long et al conducted a double blind, placebo-controlled trial, randomizing 870 patients with completely resected stage III melanoma with BRAF mutation to either BRAF targeted immunotherapy or placebo tables for 12 months. The rates of distant metastasis-free survival and freedom from relapse were higher than in placebo group, with a 53% reduction in relapse or death [14].

In one case report written by Studentova et. al. following disease progression after surgical resections, the patient was treated with ipilimumab monotherapy that was initially followed by disease progression, but subsequently by disappearance of the primary tumor and overall partial response of the disease elsewhere 8 months later. However, the effect lasted only for another 8 months and disease progression occurred followed by death 3 months later[15].

A systematic review conducted by Jarrom et. al.[17] looked at treatment of mucosal melanoma of the upper airway tract. 11 studies were selected looking at surgery and radiotherapy only, with no chemotherapy or biological treatment included. It is noteworthy that since then, more trials have been conducted of which biologics including immunotherapy have been utilized and studied as potential treatment modalities for improving outcomes.

*Conclusion:*

Immunotherapy outcomes in small studies has shown good data for increasing survival rates at all yearly intervals in mucosal melanomas of the Head and Neck.

Larger clinical trials should be done to accurately distinguish the efficacy and survival outcomes of immunotherapy when compared to treatment modalities excluding immunotherapy.

We note that the ability to perform larger trials are limited by the rarity of mucosal melanomas of the Head and Neck.

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| | |
|---|---|
| 2 | (mucosal melanoma*).ti,ab |
| 7 | Exp "GENERAL SURGERY"/ |
| 8 | (surger*).ti,ab |
| 9 | Exp "DRUG THERAPY"/ |
| 10 | (chemotherapy).ti,ab |
| 11 | Exp RADIOTHERAPY |
| 12 | (radiotherapy OR "radiation therapy" OR RT).ti,ab |
| 13 | Exp IMMUNOTHERAPY/ |
| 14 | (immunotherapy).ti,ab |
| 15 | Exp "COMBINED MODALITY THERAPY"/ |
| 16 | ((multimodality OR combin*) ADJ3(therapy OR treatment)).ti,ab |
| 17 | (7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16) |
| 18 | exp MORTALITY/ |
| 19 | (mortality).ti,ab |
| 20 | Exp RECURRENCE/ |
| 21 | (recurrence*).ti,ab |
| 22 | Exp "DISEASE-FREE SURVIVAL"/ |
| 23 | ((disease OR progression) ADJ3 free survival) |
| 24 | (18 OR 19 OR 20 OR 21 OR 22 OR 23) |
| 25 | (2 AND 17 AND 24) |
| 26 | (mucosal melanoma*).ti,ab |
| 27 | exp "GENERAL SURGERY"/ |
| 28 | (surger*).ti,ab |
| 29 | exp"DRUG THERAPY"/ |
| 30 | (chemotherapy).ti,ab |
| 31 | exp RADIOTHERAPY/ |
| 32 | (radiotherapy OR "radiation therapy" OR RT).ti,ab |
| 33 | exp IMMUNOTHERAPY/ |
| 34 | (immunotherapy).ti,ab |
| 35 | exp"COMBINED MODALITY THERAPY"/ |
| 36 | ((multimodality OR combin*) ADJ3 (therapy OR treatment)).ti,ab |
| 43 | (27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36) |
| 37 | exp MORTALITY/ |
| 38 | (mortality).ti,ab |
| 39 | exp RECURRENCE/ |
| 40 | (recurrence*).ti,ab |
| 41 | exp "DISEASE-FREE SURVIVAL"/ |
| 42 | ((disease OR profression)ADJ3 free survival).ti,ab |
| 44 | (37 OR 38 O 39 OR 40 OR 41 OR 42) |
| 45 | (26 AND 43 AND 44) |

Table 1 showing search strategy

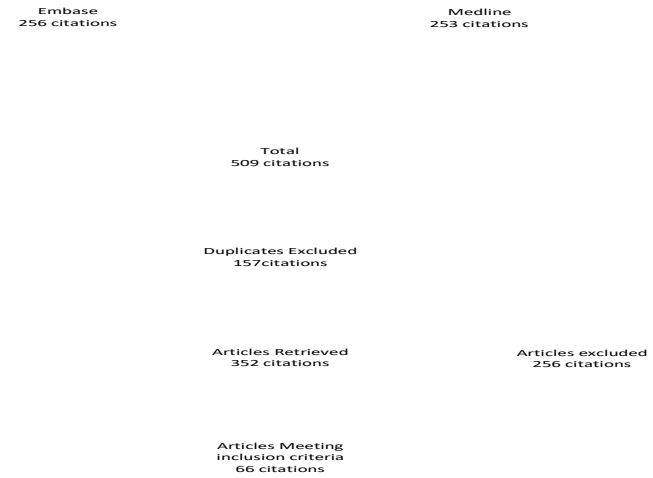


Figure 1: PRISMA chart showing inclusion and exclusion criteria

Survival at different yearly intervals with and without interferon

| | 2 year survival | 3 year survival | 5 year survival |
|---|---|---|---|
| **Overall** | 52.60% | 35% | 35.70% |
| **Interferon +/- surgery +/- chemotherapy** | 58% | 70.10% | 40.03% |
| **Surgery +/- chemotherapy +/- radiotherapy – no interferon** | 50% | 42.35% | 31.70% |

Figure 2. Table showing survival rates derived from systematic review

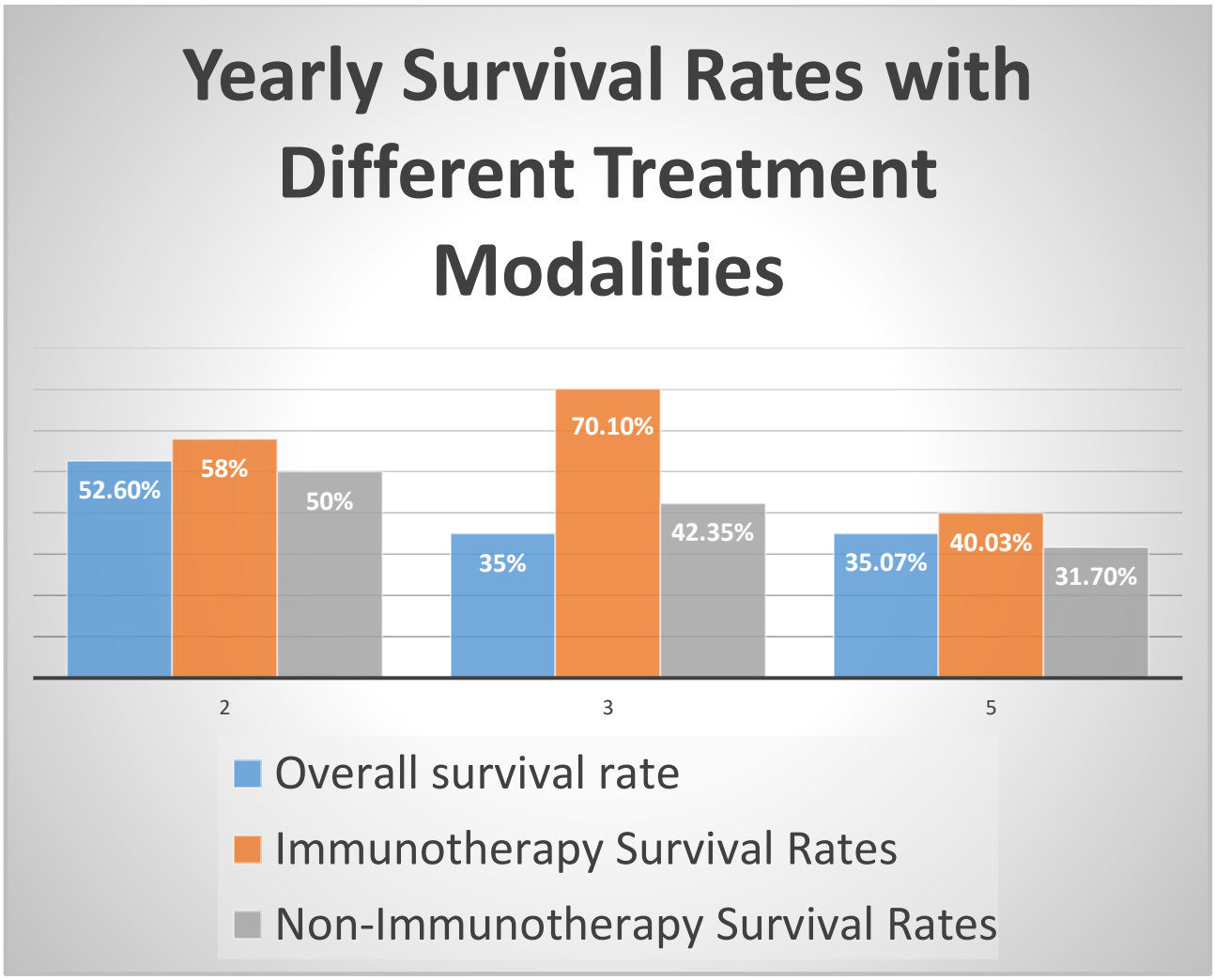


Figure 3. Graph showing comparison of yearly survival rates following different treatment modalities (Immunotherapy vs Non-immunotherapy

Table 2. Characteristics of included study

| Study | Country | # of Patients | Treatment modalities | Median Follow up | Cancer type |
|---|---|---|---|---|---|
| Zhang 2018 | China | 162 | Immunotherapy alone(n=118)<br>Chemotherapy alone(n=44) | Not Reported | Mucosal melanoma (n=41)<br>Cutaneous melanoma (n=121) |
| Namikawa 2018 | Japan | 30 | 2 immunotherapy agents (nivolumab + ipilimumab) every 3 weeks for four doses, followed by biweekly nivolumab | 14.1 months (5.2-27.7) | Mucosal melanoma (n=12)<br>Non-acral cutaneous (n=8)<br>Acral cutaneous (n=7)<br>Uveal (n=2)<br>Unknown primary (n=1) |
| Maxwell 2018 | USA | 1 | Surgery + Radiation +immunotherapy | Not applicable | Mucosal melanoma (n=1) |
| Theirauf 2018 | Germany | 21 | Surgery (n=7) Surgery + radiation (n=9) Surgery + interferon (n=4) Chemotherapy (n=1) | 51 months (2-202 moths) | Mucosal Melanoma (n=21) |
| Kiyohara 2018 | Japan | 610 | Immunotherapy (n=610)<br>Number of Previous therapy (not specified)<br>1 (n=205)<br>2 (n=116)<br>3 or more (n=197)<br>unknown (n=162) | Not Specified | Cutaneous (n=389)<br>Mucosal (n=208)<br>Other (n=50)<br>Unknown (n=34) |
| Tsui 2018 | Not specified | 1 | Surgery + radiotherapy + immunotherapy | Not applicable | Mucosal melanoma (n=1) |
| Fujisawa 2017 | Japan | 60 | Immunotherapy (n= 53)<br>Radiotherapy + immunotherapy (n=7) | Not specified | Acral lentiginous (n=18)<br>Mucosal (n=14)<br>Nodular (n=12)<br>Superficial spreading (n=8)<br>Lentigo (n=2) |

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| | | | | | Others/unknown (n=6) |
| Yamada 2017 | Japan | 38 | Surgery (n=16)<br>Surgery + immunotherapy (n=3)<br>Surgery + chemotherapy + immunotherapy (n=9)<br>Surgery + chemo (n=9)<br>Surgery + chemoradiotherapy (n=1) | 41.1 months (1-137 months) | Mucosal melanoma (n=38) |
| Liu 2017 | China | 51 | Surgery (n=48)<br>Radiotherapy (n=33)<br>Chemotherapy (n=10)<br>Immunotherapy (n=13) | 59.0 months | Mucosal melanoma (n=51) |
| Kuo 2017 | Toronto | 17 | Immunotherapy (n=17) | 10.1 months (0.8-56.6) | Mucosal melanoma (n=17) |
| Shoushtari 2018 | USA | 81 | Other modalities + Immunotherapy (n=20)<br>Other modalities without immunotherapy (n=61) | 10.3 (0.5 – 90.8) | Mucosal melanoma (n=81) |
| D'angelo 2017 | USA | 889 | Immunotherapy (n=889) | 7.4 (6.2-8.6) | Mucosal melanoma (n=86)<br>Cutaenous melanoma (n=665) |
| Simeone 2016 | Italy | 42 | Immunotherapy | 5.6 months | Cutaneous Melanoma (n=40)<br>Mucosal melanoma (n=2) |
| Schaefer 2017 | USA | 75 | Surgery + immunotherapy (n=21)<br>Surgery + immunotherapy + radiotherapy (n=5) | 32 months (2-231 months) | Mucosal melanoma (n=75) |
| Jung 2017 | Korea | 104 | Immunotherapy (n=104)<br>Number of Previous therapy (not specified)<br>1 (n=41) | 7.1 months (5.9-8.3 months) | Acral (n=33)<br>Mucosal (n=27)<br>Cutaneous (n=27) |

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|---|---|---|---|---|---|
| | | | 2 (n=34)<br>3 (n=29) | | Uveal (n=10)<br>Unknown (n=7) |
| Shoushtari 2016 | USA | 60 | Immunotherapy (n=60)<br>Previous systemic therapy (not specified)<br>(n=51) | 15.3 months | Acral (n=25)<br>Mucosal(n=35) |
| Frakes 2015 | USA | 38 | Immunotherapy (n=6)<br>Other modalities (n=32) | Not specified | Mucosal (n=38) |
| Kirchoff 2016 | USA | 227 | Surgery (n=53)<br>Surgery + other modalities[immunotherapy inclusive] (n=149) | Not Specified | Mucosal (n=227) |
| Wu 2015 | Taiwan | 31 | Immunotherapy + chemotherapy (n=31) | 55 months (14.7-95.4 months) | Acral (n=11)<br>Nodular (n=4)<br>Superficial spreading (n=1)<br>Mucosal (n=10)<br>Other (n=5) |
| Bakkal 2015 | Turkey | 10 | Surgery + chemoradiotherapy (n=4)<br>Surgery + radiotherapy (n=5)<br>Surgery + chemotherapy + immunotherapy (n=3) | Not specifiied | Mucosal (n=10) |
| Lian 2013 | China | 189 | Surgery (n=63)<br>Surgery + immunotherapy (n=63)<br>Surgery + chemotherapy (n=63) | 26.8 months (5.9-53.9 months) | Mucosal (n=189) |
| Alexander 2014 | Australia | 104 | Immunotherapy (n=104) | 7 months (0-30 months) | Cutaneous (n=79)<br>Mucosal (n=8)<br>Uveal (n=11) |
| Sun 2013 | China | 68 | Immunotherapy (n=15)<br>Chemotherapy (n=29)<br>Multimodal treatment not specified (n=37)<br>Radiotherapy (n=20) | Not specified | Mucosal (n=68) |
| Vecchio 2014 | Italy | 71 | Previous treatments not specified: 1 (n=47)<br>2 (n=14)<br>3 or more (n=10) | 21.8 months (1.0-32.7 months) | Mucosal (n=71) |
| Keller 2013 | USA | 73 | Surgery (n=26) | 27.5 months | Mucosal (n=73) |

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|---|---|---|---|---|---|
| | | | Surgery + immunotherapy (n=7)<br>Surgery + chemotherapy (n=22)<br>Surgery + radiotherapy (n=18) | (0-183 months) | |
| Adenis 2013 | UK | 26 | Previous treatment modalities (combinations not specified) n=26<br>Immunotherapy (n=26) | Not specified for all cancers | GIST (n=17)<br>Chordoma (n=7)<br>Mucosal (n=2) |
| Mun 2013 | Korea | 1 | Surgery + immunotherapy + chemotherapy | Not applicable | Mucosal (n=1) |
| Sun 2012 | China | 51 | Surgery + immunotherapy +/- chemotherapy (n=11)<br>Other therapy [not specified] (n=40) | Not specified | Mucosal (n=51) |
| Wang 2012 | China | 61 | Immunotherapy+chemotherapy + other unspecified (n=34)<br>Surgery alone (n=13)<br>Radiotherapy (n=17) | 21.0 months (5-80 months) | Mucosal (n=61) |
| Saigal 2012 | USA | 17 | Surgery alone (n=5)<br>Surgery + immunotherapy + other modalities (n=7)<br>Surgery + other modalities excluding immunotherapy (n=5) | 35.2 months (5-225 months) | Mucosal (n=17) |
| Moreno 2010 | USA | 58 | Immunotherapy + other modalities not specified (n=21) | Not specified | Mucosal (n=58) |
| Narasimhan 2009 | USA | 18 | Surgery alone (n=8)<br>Surgery + immunotherapy +/- other modalities not specified(n=8)<br>Surgery + other modalities [excluding immunotherapy] (n=18) | Not specified | Mucosal (n=18) |
| Bedlikian 2008 | USA | 616 | Chemo therapy +/- interferon (n=352)<br>Biochemotherapy (n=264) | Not specified | Skin (n=497)<br>Unknown primary (n=83)<br>Mucosal (n=21)<br>Uveal (n=15) |
| Krengli 2006 | Italy | 74 | Surgery (n=17)<br>Surgery + radiotherapy (n=42)<br>Radiotherapy (n=11)<br>Chemo-immunotherapy (n=4) | 20 months (1-207 months) | Mucosal (n=74) |

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| Garzino-Demo 2004 | Italy | 10 | Surgery + immunotherapy + other modalities (n=8)<br>Surgery + other modalities [excluding immunotherapy] (n=2) | Not specified | Mucosal (n=10) |
| Maxwell 2018 | USA | 20 | Surgery + other modalities [excluding immunotherapy] (n=10)<br>Surgery + chemotherapy + immunotherapy (n=10) | 9.5 months (4-24 months) | Mucosal (n=21) |
| Hamid 2018 | USA | 1567 | Immunotherapy + prior modalities not specified (n=1567) | Not specified | Mucosal (n=84)<br>Non mucosal not specified (n=1483) |
| Sayed 2017 | USA | 72 | Surgery + immunotherapy (n=17)<br>Surgery + other modalities [excluding immunotherapy] (n=55) | Not specified | Mucosal (n=72) |
| Liu 2017 | China | 51 | Immunotherapy +/- other modalities (n=13)<br>Other modalities excluding immunotherapy (n=38) | 59.0 months (11-123 months) | Mucosal (n=51) |
| Simeone 2017 | Italy | 42 | Immunotherapy +/- other therapies (n=42) | 5.6 months | Cutaneous (n=40)<br>Mucosal (n=2) |
| Ascierto 2016 | Italy | 1 | Immunotherapy | Not applicable | Mucosal (n=1) |
| Shoushtari 2016 | USA | 60 | Immunotherapy + other modalities (n=51)<br>Immunotherapy alone (n=9) | 10.6 months | Mucosal (n=35)<br>Acral (n=25) |
| Frakes 2015 | USA | 38 | Immunotherapy + other modalities (n=6)<br>Other modalities excluding immunotherapy (n=32) | 58 months (7-118 months) | Mucosal (n=38) |
| Swegal 2014 | USA | 25 | Immunotherapy + other modalities (n=6)<br>Other modalities excluding immunotherapy (n=19) | 20.4 months (2.4 - 172 months- | Mucosal (n=25) |
| Tajudeen 2014 | USA | 14 | Immunotherapy + other modalities (n=1)<br>Other modalities excluding immunotherapy (n=13) | Not specified | Mucosal (n=14) |

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|---|---|---|---|---|---|
| Keller 2013 | USA | 73 | Surgery + immunotherapy (n=22)<br>Other modalities excluding immunotherapy (n=51) | 27.5 months (0-183 months) | Mucosal (n=73) |
| Krengli 2006 | Italy | 74 | Immunotherapy with chemotherapy (n=4)<br>Other modalities excluding immunotherapy (n=70) | 20 months | Mucosal (n=74) |
| Wada 2004 | Japan | 31 | Immunotherapy +/- other modalities (n=11) | 16 months (1-214 months) | Mucosal (n=31) |
| Owens 2003 | USA | 48 | Biochemotherapy +/- immunotherapy (n=12)<br>Other modalities (n=36) | Not specified | Mucosal (n=48) |
| Stern 1991 | USA | 42 | Immunotherapy +/- chemotherapy (n=29)<br>Other modalities excluding immunotherapy (n=13) | 46 months | Mucosal (n=42) |
| Kim 2016 | Korea | 27 | Immunotherapy +/- other modalities (n=28) | 32.1 months (24.9-39.1months) | Acral (n=10)<br>Mucosal (n=9)<br>Cutaneous (n=8) |
| Liao 2014 | USA | 14 | Immunotherapy with other modalities (n=1)<br>Other modalities excluding immunotherapy (n=13) | 49 months | Mucosal (n=14) |